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Scope

The Atlas of Genetics and Cytogenetics in Oncology and Haematology is a peer reviewed on-line journal in open access, devoted to genes, cytogenetics, and clinical entities in cancer, and cancer-prone diseases. It presents structured review articles ("cards") on genes, leukaemias, solid tumours, cancer-prone diseases, more traditional review articles on these and also on surrounding topics ("deep insights"), case reports in hematology, and educational items in the various related topics for students in Medicine and in Sciences.

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Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycythemic myelofibrosis
Francesca Cambosu, Giuseppina Fogu, Paola Maria Campus, Claudio Fozza, Luigi Podda, Andrea Montella, Maurizio Longinotti

Educational Items Section

Weird animal genomes and sex chromosome evolution
Jenny Graves
ADAM10 (ADAM metallopeptidase domain 10)

Pascal Gelebart, Hanan Armanious, Raymond Lai

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Identity

Other names: AD10, CD156c, HsT18717, MADM, kuz

HGNC (Hugo): ADAM10

Location: 15q21.3

DNA/RNA

Description

The gene spans a region of 15.36 kb and the coding part is divided into 16 exons.

Transcription

Only one type of transcript has been described. The 2247-nucleotide transcript encodes a protein of 748 amino acid residues. The first and last exons are partially untranslated.

Pseudogene

None described so far.

Figure 1. Representation of the ADAM10 gene organization.
ADAM10 (ADAM metallopeptidase domain 10) Gelebart P, et al.

Protein

Description
ADAM10 is a metalloproteinase composed of 748 residues.

Expression
ADAM10 RNA has been reported to be present in wide range of human tissue (Yanai et al., 2005). Data obtained from GeneAtlas have shown that ADAM10 transcript is the most highly expressed in myeloid, NK cells and monocytes as well as cardiomyocytes and smooth muscle cells (figure 3). At the protein level, ADAM10 has been reported in epithelial tissue of the heart, liver and kidney (Hall and Erickson, 2003).

Localisation
ADAM10 is localized at the plasma membrane. However, nuclear localization of ADAM10 has been reported in prostate cancer and in mantle cell lymphoma cells (Armanious et al., 2011).

Function
ADAM10 belongs to the family of metalloproteinases (Chantry et al., 1989; Chantry and Glynn, 1990; Edwards et al., 2008). ADAM10 protein is composed of multiple functional domains that include: a prodomain, a catalytic domain, a cysteine-rich domain, a transmembrane domain, a cytoplasmic domain and a SH3 domain (Seals and Courtneidge, 2003; Edwards et al., 2008) (see figure 4). ADAM10 is synthesized as a pro-protein and therefore needs to be cleaved to be activated (Anders et al., 2001). Two proteins, the convertase 7 and the furin, have been implicated in the activation of ADAM10 (Anders et al., 2001). To date the major function of ADAM10 appears to be attributed to its enzymatic activity as a metalloproteinase. In fact, ADAM10 is involved in the intra-membrane proteolysis process, whereby it mediates ectodomain shedding of various membrane bound receptors, adhesion molecules, growth factors and cytokines like TNF-alpha (Rosendahl et al., 1997; Lunn et al., 1997; Hikita et al., 2009; Mezyk-Kopec et al., 2009), Notch (Hartmann et al., 2002; Gibb et al., 2010), E-cadherin (Maretzky et al., 2005), Ephrin (Janes et al., 2005), HER-2 (Liu et al., 2006), CD30 (Eichenauer et al., 2007), CD44 (Anderegg et al., 2009) and IL-6 receptor to name a few. The functional role of the SH3 domains of ADAM10 has never been studied. Moreover, the recent observation that ADAM10 can be found in the nucleus of some cells raises the possibility of new and uncovers function of ADAM10 (Arima et al., 2007).

ADAM10 seems to be detrimental for embryogenesis as the knockout mice for ADAM10 die at day 9.5 of embryogenesis (Hartmann et al., 2002). The mice present several developmental defects in the nervous central system as well in the cardiovascular system. This latest observation correlates well with the fact that ADAM10 transcript is highly expressed in cardiomyocyte.

In human, ADAM10 was recently been demonstrated to be a regulator of the lymphocyte development (Gibb et al., 2011).

Figure 2. Crystal structure of ADAM10 Disintegrin and cysteine-rich domain at 2.9 A resolution. Adapted from PDB (access number: 2AO7).
ADAM10 (ADAM metallopeptidase domain 10) Gelebart P, et al.

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**Figure 3. ADAM10 tissue expression profile.** Adapted from GeneAtlas U113A.

**Figure 4. ADAM10 protein structure organization.**

### Mutations

**Note**
No mutation has been reported so far.

### Implicated in

**Various cancers**

**Note**
ADAM family members have been recently involved in malignant progression and development (Mochizuki and Okada, 2007; Rocks et al., 2008; Wagstaff et al., 2011; Duffy et al., 2009). ADAM10 has been shown to be constitutively active in a number of solid tumors, and this biochemical defect is implicated in the pathogenesis of many tumors. The following paragraphs will summarize what has been discovered about the function of ADAM10 in cancer.

### Brain tumors

**Note**
ADAM10 protein has been reported to be highly expressed in the human central nervous system (Kärkkäinen et al., 2000). Recently, two different studies (Kohutek et al., 2009; Formolo et al., 2011) have uncovered the function of ADAM10 in the cell migration and invasiveness process of glioblastoma cells. In fact the authors have shown that ADAM10 by mediating the cleavage of N-cadherin was found to regulate the migratory properties of glioblastoma cells (Kohutek et al., 2009). On the other hand, the protein expression of ADAM10 was found to be higher in cell with strong invasiveness capability.

### Prostate cancer

**Note**
Prostate cancer is one of the most frequent cancers in men. The cause of prostate cancer development is
unknown but is likely to be arising from several factors. Development of prostate cancer is androgen-dependent in early stages of the disease but cell growth became androgen-independent. ADAM10 have been found to be expressed in all prostate tumor samples (Karan et al., 2003). Interestingly, McCulloch et al. have observed that ADAM10 expression was up-regulated by androgen stimulation. Those observations were confirmed in a study published by Arima et al. However, in this work they reveal that ADAM10 was predominantly localized in the nucleus of cancer cells and show that ADAM10 can co-immunoprecipitate with androgen receptor in the nucleus. Moreover, they also observed that nuclear expression of ADAM10 was correlating with several biological parameters like the Gleason score and prostate specific antigen expression. Inhibition of ADAM10 expression by a siRNA approach was able to induce a cell proliferation decrease of prostate cancer cells. This study suggests for the first time that ADAM10 may have some function in the nucleus by regulating androgen receptor function.

Breast cancer

Note
Expressions of different members of the ADAM family have been investigated in breast cancer. Despite that some ADAM family members present differential expression between non neoplastic and breast cancer tissue, no difference was observed for ADAM10 (Lendeckel et al., 2005). Nevertheless, Liu and co-workers have recently described than ADAM10 was the principal responsible for HER2 shedding in HER2 over-expressing breast cancer. The cleavage of HER2 liberates the extracellular domain of HER2 leaving a p95 fragment containing the transmembrane domain as well as the intracellular domain. This p95 fragment presents constitutive kinase activation and its expression correlates with a poor prognosis. The author demonstrated that in conjunction with low amount of HER2 inhibitor, ADAM10 inhibition was inducing a decrease in cell proliferation.

Colon and gastric and oral carcinomas

Note
Deregulation of ADAM10 in colon cancer development has been reported in several studies. Knösel et al. have reported that ADAM10 expression in colorectal cancer patient samples, detectable by immunohistochemistry was found to correlate with higher clinical stage. Moreover, it has been demonstrated that xenografting of colorectal cancer cells with enforced expression of ADAM10 in nude mice induced formation of liver metastasis compared to the negative control cells, and this effect can be attributed to ADAM10-mediated cleavage and release of L1-CAM, a cell adhesion molecule (Gavert et al., 2007). Similarly to Knösel et al., ADAM10 expression was associated with gastric cancer progression and correlates with worst prognostic outcome (Wang et al., 2011). Using immunohistochemistry, it was also found that ADAM10 is over-expressed in squamous cell carcinomas of the oral cavity, as compared to the benign epithelial cells; knockdown of ADAM10 expression using siRNA in the cell lines derived from those tumors induces a significant decrease in cell growth (Ko et al., 2007).

Melanoma, pancreatic cancer and adenoid cystic carcinoma

Note
The expression of ADAM10 has been investigated in melanoma and Lee et al. have reported that ADAM10 is over-expressed in melanoma metastasis in comparison to primary melanoma cells. Similar findings were made in pancreatic cancer, where inhibition of ADAM10 expression in pancreatic carcinoma cell lines also resulted in a significant decrease in invasiveness and migration (Gaida et al., 2010).

Hematologic malignancies

Note
Recently, Armanious et al. have described for the first time the function of ADAM10 in non solid tumors. They have reported that ADAM10 is constitutively activated and over-expressed in different form of B-cell lymphoma like mantle cell lymphoma and diffuse large B-cell lymphoma. Moreover, the authors have described that inhibition of ADAM10 leads to a decrease of cell proliferation. On the other hand, stimulation of mantle cells with the recombinant active form of ADAM10 increases further their proliferation. Additionally, they also demonstrated, as reported previously in the literature, that ADAM10 was responsible for the release of active form of TNF-alpha that in turn was contributing to the activation of the NF-kappaB pathways.

To be noted

Note
To summarize, the function of ADAM protein family members emerge as an important player in the pathobiology of various form of cancers. Therefore, they represent today a new therapeutic target of choice for cancer therapy. In particular, ADAM10 is the object of intense drug development (Soundararajan et al., 2009; Crawford et al., 2009; Yavari et al., 1998; Moss et al., 2008).

References


Chantry A, Glynn P. A novel metalloproteinase originally isolated from brain myelin membranes is present in many tissues. Biochem J. 1990 May 15;268(1):245-8


Mochizuki S, Okada Y, ADAMs in cancer cell proliferation and progression. Cancer Sci. 2007 May;98(5):621-8


Kohutek ZA, diPierro CG, Redpath GT, Hussaini IM. ADAM-10-mediated N-cadherin cleavage is protein kinase C-alpha dependent and promotes glioblastoma cell migration. J Neurosci. 2009 Apr;29(14):4606-15


Wang YY, Ye ZY, Li L, Zhao ZS, Shao QS, Tao HQ. ADAM 10 is associated with gastric cancer progression and prognosis of patients. J Surg Oncol. 2011 Feb;103(2):116-23

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BUB1 (budding uninhibited by benzimidazoles 1 homolog (yeast))

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Identity

Other names: BUB1A, BUB1L, hBUB1
HGNC (Hugo): BUB1
Location: 2q13

Note

The multidomain protein kinase BUB1 is a central component of the mitotic checkpoint for spindle assembly (SAC). This evolutionary conserved and essential self-monitoring system of the eukaryotic cell cycle ensures the high fidelity of chromosome segregation by delaying the onset of anaphase until all chromosomes are properly bi-oriented on the microtubule spindle.

DNA/RNA

Description
The gene spans 40.2 kb and is composed of 25 exons.

Transcription
NM_004336.3

Protein

Note

Uniprot accession number: NP_004327.1.
ENZYME entry (serine/threonine protein kinase): EC 2.7.11.1.

Amino acid sequence (FASTA format).

Description
1085 amino acids, 122.37 kDa.

Expression
Ubiquitously expressed.

Localisation
Cytoplasmic in interphase cells. It is localized in nuclear kinetochores in cells with an unsatisfied mitotic checkpoint in a process that requires BUB1 binding to Blinkin and BUB3.

Function

BUB1 is required for chromosome congression, kinetochore localization of BUB1, CENP-E, CENP-F and Mad2 in cells with mitotic checkpoint unsatisfied and for the establishment and/or maintenance of efficient bipolar attachment to spindle microtubules (Johnson et al., 2004; Lampson and Kapoor, 2005; McGuinness et al., 2009). Deletion of Bub1 from S. pombe increases the rate of chromosome missegregation (Bernard et al., 1998) while deletion of Bub1 from S. cerevisiae results in slow growth and elevated chromosome loss (Warren et al., 2002). BUB1 is recruited very early in prophase (Wong and Fang, 2006) and is essential for assembly of the functional inner centromere (Taylor et al., 1998; Boyarchuk et al., 2007).

Figure 1. Schematic representation of the human bub1 gene demonstrating the relative size of each of the 25 exons (introns are not drawn to scale).
It accumulates at the kinetochore in SAC-activated cells and assures the correct kinetochore formation. The N-terminal region mediates the binding of BUB1 to the mitotic kinetochore protein Blinkin (a protein also commonly referred to as KNL1/Spc105/AF15q14); the interaction is essential for the kinetochore localization of BUB1 induced in cells with an unsatisfied mitotic checkpoint (Kiyomitsu et al., 2007). N-terminal BUB1 is organised as a triple tandem of the TPR motif (Bolanos-Garcia et al., 2009). In fission yeast, the Bub1 N-terminal residues 1-179 are required for targeting the protein Shugoshin 1 (SGO1) to centromeres (Vaur et al., 2005) while deletion of residues 28-160 results in a truncated protein unable to recruit Bub3 and Mad3/BUB1B to kinetochores (Vanoosthuyse et al., 2004). The C-terminal region contains a catalytic, serine threonine kinase domain that resembles the mechanism of activation of CDKs by cyclins (Kang et al., 2008).

**Homology**

The bub1 gene is conserved in chimpanzee, cow, mouse, rat, chicken, and zebrafish. Homology exists with the gene encoding for the mitotic checkpoint kinase BUBR1 (a BUB1 paralogue) (Bolanos-Garcia and Blundell, 2011).

**Mutations**

The following somatic mutations have been reported to date: A130->S (Shichiri et al., 2002); deletion delta76-141 (Cahill et al., 1998); 140, transition of the splicing donor site (Cahill et al., 1998); S492->Y (Cahill et al., 1998); deletion delta827 (Ouyang et al., 2002); G250->N (Ohshima et al., 2000); S950->G (Imai et al., 1999); Y259->C (Hempen et al., 2003); H265->N (Hempen et al., 2003). It could not be determined whether the R209->Q substitution was the result of a somatic mutation or due to a rare polymorphism because constitutional DNA from the patient harbouring this mutation was not available (Sato et al., 2000). The clinical condition associated to each mutation is described in Table 1. The mapping of residues substitutions onto the BUB1 domains is depicted in Figure 3.

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Table 1. Human bub1 mutations associated with cancer. *These authors incorrectly number these residues; the numbering shown here is the correct.
Colorectal cancer

*Disease*

Colorectal cancer, also referred to as bowel cancer, is characterized by neoplasia in the colon, rectum, or vermiform appendix. Colorectal cancer is the third most commonly diagnosed cancer in the world and fourth most frequent cause of cancer death in males. More than half of the people who die of colorectal cancer live in a developed region of the world.

*Cytenogenetics*

RT-PCR mediated amplification and direct sequencing of the entire BUB1 coding region in the colorectal cancer cell line V400 revealed an internal deletion of 197 bp of this gene (Cahill et al., 1998). The deletion results in the remotion of codons 76 to 141 and creates a frameshift immediately thereafter. Sequence analysis of cDNA from another colorectal cancer cell line, V429, revealed a missense mutation at codon 492 that resulted in the substitution of tyrosine for a conserved serine (Cahill et al., 1998). The V400 and V429 mutations were heterozygous, somatic and present in primary tumours but not in normal tissues. Another heterozygous BUB1 missense mutation (AGT to GGT) at codon 950 has been identified (Imai et al., 1999).

Hepatocellular carcinoma (HCC)

*Disease*

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide and it accounts for most liver cancers. HCC occurs more often in men than women and is more common in people ages 30-50. Hepatitis virus infection, alcohol consumption, and dietary exposure to toxins such as aflatoxin B1 are associated with the occurrence of HCC.

*Cytenogenetics*

Two BUB1 gene variants have been identified in HCC specimens (Saeki et al., 2002). The expression product of one variant has a serine (TCC) substituted for phenylalanine (TTC) at codon 375 while the other has a lysine (AAG) substituted for arginine (AGG) at codon 566 (Saeki et al., 2002). S375F showed a well-differentiated HCC in cirrhotic liver caused by hepatitis B virus, whereas K566R showed a moderately differentiated HCC in hepatitis C virus induced cirrhotic liver. Genomic DNA extracted from nontumorous liver tissue revealed the same variants in both cases.

Lung cancer

*Disease*

Lung cancer is the most frequently diagnosed cancer among men. The mortality rate is the highest among men and the second highest among women worldwide. The main types of lung cancer are small-cell lung carcinoma and non-small-cell lung carcinoma. Non-small-cell lung carcinoma is sometimes treated with surgery, while small-cell lung carcinoma usually responds better to chemotherapy and radiation. Lung cancer cells harbour many cytogenetic abnormalities suggestive of allele loss, including non-reciprocal translocations and aneuploidy. The stage of the disease is a strong predictor of survival, suggesting that early detection is needed for improvement in treatment outcomes.

*Cytenogenetics*

A nucleotide change of the BUB1 gene that results in the substitution of Arginine by Glutamine R209Q has been identified in the cell line NCI-H345 (Sato et al., 2000). Unfortunately, it was not possible to determine whether the change was a somatic mutation or a rare polymorphism because constitutional DNA from this patient was not available.

Adult T-cell leukaemia/lymphoma (ATLL)

*Disease*

Lymphomas, malignancies of the lymphoid cells, are divided on the basis of their pathologic features into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma.
(NHL). Adult T-cell leukemia/lymphoma (ATLL) is usually a highly aggressive non-Hodgkin's lymphoma of the patient's own T-cells with no characteristic histologic appearance except for a diffuse pattern and a mature T-cell phenotype. The frequent isolation of HTLV-1 from patients with this disease and the detection of HTLV-1 proviral genome in ATLL leukemic cells suggest that HTLV-1 causes ATLL.

Cytogenetics

A BUB1 missense mutation of G to A at codon 250 (GGT to GAT) has been reported (Ohshima et al., 2000).

Pancreatic cancer

Disease

The term pancreatic cancer usually refers to adenocarcinoma that arises within the exocrine component of the pancreas. Pancreatic cancer is one of the most aggressive diseases with most cancers and often has a poor prognosis: for all stages combined, the 1- and 5-year relative survival rates are 25% and 6%, respectively; for local disease the 5-year survival is approximately 20% while the median survival for locally advanced and for metastatic disease, which collectively represent over 80% of individuals, is about 10 and 6 months respectively.

Cytogenetics

Two missense variants in the BUB1 gene have been identified in the aneuploid pancreatic cell line HS766T (Hempen et al., 2003). These mutations are found in the same allele, accompanied by a wild-type BUB1 allele. Mutation of nucleotide 776 from an adenine to a guanine results in an amino acid change at codon 259 from tyrosine to cysteine (Y259C). A second mutation at nucleotide 793 changed a cytosine to an adenine (C to A) thus resulting in the mutant H265N (Hempen et al., 2003).

Thyroid follicular adenoma

Disease

Almost all thyroid adenomas are follicular adenomas. Follicular adenomas can be described as "cold", "warm" or "hot" depending on their level of function. Histopathologically, follicular adenomas can be classified according to their cellular architecture and relative amounts of cellularity and colloid into the following types:

- fetal (microfollicular), which have the potential for microinvasion,
- colloid (macrofollicular), which do not have any potential for microinvasion,
- embryonal (atypical), which have the potential for microinvasion.

Cytogenetics

A thyroid follicular carcinoma that has a 2-bp somatic deletion (G2480/A2481) of BUB1 has been reported by Ouyang and collaborators (2002).

Lymph node metastasis

Disease

Certain cancers spread in a predictable fashion from where the cancer started. Because the flow of lymph is directional, if the cancer spreads it will spread first to lymph nodes close to the tumor before it spreads to other parts of the body.

Cytogenetics

A BUB1 missense somatic mutation (nucleotide 437 GCT to TCT transition) that replaces Ala to Ser at codon 130 has been identified in an ascending colorectal carcinoma (Shichiri et al., 2002).

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This article should be referenced as such:
Gene Section

Review

FAU (Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV) ubiquitously expressed)

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Identity

Other names: FAU1, FLJ22986, Fub1, Fubi, MNSFbeta, RPS30, asr1

HGNC (Hugo): FAU

Location: 11q13.1

Local order: FAU is flanked by SYVN1 and ZNHIT2 on the negative strand.

Note

FAU was originally identified as the cellular homologue of the fox gene of the retrovirus Finkel-Biskis-Reilly murine sarcoma virus (FBR-MuSV); fox is antisense to FAU, and has been shown to increase the tumorigenicity of FBR-MuSV. FAU encodes a ubiquitin-like protein fused to ribosomal protein S30 as a carboxy-terminal extension; the two products are thought to be cleaved post-translationally. The S30 protein is a member of the S30E family of ribosomal proteins and is a constituent of the 40S subunit of the ribosome; additionally it is secreted and has antimicrobial activity (ubiquicidin). The function of the ubiquitin-like protein, termed FUBI, is unclear; in murine cells, it has been reported to covalently modify inter alia a T-cell receptor alpha-like protein and Bcl-G, suggestive of roles in immunomodulation and apoptosis regulation, respectively. In human cells, ectopic FAU expression enhances basal apoptosis, whereas siRNA-mediated silencing of FAU gene expression induces resistance to apoptosis induction in response to a range of stimuli. FAU gene expression is down-regulated in a number of human cancers, including breast, prostate and ovarian cancers.

DNA/RNA

Description

Gene is located on the negative strand at -64889908: -64887863 (2046 bases). The promoter contains a number of regulatory elements, including binding sites for transcription factors such as AP-1, IRF-1, Max, c-Myc, glucocorticoid receptor isoforms and ATF.

Transcription

Comprises 5 exons spanning -64888099: -64889672. The mRNA product length is 579 bases.

Pseudogene

A retropseudogene, FAU1P, has been described in the human genome and is located on chromosome 18. Retropseudogenes of FAU have also been described in the mouse genome.

FAU comprises 5 exons - the coding sequence for FUBI is located within exons 2 and 3, whereas the coding sequence for S30 is located within exons 4 and 5.
A. Protein products of FAU - FAU encodes a ubiquitin-like protein (FUBI) with ribosomal protein S30 as a C-terminal extension protein (CEP). These are cleaved post-translationally. B. FUBI has 37/57% sequence identity/similarity to ubiquitin (Ub; latter is fused to CEP80/S27a ribosomal protein). The C-terminal G-G dipeptide (shown in orange), which is required for cleavage from the CEP and for isopeptide bond formation to lysine of targets, is conserved. Note however, that lysine residues (shown in green) which serve as sites for polyubiquitin chain formation are absent. Consequently, FUBI is unlikely to have an analogous role to ubiquitin in protein degradation.

**Protein**

**Description**

The protein product comprises a ubiquitin-like protein, FUBI, with ribosomal protein S30 as a carboxy-terminal extension protein (CEP); other ribosomal proteins are produced as CEPs fused to ubiquitin. FUBI and S30 are thought to be cleaved post-translationally, but the enzyme catalyzing this step has not been identified. Whilst FUBI shows a high degree of sequence similarity to ubiquitin, notably retaining the C-terminal G-G dipeptide motif that is required for isopeptide bond formation between ubiquitin and lysines of target proteins, it lacks internal lysine residues (especially lysine-48) which serve as sites of polyubiquitin chain formation and usually facilitate proteasomal degradation of target molecules. Rather, modification of proteins with monomers of ubiquitin or ubiquitin-like proteins may influence the activity, intracellular localisation or inter-molecular interactions of target proteins. Little information exists regarding target proteins for FUBI in human cells. In mouse, four target proteins have been identified. Covalent modification occurs for: (i) a T-cell receptor alpha-like protein (resulting in the production of murine monoclonal non-specific suppressor factor, which exhibits immunomodulatory activity); (ii) Bcl-G (a pro-apoptotic member of the Bcl-2 family; and (iii) endophilin II (regulates phagocytosis in mouse macrophages). Non-covalent modification of histone 2A has also been reported.

**Expression**

Steady state FAU mRNA levels are highly abundant and largely invariant in normal tissues indicative of a house-keeping gene role. However, physiological variations occur in FAU expression, notably in endometrium. FAU transcript levels have been reported to be reduced in a number of human cancers, including those affecting the breast, the prostate and the ovary.
Localisation
Cytosolic, ribosomal and nuclear localisations have been reported for FAU products. In addition, secretion of FUBI (in association with a T-cell receptor-alpha-like molecule) has been reported for some immune system cell types.

Function
FAU regulates apoptosis in human epithelial and T-cell lines. It also possesses immunomodulatory and anti-microbial activities, and encodes a constituent of the ribosome.

Regulation of apoptosis
Functional expression cloning in mouse leukemic cell lines, with selection (dexamethasone and gamma-irradiation) for suppression of cell death, led to the isolation of a sequence which was antisense to FAU (Mourtada-Maarabouni et al., 2004). Subcloning experiments confirmed that this antisense sequence produced resistance to apoptosis induced by dexamethasone and, additionally, by cisplatin and by ultraviolet-C irradiation. The antisense sequence reduced endogenous FAU expression. Conversely, overexpression of FAU promoted cell death, and this effect could be prevented by co-transfection with a plasmid encoding Bcl-2 (an anti-apoptotic factor) or by inhibition of caspases. Further work in human T-cell lines and the epithelial cell line, 293T/17, has confirmed that ectopic FAU expression increases basal apoptosis, and that siRNA-mediated silencing of FAU attenuates apoptosis in response to ultraviolet-C irradiation (Pickard et al., 2011). FAU also regulates apoptosis in other human epithelial cell lines derived from breast (Pickard et al., 2009), ovarian (Moss et al., 2010) and prostate (Pickard et al., 2010) tumours (see ‘Implicated in’). FUBI has been shown to covalently modify Bcl-G (a pro-apoptotic member of the Bcl-2 family) in mouse cells (Nakamura and Tanigawa, 2003), and it is feasible therefore, that FAU regulates apoptosis via Bcl-G. Indeed, prior knockdown of Bcl-G ablated the stimulation of basal apoptosis by FAU in human cells (Pickard et al., 2011). This pro-apoptotic activity may underlie the putative tumour suppressor role of FAU, since failure of apoptosis is known to play a central role in the development of many cancers.

Immunomodulation
Monoclonal non-specific suppressor factor (MNSF) was first isolated from mouse cells in 1986 (Nakamura et al., 1988) and subsequently, from ascites fluid of a patient with systemic lupus erythematosus (Xavier et al., 1994); most studies of MNSF to-date have focussed on murine cells. This lymphokine-like molecule, which comprises alpha- and beta-chains, is secreted by CD8+ T-cells (Xavier et al., 1995). cDNA encoding MNSF-beta was first isolated from the mouse in 1995, and it was shown to be identical to FAU (Nakamura et al., 1995). MNSF inhibits, inter alia, proliferation of mitogen-stimulated T- and B-cells, immunoglobulin secretion by B-cells in an isotype-specific manner (IgE and IgG3 are especially affected), TNFalpha production by activated macrophages and interleukin-4 secretion by bone marrow-derived mast cells and by a type-2 helper T-cell clone (Nakamura et al., 1988; Nakamura et al., 1994; Xavier et al., 1994; Nakamura et al., 1995; Xavier et al., 1995; Nakamura et al., 1996; Suzuki et al., 1996). Inhibitory effects on T- and B-cell proliferation are subject to negative regulation by interleukin-2 (Nakamura et al., 1988). Many of these immunosuppressive effects of MNSF can be ascribed to the MNSFBeta subunit, and specifically to FUBI (aka Ubi-L) (Nakamura et al., 1996). Cell surface receptors for MNSF have been described in target cells (Nakamura et al., 1992), and these exhibit similarities to cytokine receptors (Nakamura and Tanigawa, 1999), with tyrosine phosphorylation being implicated in transmembrane signalling (Nakamura and Tanigawa, 2000; Nakamura et al., 2002). Both the expression of cell surface receptors on target cells and the secretion of MNSFBeta/FUBI by splenocytes are stimulated by interferon-gamma (Nakamura et al., 1992; Nakamura et al., 1996). In splenocytes, FUBI conjugates to a range of intracellular proteins, including a T-cell receptor-alpha-like molecule; the resulting complex, which comprises intact MNSF, is secreted by cells (Nakamura et al., 1998; Nakamura et al., 2002). FUBI also covalently modifies Bcl-G in spleen but not in testis, despite high levels of Bcl-G expression in the latter tissue (Nakamura and Tanigawa, 2003). In macrophages, the FUBI/Bcl-G adduct binds to ERKs and inhibits ERK activation by MEK1 (Nakamura and Yamaguchi, 2006). In liver and macrophages, FUBI also forms an adduct with endophilin II and inhibits phagocytosis by macrophages (Nakamura and Shimosaki, 2009; Nakamura and Watanabe, 2010).

Host defence
An anti-microbial protein, termed ubiquicidin, has been isolated from the cytosol of a mouse macrophage cell line treated with interferon-gamma; the protein is active against Listeria monocytogenes, Salmonella typhimurium, Escherichia coli, Staphylococcus aureus and Yersinia enterocolitica (Hiemstra et al., 1999). Ubiquicidin is identical to FAU-encoded ribosomal protein S30 (Hiemstra et al., 1999). Ubiquicidin is also produced by human colonic mucosa (Tollin et al., 2003) and rainbow trout skin (Fernandes and Smith, 2002). It is also active against methicillin-resistant Staphylococcus aureus and accumulates at sites of infection in mice (Brouwer et al., 2006). Radiolabelled ubiquicidin has applications in clinical imaging for microbial infections (Brouwer et al., 2008).

Homology
At the amino acid level, FUBI has 37/57% sequence identity/similarity to ubiquitin.
Implicated in

Various cancers

Note

Tumor suppression: The retrovirus, FBR-MuSV, which contains the transduced genes v-fos and fox, can induce osteosarcomas in mice. In vitro experiments have shown that fox increases the transforming capacity of FBR-MuSV approximately two-fold (Michiels et al., 1993). Fox is an antisense sequence to the cellular gene FAU, indicative of a tumour suppressor role for FAU. Retropseudogenes of FAU have been identified in human (Kas et al., 1995) and mouse (Casteels et al., 1995) genomes, suggesting a possible source for the viral fox gene (which is antisense to FAU). Further evidence for a tumour suppressor role for FAU has come from studies of the human carcinogen arsenite. Thus, functional cloning approaches in Chinese hamster V79 cells with selection for arsenite resistance, resulted in the isolation of the asr1 gene, which is homologous to FAU (Rossman and Wang, 1999). Subsequent work by this group using human osteosarcoma cell lines, indicated that the ability to confer arsenite resistance resided in the S30 domain of FAU (Rossman et al., 2003).

Oncogenesis

Expression of the FUBI domain of FAU has been shown to transform human osteosarcoma cells to anchorage-independent growth (Rossman et al., 2003).

Breast cancer

Note

Serial analysis of gene expression (SAGE) identified FAU as an underexpressed gene in ductal carcinoma in situ when compared with normal breast epithelium (Abba et al., 2004). This was subsequently confirmed using quantitative RT-PCR analysis of matched (same patient) samples of breast cancer tissue and adjacent breast epithelial tissue (Pickard et al., 2009). Furthermore, in a separate group of breast cancer patients, expression levels of FAU (determined by cDNA microarray analysis) were shown to be related to patient survival in Kaplan-Meier analyses (Pickard et al., 2009). This analysis indicated that higher expression of Faup has a protective effect, consistent with its candidate tumour suppressor role. Whilst Bcl-G expression was also shown to be down-regulated in breast cancer, Bcl-G expression was not related to patient survival (Pickard et al., 2009), suggesting that the regulation of Bcl-G activity by post-translational modification is more important than Bcl-G expression per se in determining breast cancer patient survival. Functional studies in the T-47D breast cancer cell line demonstrated that down-regulation of either FAU or Bcl-G expression by siRNA-mediated silencing attenuated apoptosis induction by ultraviolet-C irradiation (Pickard et al., 2009). Notably, no additional effect was observed when the two genes were simultaneously silenced, consistent with a role for Bcl-G in mediating the pro-apoptotic activity of FAU.

Ovarian cancer

Note

A reduction in FAU gene expression has been reported for malignant versus normal ovarian tissue, and for Type I ovarian tumours (typically include mucinous, endometrioid, clear cell, and low-grade serous cancers), in particular (Moss et al., 2010). Over-expression of FAU in a cisplatin-resistant ovarian cancer cell sub-line, A2780cis, resulted in increased sensitivity to carboplatin-induced apoptosis (Moss et al., 2010). Conversely, down-regulation of FAU in the A2780 parental cell line resulted in increased resistance to carboplatin-induced apoptosis (Moss et al., 2010). These in vitro findings suggest a role for FAU in the regulation of platinum-based drug resistance in ovarian cancer.

Prostate cancer

Note

Steady state FAU mRNA levels are down-regulated in prostate cancer when compared with normal tissue and tissue from patients with benign prostate hyperplasia; a similar trend was found for Bcl-G (Pickard et al., 2010). siRNA-mediated silencing of FAU or Bcl-G expression in the prostate cell line, 22Rv1, attenuated apoptosis induction consequent upon ultraviolet-C irradiation. A similar degree of apoptosis resistance was observed when the two genes were simultaneously down-regulated, consistent with FAU and Bcl-G acting in the same pathway.

Reproduction (implantation)

Note

FAU is expressed in endometrial stromal cells in non-pregnant mouse uterus (Salamonsen et al., 2002) and it is also expressed in human endometrium (Nie et al., 2005). In the mouse uterus, differential expression of FAU occurs during blastocyst implantation, with low expression levels noted in implantation versus non-implantation sites (Nie et al., 2000). Expression levels remain low as implantation advances (Nie et al., 2000). Administration of antisera to FAU into the mouse uterine lumen inhibits implantation in a dose-dependent manner (Wang et al., 2005), suggesting an essential role for secreted products in implantation. Trophoblast-derived interferons have been shown to induce endometrial FAU expression in pigs (Chwetzoff and d'Andrea, 1997), also supporting an important role for FAU in early pregnancy.

Breakpoints

Note

A t(11;14)(q13;q21)-positive B-cell non-Hodgkin's lymphoma patient has been described with an additional translocation of t(11;17)(q13;q21). The
chromosome 11 breakpoint in the latter translocation was reported as a 40 kbp region around FAU.

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This article should be referenced as such:

GUCY2C (guanylate cyclase 2C (heat stable enterotoxin receptor))

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Identity
Other names: GUC2C, STAR
HGNC (Hugo): GUCY2C
Location: 12p13.1
Local order: ATF7IP - PLBD1 - GUCY2C - H2AFJ - HIST4H4.

DNA/RNA

Description
The GUCY2C gene is approximately 84 kb in length and has 27 exons.

Transcription
An approximately 3.8 mRNA is transcribed from the gene.

Pseudogene
None known.

Protein

Note
GUCY2C encodes a guanylyl cyclase.

Description
1073 amino acid protein with guanylyl cyclase catalytic activity (4.6.1.2).

Expression
Primarily intestinal epithelial cells.

Localisation
Apical membrane.

Function
In response to binding endogenous hormones guanylin and uroguanylin, or the exogenous ligand E. coli heat-stable enterotoxin, GUCY2C synthesizes cyclic GMP. Cyclic GMP activates downstream signaling pathways via cGMP-dependent protein kinases, phosphodiesterases and cGMP-gated ion channels.

Homology
Adenylyl cyclase.
Implicated in

**Colorectal cancer**

Note

The endogenous GUCY2C ligands, guanylin and uroguanylin, are lost early in the neoplastic process. Targeted deletion of Gucy2c in mice results in a phenotype of intestinal cancer susceptibility in the context of predisposing genetic mutations (apc\textsuperscript{min}) or exposure to carcinogen (azoxymethane).

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**This article should be referenced as such:**

LIN28B (lin-28 homolog B (C. elegans))

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Identity

Other names: CSDD2, FLJ16517, Lin28.2
HGNC (Hugo): LIN28B
Location: 6q16.3
Note
Size: 146.72 kb. Orientation: plus strand.

DNA/RNA

Description
The gene spans over 125 kb on plus strand; 4 exons.

Transcription
The gene is mainly expressed in fetal tissues and not expressed in adult tissue and reexpressed in cancer tissue.

Protein

Description
Lin28B is an oncofetal RNA-binding protein. Lin-28B protein consists of two domains that contain RNA-binding motif: the N-terminal cold shock domain and a pair of retroviral-type CCHC zinc fingers. It inhibits biosynthesis of let-7 microRNA through binding to the 5’-GGAG-3’ motif in the terminal loop of pre-let-7 and promoting terminal uridylation of let-7 precursor by TUTase4. Uridylated pre-let-7 miRNAs fail to be processed by Dicer and undergo degradation.

Expression
Cytoplasm.

Function
It inhibits biosynthesis of let-7 microRNA through promoting terminal uridylation of let-7 precursor by TUTase4.

Homology
Lin28

Mutations
Note
No somatic mutation of Lin28B was identified in cancer.

Implicated in

Hepatocellular carcinoma
Note
Lin28B expression is more frequently noted in high-grade hepatocellular carcinoma with high alpha-fetoprotein levels. Knockdown of Lin28B by RNA interference in the HCC cell line suppressed proliferation in vitro and reduced in vivo tumor growth in NOD/SCID mice. In contrast, overexpression of Lin28B in the HCC cell line enhanced tumorigenicity. Overexpression of Lin28B also induced epithelial-mesenchymal transition in HA22T cells and hence, invasion capacity.

Colorectal cancer
Note
Lin28B is overexpressed in colorectal cancer. It promotes cell migration, invasion and transforms...
immortalized colonic epithelial cells. In addition, constitutive LIN28B expression increases expression of intestinal stem cell markers LGR5 and PROM1 in the presence of let-7 restoration.

**Ovarian cancer**

**Note**
Lin28B is overexpressed in high grade serous ovarian cancer. Pleomorphism in Lin28B promoter region is associated with susceptibility to epithelium ovarian cancer. Patients with high Lin28B ovarian cancer had shorter progression-free and overall survival than those with low Lin28B ovarian cancer.

**Age at menarche**

**Note**
A sequence variation in Lin28B is identified as the SNP most significant associated with age at menarche in one genome wide study. Besides, a meta-analysis of 32 genome-wide association studies in 87802 women found polymorphism of Lin28B is strongly associated with age at menarche. Knockout mice of Lin28B also show delay in puberty onset.

**Body height**

**Note**
A LIN28B SNP, rs314277, is associated with final body height.

**References**


This article should be referenced as such:

PKD1 (polycystic kidney disease 1 (autosomal dominant))

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Identity

Other names: PBP, Pc-1, polycystin-1, TRPP1
HGNC (Hugo): PKD1
Location: 16p13.3

DNA/RNA

Description

This gene has 46 exons that span ~52 kb of genomic sequence. Exons 1-33 are located in a genomic region which is duplicated six times on the same chromosome (~13-16 Mb proximal to PKD1 on the short arm of chromosome 16), resulting in six pseudogenes. A Mirtron family microRNA gene, miR-1225, is lying within intron 45 of PKD1, the function of this microRNA is currently unknown.

Transcription

The 14.5 kb transcript has two different isoforms as a result of alternative splicing. The longer variant, isoform I (NM_001009944), has a 12909 bp open reading frame. The short variant, isoform II (NM_000293), uses an alternate acceptor splice site, 3 nt downstream of that used by isoform I, at the junction of intron 31 and exon 32. This results in an isoform (variant II) that is one amino acid shorter than isoform I.

Pseudogene

The six pseudogenes that result from duplication of PKD1 exon 1 through 33 are located on chromosome 16p13.1 and have 97.99% identity to PKD1. Those pseudogenes are transcripted into mRNA species with suboptimal start codons, thus they are not translated.

Ideogram of human chromosome 16, the location of PKD1 gene is indicated by the red vertical line. This graph was generated by using UCSC genome browser.

Gene structure of PKD1, showing the intron/exon structure. Exons are shown with solid box; introns are shown with thin line arrow heads; 3’ and 5’ UTR regions are indicated by open boxes. Some exons numbers are labelled above. This graph was generated by using UCSC genome browser.
**Protein**

**Description**

The longer form of polycystin-1, isoform I, has 4303 aa. It is a 460 kDa membrane protein which has the structure of a receptor or adhesion molecule. The large extracellular N-terminal region consisting of a variety of domains, including 12 PKD domains (an immunoglobulin-like fold), two leucine-rich repeats, C-type lectin domain, WSC domain, GPS domain and REJ domain. The short intracellular C-terminal region has 197 aa, containing a coiled-coil domain that interact with polycystin-2 and a G-protein binding domain. Between the N and C-terminal is a large transmembrane region (1032 aa) that has 11 transmembrane domains. Polycystin-1 is cleaved at the G protein-coupled receptor proteolytic site (GPS) domain, resulting in a 150 kDa C-terminal fragment and a 400 kDa N-terminal fragment that tether to the membrane. This cleavage is suggested to be important for protein activation.

**Expression**

Polycystin-1 is widely expressed in adult tissue, with high levels in brain and moderate expression in kidney. In fetal and adult kidney, the expression was restricted to the epithelial cells with highest expression in the embryo and downregulation in adult. In smooth, skeletal and cardiac muscles, expression is also found.

**Localisation**

Polycystin-1 is located in the primary cilium, a single hair-like organelle projecting from the surface of most mammalian cells. It is also found in the plasma membrane at focal adhesions, desmosomes, and adherens junctions. The C-terminal tail of PC1 has been reported to be cleaved and migrate to the nucleus, regulating gene expression.

**Function**

In the kidney tubule, polycystin-1 was shown to serve as a mechanoreceptor that senses fluid flow in the tubular lumen, triggering Ca\(^{2+}\) influx through polycystin-2, a Ca\(^{2+}\) channel that interact with PC1 in the C-terminal tail, consequently affecting the intracellular calcium and cyclic AMP (cAMP) levels. It is also involved in cell-to-cell or cell-to-matrix interactions.

**Homology**

The characterized domains of polycystin-1 are regions highly conserved among species (from human to fish). A homology and also an interaction partner in the same signaling passway, polycystin-2, is located on 4q21.

**Mutations**

**Germinal**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. Up to 85% of ADPKD cases are caused by mutations in PKD1 gene. With the current mutation detection methods, definite pathogenic mutations (nonsense, truncation and canonical splice defects) are identified in approximately 60% of the cases. Large deletions/insertions can be found in ~4% of cases. Comprehensive analyses, using bioinformatics analysis tools can identify missense mutations that may account for the disease in an additional 22% to 37% of the ADPKD patients. There are no mutation hot spots for PKD1, which means mutations are usually private, with 70% of the mutations unique to a single family, and spread throughout the entire gene. Mutations on 5’ of the gene are associated with a more severe disease compared to those occurring in 3’ region. The ADPKD Mutation Database at Mayo Clinic (http://pkdb.mayo.edu/), the most complete one for...
ADPKD, documents 416 pathogenic mutations for PKD1 in a total of 616 families.

**Somatic**

The pathogenesis of ADPKD has been attributed to a two-hit mechanism, with somatic and germline mutations combining to inactivate one of the PKD genes, leading to loss of function, thus initiating the disease process. There are significantly less somatic PKD mutations listed in the ADPKD Mutation Database, only 9 for PKD1 (http://pkdb.mayo.edu/). Due to the limited availability of kidney cyst DNA and the complications associated with PKD1 genotyping, analyzing somatic mutations in ADPKD was proven to be difficult.

**Implicated in**

**Autosomal dominant polycystic kidney disease (ADPKD)**

**Disease**

ADPKD is a monogenic multi-systemic disorder characterized by age-dependent development and progressive enlargement of bilateral, multiple renal cysts, resulting in chronic renal failure typically in mid to late adulthood. The cysts are caused by abnormal proliferation of renal tubule epithelial cells as a result of inactivation of the PKD genes by mutations. Mutations in PKD1 gene account for 85% of the ADPKD cases and for the early-onset, more severe form. Those cysts will increase gradually in both size and number, leading to massive kidney enlargement and progressive decline in renal function. ADPKD has a prevalence of approximately 1 in 400 to 1 in 1000 live births in all races, affecting approximately 12.5 million individuals worldwide. Although ADPKD accounts for 4.4% of all patients requiring renal replacement therapy, it is characterized by very large phenotypic variability, ranging from presentation in-utero with enlarged, cystic kidneys to incidental diagnosis in the elderly with adequate renal function. Extra-renal manifestations include cysts in the liver, pancreas, seminal vesicles and arachnoid membranes. Intracranial aneurysm is about five times more common than in the general population and is associated with significant morbidity and mortality.

**Prognosis**

About 50% of patients with ADPKD will progress to end stage renal disease (ESRD) by the age of 60 years, with hemodialysis or kidney transplant being the only currently available treatment, though several potential drugs have been entered into clinical trials. Hypertension is present in about 50% of ADPKD patients age 20-30 years with clinically normal renal function; this is approximately one decade earlier than the onset of primary hypertension in the general population.

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Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. Kidney Int. 2009 Jul;76(2):149-68


This article should be referenced as such:

AMFR (autocrine motility factor receptor)
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Identity
Other names: GP78, RNF45
HGNC (Hugo): AMFR
Location: 16q12.2

DNA/RNA

Description
The AMFR gene spans 64081 bases on minus strand. The DNA of AMFR consists of 14 exons and the coding sequence starts in the first exon.

Transcription
The AMFR gene has two transcripts. One of these transcripts is 2249 bp long and is a processed transcript with no protein product. 3598 bp long second AMFR transcript is a protein coding transcript (accession number: NM_001144). The DNA has been cloned in 1999 (Shimizu et al., 1999).

AMFR gene genomic location at chromosome 16q12.2 (minus strand).

A. The alignment of AMFR mRNA to its genomic sequence. B. AMFR mRNA and its amino acid coding.
AMFR (autocrine motility factor receptor) Erzurumlu Y, Ballar P

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A schematic representation of the domain structure.

Protein

Description
AMFR belongs to the family of RING-Finger ubiquitin ligases. The complete protein contains 643 amino acids. The calculated molecular weight of AMFR is 73.0 kDa.

AMFR was originally isolated as a membrane glycoprotein from murine melanoma cells and was implicated in cell migration (Nabi and Raz, 1987). Subsequently, gp78/AMFR was identified as the tumor autocrine motility factor receptor mediating tumor invasion and metastasis (Nabi et al., 1990). A monoclonal antibody named 3F3A was generated against this protein and first sequence reported for human gp78/AMFR was in 1991 using this antibody (Watanabe et al., 1991). However, the protein product was only 321 amino acids (Watanabe et al., 1991). A sequence giving 643 amino acids protein product was cloned in 1999 (Shimizu et al., 1999).

gp78/AMFR has five to seven transmembrane domains according to different softwares like SACS MEMSAT and SOSUI. The protein has a long cytoplasmic tail composed of around 350 amino acids (Shimizu et al., 1999). Besides conveying E3 activity the multifunctional cytoplasmic tail is responsible for interaction with polyubiquitin, ubiquitin conjugating enzyme, p97/VCP and Ufd1. The RING finger domain of gp78/AMFR residing between amino acids 341 and 383 is a RING-H2 type domain containing two His residues in positions 4 and 5 (Fang et al., 2001). The Cue domain of gp78/AMFR residing between amino acids 456 and 497 is responsible for polyubiquitin binding and has been identified by having homologous sequences of yeast protein Cue1p (Ponting, 2000). The p97/VCP-interacting motif of gp78/AMFR consists of C-terminal amino acid residues between 614-643 and it is sufficient to bind to p97/VCP protein (Ballar et al., 2006). gp78/AMFR binds to its ubiquitin conjugating enzyme via a region called UBE2G2 binding region (G2BR) and this region is resides between amino acids 579 and 600 (Chen et al., 2006). Additionally, gp78/AMFR interacts directly with Ufd1 through residues 383-497 (Cao et al., 2007) and with INSIGs through its transmembrane domains (Song et al., 2005).

Expression
gp78/AMFR is relatively ubiquitously expressed in normal human cells, especially highly in liver, heart and lung. Northern blot analysis detected a 3.5-kb AMFR transcript in mouse heart, brain, lung, liver, skeletal muscle, kidney, and testis, but not in spleen (Shimizu et al., 1999). gp78/AMFR is overexpressed in certain malignant tumors and human cancers of the lung, gastrointestinal tract, breast, liver, thymus, and skin (Chiu et al., 2008; Sjöblom et al., 2006; Tsai et al., 2007; Joshi et al., 2010).

Localisation
Endoplasmic reticulum membrane, multi-pass transmembrane protein (Fang et al., 2001).

Function
In 2001, it has been reported that gp78/AMFR possesses ubiquitin ligase (E3) activity (Fang et al., 2001) and can ubiquitinate both itself and other proteins for proteasomal degradation. gp78/AMFR is a member of multiprotein complex functioning in endoplasmic reticulum associated degradation (ERAD). gp78/AMFR not only functions as an E3 during ERAD but also couples retrotranslocation and deglycosylation to ubiquitination (Ballar et al., 2006; Li et al., 2005).

Homology
Homologues have been found in various species like bovine, chimpanzee (99.8 % homology), chicken, zebra fish, rat, C. elegans and mouse. gp78/AMFR shares 94.7 % of homology with murine gp78/AMFR.

Mutations

Somatic
D605V mutation has been reported in breast cancer (Sjöblom et al., 2006). Several SNPs have been found in gp78/AMFR gene both at coding regions and at UTRs and introns. See SNP database at NCBI.

Implicated in

Sarcoma metastasis

Note
gp78/AMFR targets KAI1, a known metastasis
suppressor protein for ubiquitin mediated proteasomal degradation (Tsai et al., 2007). Thus gp78/AMFR has role in metastasis of human sarcoma. Furthermore, a human sarcoma tissue microarray study documents that tumors with low gp78 expression has higher levels of KAI1 and high gp78 level lower KAI1 expression in tumors (Tsai et al., 2007).

**Breast cancer**

**Note**

gp78/AMFR expression in gp78 transgenic mammary glands induces mammary gland hyperplasia, increases duct number and network density and shows down-regulation of KAI1 metastasis suppressor (Joshi et al., 2010). Additionally, gp78/AMFR has been identified as one of the most mutated genes in breast cancer (Sjöblom et al., 2006). Consistently, gp78/AMFR is overexpressed in human breast cancer and is negatively associated with patients’ clinical outcome (Jiang et al., 2006).

**Gastric carcinoma**

**Note**

gp78/AMFR expression may be associated with the progression and invasion of gastric carcinoma as well as the prognoses of the patients (Hirono et al., 1996). Furthermore, by using same 3F3A antibody it was reported that gp78/AMFR expression is associated with lymph node metastasis and peritoneal dissemination in gastric carcinoma (Taniguchi et al., 1998).

**Colorectal cancer**

**Note**

gp78/AMFR expression is correlated high incidence of recurrence of the patients with colorectal cancer (Nakamori et al., 1994).

**Melanoma**

**Note**

It was showed by using 3F3A antibody that gp78/AMFR protein expression in human melanoma cell lines correlates to their metastatic potential. While in thin tumors weak/heterogenous gp78/AMFR expression predominated, in thick tumors the strong gp78/AMFR expression profile was predominant (Tímár et al., 2002).

**Lung cancer**

**Note**

Using immunohistochemical staining the gp78/AMFR expression was showed to be associated with histologic type of tumor, mainly in adenocarcinoma (Kara et al., 2001).

**Hepatocellular carcinoma**

**Note**

The expression of gp78/AMFR significantly increased in hepatocellular carcinoma compared with pericarcinomatous liver tissues. Furthermore, there is a strong correlation between AMFR expression and invasion and metastasis of HCC (Wang et al., 2007).

**Bladder carcinoma**

**Note**

While in normal urothelium gp78/AMFR is not expressed, its expression is increased in bladder carcinoma specimens (Otto et al., 1994).

**Cardiovascular diseases and hypercholesterolemia**

**Note**

Accumulation of sterols in ER membranes triggers the binding of HMG CoA reductase, the rate limiting enzyme of cholesterol biosynthesis, to the Insig1-gp78/AMFR complex which is essential for the ubiquitination and proteasomal degradation of HMGCoA-reductase (Goldstein et al., 2006; Jo and DeBose-Boyd, 2010). gp78/AMFR is also the E3 ligase of apolipoprotein B100, the protein component of atherogenic lipoproteins, overproduction of which is a common feature of human dyslipidemia (Liang et al., 2003).

**Cystic fibrosis**

**Note**

gp78/AMFR degrades mutant cystic fibrosis transmembrane conductance regulator (CFTRΔF508) associated with cystic fibrosis (Ballar et al., 2010; Morito et al., 2008).

**Metabolism and disposition of drugs**

**Note**

gp78/AMFR participates in proteasomal degradation of CYP3A4, a dominant human liver cytochrome P450 enzyme functioning in the metabolism and disposition of drugs and responsible for many adverse drug-drug interactions (Kim et al., 2010; Pabarcus et al., 2009).

**Chronic obstructive pulmonary disease**

**Note**

gp78/AMFR expression is increased with the severity of emphysema (Min et al., 2011).

**Neurodegenerative diseases**

**Note**

gp78/AMFR may play a protective role against mutant huntingtin toxicity. Mutant huntingtin hinders polyubiquitin binding to the cue domain of gp78/AMFR and causes aggregation of ligase (Yang et al., 2010). gp78/AMFR also enhances ubiquitination, degradation, suppression of aggregation of mutant SOD1 associated with amyotrophic lateral sclerosis (ALS), and mutant ataxin-3 associated with Machado-Joseph disease. Furthermore, in spinal cords of ALS mice, gp78/AMFR expression is significantly up-regulated (Ying et al., 2009).
**Alpha-1-antitrypsin deficiency**

**Note**
gp78/AMFR targets mutant ATZ (Z-variant alpha-1-antitrypsin) associated with alpha-1-antitrypsin deficiency for the proteasomal degradation and increases its solubility (Shen et al., 2006).

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ASH2L (ash2 (absent, small, or homeotic)-like (Drosophila))

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Identity
Other names: ASH2, ASH2L1, ASH2L2, Bre2
HGNC (Hugo): ASH2L
Location: 8p11.23

DNA/RNA
Description
16 exons spanning over 34218 base pairs.

Transcription
mRNA is 2368 base pairs long.

Protein
Description
There are three known isoforms of ASH2L (Wang et al., 2001). Isoform 1 is considered the canonical sequence and consists of 628 amino acids (Wang et al., 2001). Isoform 2 is missing amino acids 1-94 and 541-573 from isoform 1 (Wang et al., 2001). Isoform 3 is missing the amino acids 1-94 from isoform 1 (figure 2) (Wang et al., 2001). There are four identified domains within ASH2L which include a N-terminus containing a PHD finger and a winged helix motif (WH) and the C-terminus containing a SPRY domain and the Sdc1 DPY-30 Interacting domain (SDI) (figure 2) (Chen et al., 2011; Roguev et al., 2001; Sarvan et al., 2011; South et al., 2010; Wang et al., 2001). The largest of the three identified domains within ASH2L is the SPRY domain, which is also conserved from yeast to humans. SPRY domains were originally named after the SPla kinase and the RYanodine receptor proteins in which it was first identified (Rhodes et al., 2005). Crystal structures of SPRY domain containing proteins show primarily a beta-sandwich structure with extending loops (Filippakopoulos et al., 2010; Kuang et al., 2009; Simonet et al., 2007; Woo et al., 2006b). The SPRY domain is thought to be a specific protein-protein interaction domain.

Figure 1. Map of chromosome 8 with region 8p11.2 highlighted as the location of the gene ASH2L.
with specific partners, but instead of recognizing a particular motif or interaction domain the SPRY domain binds to interaction partners using non-conserved binding loops (Filippakopoulos et al., 2010; Woo et al., 2006a; Woo et al., 2006b). Recent work has shown that the C-terminus of ASH2L that contains the SPRY domain and the SDI domain are able to interact with the other MLL complex member RBBP5 in vitro (Avdic et al., 2011).

ASH2L also contains a putative Plant Homeo Domain (PHD) finger in its N-terminus (Wang et al., 2001). The structure of PHD fingers shows that conserved cysteine and histidine residues bind to Zn$^{2+}$ ions (Champagne et al., 2008; Champagne and Kutateladze, 2009; van Ingen et al., 2008). There is no known function attributed to the PHD finger in ASH2L, though in conjunction with the winged helix motif it may be necessary for DNA binding.

The N-terminal winged helix (WH) motif was recently discovered when the crystal structure of the N-terminus of ASH2L was solved (Chen et al., 2011; Sarvan et al., 2011). Using in vitro DNA binding analyses as well as chromatin immunoprecipitation, it was determined that ASH2L can bind DNA at the HS2 promoter region and the beta-globin locus as well as non-specific DNA sequence (Chen et al., 2011; Sarvan et al., 2011). The last identifiable domain within ASH2L is the SDI domain. There is no structural information on the SDI domain but the functional importance was determined biochemically. The function of the SDI domain was determined using in vitro binding experiments. ASH2L was shown to directly interact with DPY-30 without any additional MLL or Set1 complex components (South et al., 2010). The function of the SDI domain is conserved from yeast to humans because the yeast ASH2L homolog Bre2 was also shown to interact with the DPY-30 homolog Sdc1 (South et al., 2010). There are conserved hydrophobic residues in both the SDI domain of ASH2L and the Dpy-30 domain of DPY-30 that are important for binding, which suggests that the interaction between the SDI domain of ASH2L and the DPY-30 domain of DPY-30 is through hydrophobic interactions (South et al., 2010).

Expression
Northern blot analysis from multiple tissues revealed that ASH2L expression is expressed in 14 different tissue types with the highest expression in fetal liver and testes (Lüscher-Firzlaff et al., 2008). ASH2L transcripts were also found to be expressed higher in various Leukemia cell lines, such as K562, Hel, and Dami cells (Lüscher-Firzlaff et al., 2008).

Localisation
Nucleus.

Function
Biochemical data has shown that ASH2L is found in a methyltransferase core complex composed of ASH2L, RBBP5, DPY30, WDR5, and the catalytic SET domain containing protein. This core complex is highly conserved and similar to the budding yeast Set1 complex that consists of Set1 (MLL/SET1), Bre2 (ASH2L), Swd1 (RBBP5), Swd3 (WDR5), Swd2 (WDR82), Sdc1 (DPY-30), Spp1 (CFP1/CGBP). ASH2L is also known to associate with numerous additional factors. Many of these additional factors are thought to associate with ASH2L and the H3K4 methyltransferase complexes to target the complex to specific sites within the genome (Cho et al., 2007; Dou et al., 2006; Hughes et al., 2004; Steward et al., 2006; Stoller et al., 2010). Knock-down of ASH2L using siRNA globally decreases H3K4 trimethylation (Dou et al., 2006; Steward et al., 2006). ASH2L and H3K4 methylation both appear to play a key role in oncogenesis (Hess, 2006). ASH2L is found to be over abundant in many cancer cell lines and knock-down of ASH2L by siRNA can prevent tumorigenesis (Lüscher-Firzlaff et al., 2008). Recent work has suggested that ASH2L in combination with WDR5 and RBBP5 exhibits H3K4 methyltransferase activity (Cao et al., 2011).
ASH2L (ash2 (absent, small, or homeotic)-like (Drosophila))

2010; Patel et al., 2009; Patel et al., 2011). In addition, this catalytic activity is not dependent on the SET domain containing proteins such as MLL1 (Cao et al., 2010; Patel et al., 2009; Patel et al., 2011). Alternative to ASH2L’s function in H3K4 methylation ASH2L may also be playing a role in endosomal trafficking (Xu et al., 2009). ASH2L, DPY-30 and WDR5 were originally implicated in endosomal trafficking when siRNA knock-down of these genes increased the amount of internalized CD8-CIMPR and overexpression increased the amount of cells displaying a altered CIMPR distribution (Xu et al., 2009).

**Homology**

ASH2L has homologs in eukaryotes from yeast to humans.

**Implicated in**

**Various cancers**

**Note**

ASH2L mRNA expression does not appear to be misregulated in human cancer cell or primary cell lines. However, expression of ASH2L protein is increased in many cancer cell lines as well as tumor samples (Lüscher-Firzlaff et al., 2008). There was detectable increased staining in the nucleus of ASH2L protein in a wide array of tumors including squamous cell carcinoma of the larynx and the cervix, melanomas, adenocarcinoma of the pancreas, and acinar and ductal breast cancers (Lüscher-Firzlaff et al., 2008). ASH2L protein appears to be more stable in cancer cell lines compared to the normal cell line counterparts and knockdown of ASH2L can prevent tumorigenesis suggesting a role in tumor cell proliferation (Lüscher-Firzlaff et al., 2008).

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This article should be referenced as such:
South PF, Briggs SD. ASH2L (ash2 (absent, small, or homeotic)-like (Drosophila)). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(1):30-33.
CD109 (CD109 molecule)

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Identity

Other names: CPAMD7, DKFZp762L1111, FLJ38569, FLJ41966, RP11-525G3.1
HGNC (Hugo): CD109
Location: 6q13
Note
CD109 is a glycosylphosphatidylinositol (GPI)-anchored cell-surface glycoprotein and is a member of the alpha-2-macroglobulin/C3,C4,C5 family of thioester-containing proteins.

DNA/RNA

Description
CD109 is a gene of 132.53 kb comprising 33 exons and 32 introns. The 5’ part of exon 1 and the 3’ part of exon 33 are non-coding.

Transcription
Three splice variants are known. The length of the longest variant is 9464 bp (CDS: 426-4763). mRNA is mainly expressed in skin and testis.

Pseudogene
Not known.

Protein

Description
CD109 is a GPI-anchored cell-surface glycoprotein and is a member of the alpha-2-macroglobulin/C3,C4,C5 family of thioester-containing proteins (Sutherland et al., 1991; Haregewoin et al., 1994; Smith et al., 1995; Lin et al., 2002). The CD109 protein was first identified as a cell-surface antigen detected by a monoclonal antibody raised against the primitive lymphoid/myeloid cell line KG1a (Sutherland et al., 1991). It was also shown that CD109 carries the biallelic platelet-specific alloantigen Gov (Kelton et al., 1990; Smith et al., 1995).

Expression
CD109 is expressed on a subset of fetal and adult CD34+ bone marrow mononuclear cells, mesenchymal stem cell subsets, phytohemagglutinin (PHA)-activated T lymphoblasts, thrombin-activated platelets, leukemic megakaryoblasts, endothelial cells, and some human tumor cell lines, but not on fresh peripheral leukocytes and normal bone marrow leukocytes (Kelton et al., 1990; Murray et al., 1999; Giesert et al., 2003).

Exon-intron structure of CD109 gene. The vertical bars correspond to exons.
In normal human tissues other than hematopoietic cells, CD109 is expressed in limited cells including the myoepithelial cells of the mammary, lacrimal, salivary and bronchial glands and the basal cells of the prostate and the bronchial epithelia (Hashimoto et al., 2004; Zhang et al., 2005; Sato et al., 2007; Hasegawa et al., 2007; Hasegawa et al., 2008).

Recently, it has been reported that CD109 is highly expressed in several types of human cancer tissues, in particular squamous cell carcinomas (Hashimoto et al., 2004; Zhang et al., 2005; Sato et al., 2007; Hasegawa et al., 2007; Hasegawa et al., 2008; Järvinen et al., 2008; Hagiwara et al., 2008; Ohshima et al., 2010; Hagikura et al., 2010).

**Representative of the CD109 protein with localization of recognized domains.** CD109 protein is a GPI-anchored protein having signal peptide, Gov antigen, thioester region, and furinase cleavage site.

**Localisation**
Plasma membrane.

**Function**
CD109 negatively regulates TGF-beta signaling in keratinocytes by directly modulating TGF-beta receptor activity in vitro (Finnson et al., 2006).

**Homology**

**Mutations**
A Tyr703Ser polymorphism of CD109 is associated with Gova and Govb alloantigenic determination (Schuh et al., 2002).

**Implicated in**
**Various cancer**
Note: CD109 is upregulated in squamous cell carcinomas (SCCs) of lung, esophagus, uterus and oral cavity, malignant melanoma of skin, and urothelial carcinoma of the urinary bladder (Hashimoto et al., 2004; Zhang et al., 2005; Sato et al., 2007; Hasegawa et al., 2007; Hasegawa et al., 2008; Järvinen et al., 2008; Hagiwara et al., 2008; Ohshima et al., 2010; Hagikura et al., 2010).

**Prognosis**
The CD109 expression is significantly higher in well-differentiated SCCs of the oral cavity and in low-grade urothelial carcinomas of the urinary bladder than in moderately- or poorly-differentiated SCCs and in high-grade urothelial carcinomas, respectively (Hagiwara et al., 2008; Hagikura et al., 2010).

**Alloimmune thrombocytopenic syndromes**
Note: Refractoriness to platelet transfusion, post-transfusion purpura, and neonatal alloimmune thrombocytopenia (Smith et al., 1995).

**Disease**
These diseases are included in alloimmune thrombocytopenic syndromes. Gova/b platelet alloantigen, which reside in the CD109 protein, are the cause of these 3 diseases.

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CLDN7 (claudin 7)

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Identity

Other names: CEPTRL2, CLDN-7, CPETRL2, Hs.84359, claudin-1
HGNC (Hugo): CLDN7
Location: 17p13.1

DNA/RNA

Description

2573 base-pairs, starts at 7163223 and ends at 7165795 bp from pter with minus strand orientation.

Transcription

This gene contains 4 exons and 3 introns. The transcription produces 3 alternatively spliced mRNA variants:
- variant 1 (NM_001307.5) encodes the longer isoform;
- variant 2 (NM_001185022.1) has an alternate 5’ UTR sequence;
- variant 3 (NM_001185023.1) lacks an exon in the 3’ CDS.

Pseudogene

The sequence named LOC100129851 claudin 7 pseudogene is a pseudogene of Claudin 7 located at Xp11.4.

Figure 1. Schematic representation of the claudin 7 chromosome location, transcript variants and protein isoforms.
Figure 2. Schematic representation of the claudin 7 protein showing the extracellular loops (EL1 and EL2), the transmembrane domains (TM1 to TM4) and its amino- and carboxy-terminal tails extending into the cytoplasm.

Protein

Description
The transcription of this gene gives 3 alternatively spliced mRNA variants that encode 2 different protein isoforms (variants 1 and 2 encode the same isoform):

- Isoform 1 is the canonical sequence with 211 amino acids and it weighs 22418 Da.
  MANSGLQLLGFSALLGWVGLVACTAIPQWQM
  SSYAGDNIITAQAQMGLWMDCVTQSTGMMSCKMYDMVLALSAALQTARALMVVLGFLAMFAVTMGKCTRCGDDKVKKARIAMGGGIIFFVAGLSALSALPSLLAGQGLP

- Isoform 2 contains 145 amino acids, with a shorter C-terminus, lacking amino acids 159 to 211 in comparison to isoform 1. It weighs 15156 Da.
  MANSGLQLLGFSALLGWVGLVACTAIPQWQM
  SSYAGDNIITAQAQMGLWMDCVTQSTGMMSCKMYDMVLALSAALQTARALMVVLGFLAMF

CLDN-7 is an integral membrane protein with four hydrophobic transmembrane domains and two extracellular loops which appear to be implicated in tight junction formation and with their amino- and carboxy-terminal tails extending into the cytoplasm (figure 2).

Localisation
The protein is localized in the cell membrane as a constituent of tight junctions.

Function
CLDN-7 encodes a member of the claudin family of integral transmembrane proteins that are components of tight junction strands. Claudins regulate the paracellular transport being essential in maintaining a functional epithelial barrier, and also play critical roles in maintaining cell polarity and signal transductions. Studies have shown that altered levels of the different claudins may be related to invasion and progression of carcinoma cells in several primary neoplasms.
**Mutations**

**Somatic**
In the catalogue of Somatic Mutations in Cancer (Sanger) reports only a heterozygous silent substitution (339G/T; V113V) in ovarian serous cystadenocarcinoma is present.

**Polymorphisms**
According to the Ensembl database 12 variations could be present in the transcripts (variants 1/2) of CLDN-7:
- Position 963/396 of mRNA a synonymous G/A polymorphism at position 61 of the amino acid sequence.
- Position 979/412 of mRNA a non-synonymous G/T polymorphism at position 77 of the amino acid sequence. Switching an Ala for an Asp residue. SIFT deleterious.
- Position 1299/732 of mRNA a non-synonymous C/T polymorphism at position 397 of the amino acid sequence. Switching an Ala for an Thr residue. SIFT tolerated.
- Position 1425/858 of mRNA a non-synonymous C/A polymorphism at position 523 of the amino acid sequence. Switching an Val for an Phe residue. SIFT deleterious.
- Position 1492/925 of mRNA a non-synonymous A/G polymorphism at position 590 of the amino acid sequence. Switching an Val for an Ala residue. SIFT tolerated.
- Position 1508/941 of mRNA a synonymous A/C polymorphism at position 606 of the amino acid sequence.

**Implicated in**

**Colorectal carcinoma**

**Prognosis**
Oshima et al. (2008) studied surgical specimens of cancer tissue and adjacent normal mucosa from patients with untreated colorectal carcinoma. The reduced expression of Claudin 7 correlated with venous invasion and liver metastasis, thus suggesting that the reduced expression of the Claudin 7 gene may be a useful predictor of liver metastasis in patients with colorectal cancer.

**Oncogenesis**
Bornholdt et al. (2011) observed that Claudin 7 gene was downregulated both at mRNA and protein levels in biopsies of colorectal tissue from mild/moderate dysplasia, severe dysplasia and carcinomas when comparing to biopsies from healthy individuals. These results suggest that Claudin 7 downregulation is an early event in colorectal carcinogenesis, probably contributing to the compromised epithelial barrier in adenomas.

**Esophageal cancer**

**Prognosis**
Usami et al. (2006) found that reduced expression of Claudin 7 at the invasive front of the esophageal cancer was significantly associated with the depth of invasion, lymphatic vessel invasion, and lymph node metastasis. Reduced Claudin 7 expression was also found in the metastatic lymph nodes. They suggest that the reduced expression of Claudin 7 at the invasive front of esophageal squamous cell carcinoma may lead to tumor progression and subsequent metastatic events.

**Epithelial ovarian carcinoma**

**Prognosis**
Kim et al. (2011) described the up-regulation of Claudin 7 transcripts in patients with epithelial ovarian carcinoma (EOCs) in comparison to normal ovarian tissues. The protein Claudin 7 was observed in the majority of the EOCs but not in normal ovarian tissues. High Claudin 7 expression in primary tumor correlated with shorter progression-free survival and poor sensitivity to platinum-based chemotherapy. Claudin 7 inhibition in 2774 and HeyA8 human ovarian cancer cells by siRNA significantly enhanced the sensitivity of these cells to cisplatin treatment. These findings suggest Claudin 7 expression as an independent prognostic factor for progression-free survival in EOCs patients and that it may play a role in regulating response to platinum-based chemotherapy in the treatment of these tumors.

**Oncogenesis**
Tassi et al. (2008) found Claudin 7 transcript and protein significantly overexpressed in both primary and metastatic EOCs compared to normal ovaries. Moreover, a strong immunoreactivity for Claudin 7 was detected in EOC cells present in ascites fluids, whereas ascites-derived inflammatory cells, histiocytes, and reactive mesothelial cells were negative. Claudin 7 is significantly overexpressed in all main histologic types of EOC and in single neoplastic cells disseminated in peritoneal cavity and pleural effusions, suggesting its potential role as novel diagnostic marker in ovarian cancer.

**Prostatic carcinoma**

**Prognosis**
Sheehan et al. (2007) reported the pattern of claudin expression in prostatic adenocarcinomas (PACs) and found that the decreased expression of Claudin 7 was correlated with high tumor grade.

**Oral squamous cell carcinoma**

**Prognosis**
Lourenço et al. (2010) showed that Claudin 7 expression was mostly negative or weakly expressed in oral squamous cell carcinoma samples. According their
results, the loss of Claudin 7 expression was associated with tumor size, clinical stage and a worse disease-free survival.

**Uterine cervical neoplasia**

Oncogenesis

Lee et al. (2005) showed that Claudin 7 expressions is associated with the progression of uterine cervical neoplasia since its expression was undetectable in normal cervical squamous epithelium and gradually increase in accordance with the progression from LSIL (low-grade squamous intraepithelial lesion) to HSIL (high-grade squamous intraepithelial lesion) and ISCC (invasive squamous cell carcinoma). Claudin 7 were detected in all cases of ISCC. These authors suggested that Claudin 7 may play a significant role in tumor progression of cervical neoplasia.

**Breast cancer**

Prognosis

Kominsky et al. (2003) conducted RT-PCR and Western Blot analysis and reported that Claudin 7 expression is lower in breast invasive ductal carcinomas (IDC) than in normal breast epithelium. They also reported immunohistochemical (IHC) analysis of ductal carcinoma in situ (DCIS) and IDC and showed that the loss of Claudin 7 expression is correlated with histological grade, occurring predominantly in high-grade lesions. According to their results, Claudin 7 expression was lost in the vast majority of in situ lobular carcinoma cases. In summary, this study provides insight into the potential role of Claudin 7 in the breast tumor progression and in the ability of breast cancer cells to disseminate.

Sauer et al. (2005) evaluated the immunocytochemical expression of Claudin 7 in fine needle aspirates of breast carcinomas and found that reduced Claudin 7 expression was correlated with grading, locoregional and distant metastases, nodal involvement and cellular cohesion in invasive carcinomas.

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This article should be referenced as such:

CSE1L (CSE1 chromosome segregation 1-like (yeast))

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Identity

Other names: CAS, CSE1, MGC117283, MGC130036, MGC130037, XPO2
HGNC (Hugo): CSE1L
Location: 20q13.13

DNA/RNA

Note
CDS: 2915 bp.

Description
The CSE1L gene consists of 25 exons (Brinkmann et al., 1999). The CSE1L gene is high-frequency amplified in various cancer types (Tai et al., 2010a).

Transcription
Multiple transcript variants encoding several different isoforms in a tissue-specific manner have been described for CSE1L gene (Brinkmann et al., 1999).

Protein

Note
CSE1L is a multiple function protein. The protein is involved in nuclear protein transport (Lindsay et al., 2002), cell apoptosis (Brinkmann et al., 1996), microtubule assembly (Scherf et al., 1996), cell secretion (Tsao et al., 2009), and cancer cell invasion (Liao et al., 2008; Tung et al., 2009; Stella Tsai et al., 2010) etc.

Description
CSE1L gene encodes a 971-amino acid protein with an approximately 100-kDa molecular mass (Brinkmann et al., 1995).

Expression
CSE1L is expressed in various tissues, and particularly it is highly expressed in most cancer (Tai et al., 2010a; Brinkmann et al., 1995). The expression level CSE1L is positively correlated with high tumor stage, high tumor grade, and worse outcomes of cancer patients (Tai et al., 2010a). The increased expression of CSE1L in cancer is mainly due to the amplification of the copy number of the CSE1L gene in cancer tissue (Tai et al., 2010a). The association of CSE1L with microtubules is related with pseudopodia extension and the migration of cancer cells (Tai et al., 2010b). CSE1L is also a secretory protein, and it is present in the sera of cancer patients. The secretion of CSE1L is related with the invasion of cancer cells (Tung et al., 2009; Stella Tsai et al., 2010).

Localisation
Nucleus, cytoplasm.

Function
A cell apoptosis susceptibility protein; a microtubule-associated protein; an export receptor of importin-a in the nuclear protein import cycle; involved in tumor cell invasion and metastasis in cancer progression.

Homology
The yeast chromosome segregation gene CSE1.
**Implicated in**

**Breast cancer**

**Prognosis**
Benign breast lesions show weak cytoplasmatic CSE1L staining, while in ductal and lobular in situ carcinomas, 70%-90% of breast tumor cells showed heavy CSE1L staining cytoplasm. Also, in invasive ductal and lobular carcinomas, 70-90% of the tumor cells showed heavy CSE1L staining pattern predominantly in nuclei (Behrens et al., 2001).

**Ovarian carcinoma**

**Prognosis**
In serous ovarian carcinoma, moderate to strong immunostaining of CSE1L was observed in 34 of 41 cases (83%) of serous carcinomas, and CSE1L immunoreactivity was positively related to the frequency of apoptotic bodies (p = 0.0170), the tumor grade (p = 0.0107), and adverse outcomes (p = 0.0035). CSE1L protein reactivity was present in 100% of 69 ovarian carcinomas, and a significant reciprocal correlation was observed between high levels of CSE1L and the histological type, FIGO (International Federation of Obstetrics and Gynecology) stage III and grade 3, residual tumors of > 2 cm, and 20q13.2 (ZNF217 gene) amplification (> four copies in > 20% cells). A tissue array study composed of 244 serous ovarian tumors of different grades (0-3) and stages (I-IV) showed a higher expression of CSE1L in poorly compared to highly differentiated invasive ovarian tumors (Brustmann, 2004; Peiro et al., 2002; Ouellet et al., 2006).

**Melanomas**

**Prognosis**
Analysis of the expression of CSE1L in 27 control benign and 55 malignant melanocytic lesions (including 32 primary and 23 metastatic lesions), and the results showed that only 13 of the 27 benign melanocytic lesions stained positive for CSE1L. However, 5 of 7 lentigo maligna melanomas, 11 of 12 superficial spreading melanomas, and all acroplentiginous (n = 7) and nodular (n = 6) melanomas showed medium to high intensity immunoreactivity for CSE1L staining. All metastatic melanomas (n = 23) showed strong CSE1L staining. Also, CSE1L detection in clinical stages according to the International Union Against Cancer (UICC) showed an increase from 43% ± 34% CSE1L-positive cells in stage I, to 53% ± 26% in stage II, 68% ± 24% in stage III, and 72% ± 24% in stage IV (Boni et al., 1999).

**Lymphomas**

**Prognosis**
In normal lymphoid tissue and malignant lymphomas, low-grade non-Hodgkin's lymphoma revealed weak CSE1L staining, with 10% to 60% of all cells positive. In contrast, highly malignant non-Hodgkin's lymphoma and malignant cells of Hodgkin's disease displayed very strong CSE1L positivity, with staining of up to 80% of atypical cells (Wellmann et al., 1997).

**Endometrial carcinomas**

**Prognosis**
An analysis of 89 endometrial carcinomas and 56 samples of non-neoplastic adjacent endometrium showed that CSE1L was expressed in 93% of endometrial carcinomas neoplastic tissues, while lower levels of CSE1L expression were observed in the adjacent endometrium compared to the carcinomas (p = 0.003). Also, CSE1L expression was higher in grade 3 tumors (p = 0.002) (Peiró et al., 2001).

**Hepatocellular carcinomas**

**Prognosis**
The expression of CSE1L was not detected in normal hepatocytes, while strong CSE1L expression was detected in hepatocellular carcinoma. Study also showed that the immunohistochemical staining intensity score of CSE1L was significantly higher in human hepatocellular carcinoma than in non-tumor tissue (p < 0.05) (Wellmann et al., 2001; Shiraki et al., 2006).

**Lung cancer**

**Prognosis**
The immunophenotypic profiling of non-small cell lung cancer progression using tissue microarray with 59 tissue samples, including 33 primary tumors without distant metastasis and 26 non-small cell lung cancer with brain metastases and showed that elevated expression of CSE1L was significantly associated with the metastatic potential of non-small cell lung cancer (Papay et al., 2007).

**Gliomas**

**Prognosis**
The results of array-based comparative genomic hybridization showed that 57.1% of the glioblastoma multiforme cases had high-frequency amplification of the CSE1L gene. Idbaih et al. investigated a series of 16 low-grade gliomas and their subsequent progression to higher-grade malignancies using a one-megabase bacterial artificial chromosome (BAC)-based array comparative genomic hybridization technique, and reported that the CSE1L gene was associated with the progression of gliomas (Hui et al., 2001; Idbaih et al., 2008).

**Colorectal carcinoma**

**Prognosis**
The expression of CSE1L was also reported to be higher in the primary and metastatic human colorectal carcinoma compared to the normal colon mucosa (p < 0.0001). Also, the concentration of CSE1L in serum is positively correlated with the stage of colorectal cancer (Stella Tsai et al., 2010; Seiden-Long et al., 2006).
References


This article should be referenced as such:

DDX5 (DEAD (Asp-Glu-Ala-Asp) box polypeptide 5)

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Identity

Other names: DKFZp434E109, DKFZp686J01190, G17P1, HLR1, HUMP68, p68
HGNC (Hugo): DDX5
Location: 17q23.3

Note
DDX5/p68 RNA helicase is a member of DEAD box RNA helicases. As an example of a cellular RNA helicase, the ATPase and the RNA unwinding activities of p68 RNA helicase were documented with the protein that was purified from human 293 cells (Iggo and Lane, 1989; Ford et al., 1988; Hirling et al., 1989) and recombinant protein expressed in E. coli (Huang and Liu, 2002). The gene is expressed in all dividing cells of different vertebrates (Lane and Hoeffler, 1980; Stevenson et al., 1998). p68 RNA helicase is involved in multiple cellular processes, including gene transcription (Endoh et al., 1999; Rossow and Janknecht, 2003), pre-mRNA processing (Liu, 2002; Yang et al., 2006), pre-rRNA processing (Jalal et al., 2007), pre-miRNA processing (Fukuda et al., 2007), DNA methylation and de-methylation (Jost et al., 1999), and chromatin remodeling (Carter et al., 2010). A number of different post-translational modifications of p68 are reported, including phosphorylations, sumoylation, and ubiquitylation (Causevic et al., 2001; Yang et al., 2005; Jacobs et al., 2007).

DNA/RNA

Note
DDX5/p68 RNA helicase is expressed in dividing cells of different vertebrates. Transcription of p68 RNA helicase gene generates a single mRNA precursor with 13 exons and 12 introns. Alternative splicing produces two mRNA transcripts, 2.3 kb and 4.4 kb (Rössler et al., 2000). The 2.3 kb mRNA transcript codes full length p68, while no translational product from the 4.4 kb mRNA transcript is detected in cellular and tissue extracts (Rössler et al., 2000).

Diagram of pre-mRNA of p68 RNA helicase. The red bars are exons and the blue thin lines are introns.
**Protein**

**Description**
Size of p68: 614 amino acids, 69 kDa.

**Expression**
Expressed in almost all tissue types. Its expression is increased in cancer cells.

**Localisation**
Dominately localized in the cell nucleus. It is also found in the cytoplasm in various physiological conditions. p68 is a nucleocytoplasm shuttling protein (Wang et al., 2009).

**Function**

**Pre-mRNA splicing.** The protein was demonstrated to associate with spliceosome by mass-spectroscopy and an RNA-protein crosslinking analyses (Hartmuth et al., 2002; Liu et al., 1997; Neubauer et al., 1998). p68 is functionally involved in assembly of the spliceosome by mediating the U1 snRNP and the 5'ss interaction (Liu, 2002). p68 RNA helicase is also shown to regulate the splice site selection in the alternative splicing of several growth related genes, such as c-H-ras and tau (Kar et al., 2011; Guil et al., 2003).

**Transcriptional regulation.** The protein is shown to involve in transcriptional regulation by different mechanism of actions dependent on each individual regulated gene and biological processes (Stevenson et al., 1998; Endoh et al., 1999; Yang et al., 2005; Kahlina et al., 2004; Wei and Hu, 2001; Warner et al., 2004). p68 may regulate gene transcription by direct interaction with transcription factors or activators, such as p53, ERAlpha (Endoh et al., 1999; Bates et al., 2005), or by mediating chromatin remodeling, such as modulating chromatin remodeling complex (Carter et al., 2010).

**Epithelial-Mesenchymal-Transition (EMT).** p68 becomes phosphorylated at Y593 upon growth factor stimulation by c-Abl. The tyrosine phosphorylation of p68 mediates growth factor stimulated Epithelial-Mesenchymal-Transition (EMT) (Yang et al., 2006).

**Other functions.** (1) p68 RNA helicase is shown to unwind the human let-7 microRNA precursor duplex. The protein is required for let-7-directed silencing of gene expression (Salzman et al., 2007). p68 is an indispensible part of Drosha complex. Its activity is required for primary miRNA and rRNA processing (Fukuda et al., 2007). (2) It is also demonstrated that the RNA helicases p68/p72 and the noncoding RNA SRA are coregulators of MyoD and skeletal muscle differentiation (Caretti et al., 2006). (3) Phosphorylation of p68 at Thr residues mediates cell apoptosis (Yang et al., 2007).

**Homology**
Yeast DBP2.

**Mutations**

**Note**
Very few mutations of p68 gene were reported. A recent study shows that a S480A mutation in hepatic stellate cells is associated with hepatic fibrosis (Guo et al., 2010).

**Implicated in**

**Colon cancer**

**Note**
p68 expression is significantly increased in colon cancer (Shin et al., 2007). Phosphorylation of p68 at Tyr correlation with colon cancer metastasis (Yang et al., 2006; Yang et al., 2005).
Prognosis

Phosphorylation of p68 at tyrosine can be used as a diagnosis/prognosis marker for cancer.

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This article should be referenced as such:

t(13;19)(q14;p13)

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Clinics and pathology

Disease
B cell acute lymphoblastic leukemia (B-ALL)

Note
An apparently identical t(13;19)(q14;p13) has been described in 3 cases of chronic lymphocytic leukemia (CLL) (Finn et al., 1998; Merup et al., 1998; Brown et al., 1993).

Epidemiology
Only one case to date of ALL with this translocation, a 19-year-old female patient with pre-B-ALL; she achieved complete remission and (CR) was in continuing CR 10 months later, at last follow up (Barber et al., 2007).

Genes involved and proteins

Note
The translocation involves TCF3 and an unknown partner.

TCF3

Location
19p13.3

Protein
The E2A gene encodes two distinct basic helix-loop-helix transcription factors, E12 (ITF1) and E47 (TCF3) through alternative splicing. It forms homodimers and heterodimers with other basic helix-loop-helix transcription factors. Ubiquitously expressed during development. Role in cell growth, cell commitment, and differentiation. Role in epithelial mesenchymal transition (review in Slattery et al., 2008).

References


Barber KE, Harrison CJ, Broadfield ZJ, Stewart AR, Wright SL, Martineau M, Streford JC, Moorman AV. Molecular cytogenetic characterization of TCF3 (E2A)/19p13.3 rearrangements in B-cell precursor acute lymphoblastic leukaemia. Genes Chromosomes Cancer. 2007 May;46(5):478-86


This article should be referenced as such:

t(17;17)(q21;q24), del(17)(q21q24)

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Clinics and pathology

Disease
Acute myeloid leukaemia, M3 subtype (M3-AML)

Epidemiology
Only one case to date, a 66-year-old male patient (Catalano et al., 2007).

Cytology
Auer rods and fagot cells were absent.

Evolution
Complete remission was obtained with ATRA, and the patient remains healthy 2 years after the diagnosis.

Cytogenetics

Cytogenetics morphological
Cryptic deletion, FISH studies are needed to uncover the rearrangement.

Genes involved and proteins

RARA
Location
17q21.1
Protein
Contains Zn fingers and a ligand binding region. Receptor for retinoic acid. Forms heterodimers with RXR. At the DNA level, binds to retinoic acid response elements (RARE). Ligand-dependent transcription factor specifically involved in hematopoietic cells differentiation and maturation.

PRKAR1A
Location
17q24.2
Protein
Contains two tandem cAMP-binding domains. Forms heterotetramers with PRKACA (protein kinase, cAMP-dependent, catalytic, alpha), also called PKA. Interacts with RARA, and regulates RARA transcriptional activity.

Result of the chromosomal anomaly

Hybrid gene
Description
5’ PRKAR1A - 3’ RARA. When we look closely to the DNA sequences at the fusion breakpoints, they correspond to the very end of exon 1 in PRKAR1A (AGAGGTGAGAG) and the very beginning of exon 2 in RARA (ATTGACACCCAGACAGCAGT, see sequences in Ensembl), although they were described in exon 2 and exon 3 in the first and only report of this rearrangement (Catalano et al., 2007).

Fusion protein
See figure 5’ PRKAR1A - 3’ RARA.
**Description**

The fusion protein contains the dimerization domain from PRKAR1A fused to the Zn fingers and ligand binding regions from RARA.

**References**


Catalano A, Dawson MA, Somana K, Opat S, Schwarer A, Campbell LJ, Illand H. The PRKAR1A gene is fused to RARA in a new variant acute promyelocytic leukemia. Blood. 2007 Dec 1;110(12):4073-6

This article should be referenced as such:

MicroRNAs and Cancer

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Keywords: microRNAs, non-coding RNAs, cancer, solid tumors, hematological malignancies, oncogene, tumor suppressor gene, angiogenesis, metastasis, therapy, biomarkers.

Abstract

MicroRNAs (miRNAs) are non-coding RNAs (ncRNAs) with gene expression regulatory functions, whose deregulation has been documented in almost all types of human cancer (both solid and hematological malignancies), with respect to the non-tumoral tissue counterpart. After the initial discovery that the miRNome (defined as the full spectrum of miRNAs expressed in a specific genome) is de-regulated in cancer, contributes to human carcinogenesis, and to the mechanisms of angiogenesis and metastases (which are hallmarks of the malignant phenotype), new pieces of evidence have been provided that miRNAs can be detected in several human body fluids, and can also be successfully used as tumor biomarkers with diagnostic, prognostic and theranostic implications. These findings have cast a new “translational” light on the research in the miRNA field, providing the rationale for a miRNA-based cancer therapy.

Introduction

Tumor formation and progression is a complex multistep process characterized by several consecutive events: accumulation of genomic alterations, uncontrolled proliferation, angiogenesis, invasion and metastasis. Over the past few years an increasing number of studies have highlighted the key role that microRNAs have in the regulation of processes described above.

MicroRNAs (miRNAs) are a family of single-stranded non-coding RNAs (ncRNAs) between 19-24 nucleotides in length that regulate the expression of target miRNAs both at transcriptional and translational level. In plants such regulation occurs by perfect base-pairing, usually in the 3’ untranslated region (UTR) of the targeted miRNA, whereas in mammals the base-pairing is only partial (Lagos-Quintana et al., 2001; Lee and Ambros, 2005; Hu et al., 2010).

Evolutionarily conserved among distantly related organisms (Ambros, 2003), miRNA genes represent approximately 1% of the predicted genes in the genome of different species. It has been demonstrated that each miRNA can have hundreds of different targets and that approximately 30% of the genes are regulated by at least one miRNA (Bartel, 2004). MiRNAs are known to be involved in several biological processes such as cell cycle regulation, proliferation, apoptosis, differentiation, development, metabolism, neuronal patterning and aging (Bartel, 2004; Bagga et al., 2005; Harfe, 2005; Boehm and Slack, 2006; Calin et al., 2006; Arisawa et al., 2007; Carleton et al., 2007).

The biogenesis of miRNAs starts in the nucleus (Figure 1), where for the most part an RNA polymerase II transcribes long primary precursors, up to several kilobases (pri-miRNAs) (Ambros and Lee, 2004). Such transcription occurs at the level of genomic regions located within the introns or exons of protein-coding genes (70%) or in intergenic areas (30%) (de Yebenes and Ramiro, 2010). Long, capped and polyadenylated pri-miRNAs (Cai et al., 2004) are then processed by a ribonuclease III (Drosha) and by the double-stranded DNA binding protein DGCR8/Pasha, which enzymatically cut
Figure 1. **MiRNA biogenesis.** MiRNA biogenesis begins inside the nucleus, then its processing and maturation take place in the cytoplasm of an eukaryotic cell. MiRNAs are transcribed by RNA polymerase II as long primary transcript (pri-miRNAs) characterized by a hairpin structure and then cleaved by the enzyme Drosha in smaller molecules of nearly 70-nucleotides (pre-miRNAs). These precursors are then exported to the cytoplasm by the Exportin 5/Ran-GTP complex and further processed by RNAse III Dicer, which generates double-stranded-RNAs called duplex miRNA/miRNA* of 22-24 nucleotides. The strand corresponding to the mature miRNA is incorporated into a large protein complex named RISC (RNA-induced silencing complex) and it interacts with the 3′ UTR of the targeted messenger RNA: if the complementarity between miRNA and the 3′UTR is perfect the latter is cleaved by RISC, whereas if the matching is imperfect then translational repression occurs.
### miRNAs as oncogenes

Profiling studies have revealed that several miRNAs show oncogenic properties. One of the first oncomiR identified was miR-155 (Metzler et al., 2004; Kluiver et al., 2005). It is located on chromosome 21 in a host non-coding RNA called the B cell integration cluster (BIC) and is highly expressed in pediatric Burkitt's lymphoma (Metzler et al., 2004), Hodgkin disease (Kluiver et al., 2005), primary mediastinal non-Hodgkin's lymphoma (Calin et al., 2005), chronic lymphocytic leukemia (CLL) (Kluiver et al., 2005), acute myelogenous leukemia (AML) (Calin et al., 2008), lung, breast and pancreatic cancer (Volinia et al., 2006; Greither et al., 2010). A study conducted by Costinean et al. showed that transgenic mice with a B-cell targeted overexpression of miR-155 develop a lymphoproliferative disease (polymorphic pre-leukemic pre-B-cell proliferation followed by full-blown B-cell malignancy) resembling the human diseases, indicating that the deregulation mediated by miR-155 involves both the initiation and progression of the disease (Costinean et al., 2006). Moreover the use of miR-155 knock out mouse model has revealed that miR-155 is strongly implicated into the induction of Th2 lymphocyte differentiation and altered cytokine production (de Yebenes and Ramiro, 2010).

Another miRNA which displays an oncogenic role is miR-21. Chan et al. demonstrated that knockdown of miR-21 in multiple glioblastoma cells induced caspase activation and apoptosis, indicating that miR-21 could function as an oncogene by blocking expression of critical apoptosis-related genes (Abdellatif, 2010). In fact miR-21 targets TSGs such as PTEN (phosphatase and tensin homolog) (Choong et al., 2007), PDCD4 (programmed cell death 4) (Dillhoff et al., 2008) and TPM1 (tropomyosin 1) (Beitzinger et al., 2007).

<table>
<thead>
<tr>
<th>microRNA</th>
<th>Dysregulation in cancer</th>
<th>miRNA target</th>
<th>Function</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-21</td>
<td>Upregulated in glioblastoma, AML, prostate, pancreatic, gastric, colon, breast, lung, liver cancer</td>
<td>PTEN, PCDC4, TPM1</td>
<td>Oncogene</td>
<td>Meng, Frankel, Zhu, Ciafre, Calin, Garzon, Volinia, Meng</td>
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<tr>
<td>miR-17-92 cluster</td>
<td>Upregulated in breast, colon, lung, pancreatic, prostate, gastric cancers, lymphomas</td>
<td>PTEN, Bim</td>
<td>Oncogene</td>
<td>Volinia, Venturini</td>
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<tr>
<td>miR-372/373</td>
<td>Upregulated in testicular tumor</td>
<td>LATS2</td>
<td>Oncogene</td>
<td>Voorhoeve</td>
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<td>miR-221/222</td>
<td>Upregulated in thyroid, prostate, glioblastoma, colon, pancreas, stomach</td>
<td>P27Kip1</td>
<td>Oncogene</td>
<td>Visone, Galardi, le Sage</td>
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<tr>
<td>miR-10b</td>
<td>Upregulated in breast cancer</td>
<td>HOXD10</td>
<td>Oncogene</td>
<td>Ma</td>
</tr>
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<td>miR-15a and</td>
<td>Downregulated in CLL, prostate</td>
<td>BCL2, CCND1, WNT3A</td>
<td>Tumor-suppressor gene</td>
<td>Bullrich, Cimmino, Bonci</td>
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<td>miR-16-1</td>
<td></td>
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<td>miR-29 family</td>
<td>Downregulated in lung cancer, AML, breast cancer and cholangiocarcinoma</td>
<td>TCL1, MCL1, DNMT3s</td>
<td>Tumor-suppressor gene</td>
<td>Calin, Iorio, Garzon, Mott, Fabbri, Pekarsky</td>
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<td>Let-7 family</td>
<td>Downregulated in lung and breast cancer</td>
<td>C-MYC, HMGA2, MYCN</td>
<td>Tumor-suppressor gene/oncogene</td>
<td>Johnson Sampson, Lee, Buechner, Brueckner, Iorio</td>
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<td>miR-34 family</td>
<td>Downregulated in lung and pancreatic cancer</td>
<td>BCL2, MYCN</td>
<td>Tumor-suppressor gene</td>
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<td>miR-143 and -145 cluster</td>
<td>Downregulated in colorectal cancer</td>
<td>ERK5, C-MYC</td>
<td>Tumor-suppressor gene</td>
<td>Michael, Akao, Ibrahim</td>
</tr>
</tbody>
</table>

**Table 1.** The main de-regulated miRNAs in cancer.

**Legend:** CLL= chronic lymphocytic leukemia; AML= acute myeloid leukemia.
The miR-17-92 cluster is characterized by six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92-1) highly expressed in breast, colon, lung, pancreatic, prostate and gastic cancer, lymphomas (Costinean et al., 2006; Nagel et al., 2007). It has been demonstrated that the miR-17-92 cluster induces B cell proliferation. Moreover, transgenic mice overexpressing miR-17-92 in lymphocytes developed lymphoproliferative disease and autoimmunity through the inhibition of tumor suppressor Pten and the pro-apoptotic protein Bim (de Yebenes and Ramiro, 2010). Other miRNAs that have an oncogenic role are miR-372/373, which are involved in the development of human testicular germ cell tumors by neutralizing the TP53 pathway (Voorhoeve et al., 2006), miR-221/222 which induce proliferation of thyroid (Iorio et al., 2001), miR-15a and -16 display expression levels inversely correlated to the methylation-silenced TSGs such as WWOX, FHIT, MCL1 and TCL1 (Costinean et al., 2006; Mott et al., 2007). Among the tumor suppressor miRNAs there is the let-7 family. Johnson et al. demonstrated an inverse correlation between the expression of the let-7 family members and the expression of the oncogene RAS in lung cancer tissue (Adai et al., 2005). Let-7 family targets as well other onco-genes such as C-MYC (Sampson et al., 2007), HMGA2 (high mobility group A2) (Barakat et al., 2007) and MYCN (Buechner et al., 2011). However, not all the members of this family display a tumor suppressor role since in lung adenocarcinoma let-7a-3 has an oncogenic function and promotes tumor cell proliferation (Brueckner et al., 2007).

The miR-34 family (comprising miR-34a, -34b and -34c) is downregulated in lung cancer tumor cells with respect to normal tissue and their re-expression in pancreatic cancer cell lines inhibits cell growth and invasion, and induces apoptosis and cell cycle arrest in G1 and G2/M (Gallardo et al., 2009). Similarly to the tumor suppressor miRNAs described above, the miR-34 family exerts its function by targeting anti apoptotic mRNAs such as BLC2 and MYCN (Camps et al., 2008). The list of miRNAs having a tumor suppressor function ends with the cluster miR-143 and -145. These miRNAs, downregulated in several tumors (Akao et al., 2007; Banauda et al., 2011), have been found to target ERK5 (extracellular signal-regulated kinase 5) and c-MYC with consequent inhibition of tumor proliferation and increased apoptosis (Akao et al., 2007; Ibrahim et al., 2011).

miRNAs as tumor suppressor genes

If several miRNAs are known for their pro-oncogenic role, then other miRNAs represent their counterpart by acting as a TSG. Their silencing due to mutations, chromosomal rearrangements or to promoter methylation (Calin et al., 2002; Calin et al., 2005; Ishii and Saito, 2006; Arisawa et al., 2007) contributes to the initiation and progression of cancer. MiR-15a and miR-16-1 represent a typical example of TSG miRNA. Encoded as a cluster at the level of chromosome 13q14.3, a region frequently deleted in chronic lymphocytic leukemia (CLL) (Bullrich et al., 2001), miR-15a and -16 display expression levels inversely correlated to the BCL2 ones. These miRNAs in fact induce apoptosis in leukemic cells by directly targeting the anti-apoptotic gene (Calin et al., 2005). Moreover, it has been demonstrated that miR-15a and -16 exert a tumor-suppressor role also in prostate cancer by targeting BCL2, CCND1 (cyclin D1) and WNT3A (encoding a protein which promotes cell survival, proliferation and invasion) (Bonci et al., 2008). Taken together, these findings harbor therapeutic implications and bring new insights to the comprehension and treatment of cancer.

Chromosome 7q32 hosts the miR-29 family (comprising miR-29a, -29b and -29c), which is downregulated in lung cancer, CLL, AML, breast cancer and cholangiocarcinoma (Calin et al., 2005; Mott et al., 2007; Calin et al., 2008). It has been demonstrated that in lung cancer the expression of miR-29 family members is inversely correlated with DNMT3A and -3B (DNA methyltransferases 3A and 3B) and that these miRNAs directly target these enzymes, inducing global hypomethylation of tumoral cells (Calin et al., 2007) and reactivation of methylation-silenced TSGs such as WWOX, FHIT, MiR-99b and miR-102 was found higher in adenocarcinoma (Volinia et al., 2006).

miRNAs in solid tumors

Lung cancer

Lung cancer is the leading cause of cancer death around the world (Jemal et al., 2009). Gao et al. performed miRNA microarray expression profiling in order to compare miRNAs expression in primary squamous cell lung carcinoma with normal cells and determine miRNA potential relevance to clinicopathological factors and patient postoperative survival times. They found out that miR-21 was upregulated in nearly 75% of cancer specimens and that this modulation was significantly correlated with shortened survival time (Cheng et al., 2011). Yanaihara and co-workers used the same approach and correlated miRNA expression profiles with survival of lung cancer, finding out that high miR-155 and low let-7a-2 expression were correlated with poor survival. Furthermore, they found a molecular signature for subset of lung cancer: they identified six miRNAs having a differential expression in adenocarcinoma and squamous cell cancer (mir-205, mir-99b, mir-203, mir-202, mir-102, and mir-204-Prec). Among these, the expression of miR-99b and miR-102 was found higher in adenocarcinoma (Volinia et al., 2006).
Yu et al. found a five-microRNA signature (let-7a, miR-21, miR-137, miR-372, miR-182*) associated with survival and cancer relapse in NSCLC (non-small cell lung cancer) patients (Abdurakhmonov et al., 2008). Another specific marker for squamous cell lung carcinoma is miR-205, according to a microarray study performed by Lebanony et al., who found a strong association between the expression levels of miR-205 and squamous cell lung carcinoma histology (Barshack et al., 2010).

In addition to the already mentioned miRNAs, miR-31 is found to act as an oncogenic miRNA by targeting mRNAs encoding two anti-tumoral proteins, LATS2 (large tumor-suppressor 2) and PPP2R2A (PP2A regulatory subunit B alpha isoform) (Anand et al., 2010). Chou and co-workers discovered that miR-7 promotes EGFR-mediated tumorigenesis in lung cancer by targeting ERF (Ets transcriptional repressor) thus modulating cell growth (Choudhry and Catto, 2011). However, miR-7 seems to have a dual function of oncogene/tumor-suppressor miRNA. Xiong et al. indeed found that overexpression of miR-7 in NSCLC A549 cells inhibits cell proliferation and induces apoptosis by targeting anti-tumoral protein Bcl-2 (Shao et al., 2011).

Another miRNA that displays a tumor-suppressor role in lung cancer is miR-451. Wang et al. demonstrated not only that this miRNA is the most downregulated in NSCLC tissues, but also that it regulates survival of cells partially through the downregulation of the oncogene RAB14 (Ras-related protein 14) (Bian et al., 2011).

Breast cancer
Breast cancer is the second leading cause of cancer deaths in the developed world and the most commonly diagnosed cancer in women (Bonev et al., 2011). A miRNA expression profile study for breast cancer was conducted by Iorio et al. The authors found 13 miRNAs differentially expressed between tumor and normal tissues: among the upregulated ones there were oncogenic miR-21 and miR-155, while miR-10b, let-7 miR-125b, miR-145 and miR-205 were found downregulated (Calin et al., 2005). The latter directly targets HER3 receptor and blocks the activation of downstream Akt, inhibiting cell proliferation. Moreover, miR-205 sensitizes cells to Gefitinib and Lapatinib, two tyrosine-kinase inhibitors, promoting apoptosis (Iorio et al., 2009).

Shi et al. found that miR-301 has an oncogenic role in breast tumor by targeting FOXF2, BBC3, PTEN and COL2A1. Its upregulation promotes proliferation, migration, invasion and tumor formation. Moreover, by cooperating with its host gene SKA2, miR-301 promotes the aggressive breast cancer phenotype with nodal or distant relapses (Akae et al., 2011).

Heyn and co-workers identified miR-335 as a tumor-suppressor gene. It controls different factors of the upstream BRCA1 regulatory pathway (such as ERα, IGF1R, SP1), inducing an upregulation of the tumor suppressor gene BRCA1 (Heyn et al., 2011).

Colorectal cancer
In 2008 a study conducted by Schetter et al. the authors performed miRNA microarray expression profiling comparing 84 pairs of tumors (colon adenocarcinoma) and adjacent non-tumoral tissues (Schetter et al., 2008). They found 37 differentially expressed miRNAs; among them miR-20a, -21, -106, -181b and -203 levels were higher in tumor specimens. The overexpression of miR-21 and its role in tumor proliferation in several kind of cancers has already been described before. Also miR-20a belongs to the miR-17-92 cluster, whose overexpression promotes cell proliferation (Hayashita et al., 2005) and increased tumor size.

One of the most recent tumor suppressor miRNAs found in colorectal cancer is miR-137. Balaguer et al. reported that this miRNA is constitutively expressed in the normal colonic epithelium but during the early events of colorectal carcinogenesis it is silenced through promoter hyper-methylation. Moreover, its re-expression in vitro inhibits cell proliferation in a cell specific manner. These findings suggest a prognostic role for miR-137 (Balaguer et al., 2010).

It has been recently demonstrated by Sarver et al. that miR-183 has an oncogenic role in colon cancer (but also in synovial sarcoma and rhabdomyosarcoma) through its regulation of the expression levels of 2 tumor suppressor genes, EGR1 and PTEN. The authors also provided evidence that knockdown of miR-183 affects cellular migration and they suggest that pharmaceutical intervention on tumor characterized by the upregulation of miR-183 may be useful as anti-cancer therapy (Chen et al., 2010).

Hepatocellular carcinoma
One of the most common malignant tumors is hepatocellular carcinoma. Murakami et al. analysed the miRNA expression profiles in 25 specimens of hepatocellular carcinoma compared with adjacent non-tumoral tissues and nine chronic hepatitis specimens (Murakami et al., 2006). miR-222, miR-17-92 and miR-106a exhibited higher expression in tumor tissues than in the normal ones and were found associated with the tumor differentiation status.

Pineau et al. performed profiling studies on 104 hepatocellular carcinoma tissue specimens, 90 cirrhotic, 21 normal and 35 hepatocellular carcinoma cell lines (Pineau et al., 2010). They found a 12 miRNA signature that characterizes tumor progression starting from normal liver, to cirrhosis to full blown tumor. Among them, miR-21, miR-221/222, miR-34a and miR-224 were found overexpressed in the progression signature. miR-224 overexpression is connected with the regulation of cell proliferation, cell migration and metastasis (Chemistry, 2010).

Su et al. reported that miR-101 is significantly downregulated in hepatocellular carcinoma and that its overexpression inhibits tumor development in nude
mice, sensitis tumor cell lines to serum starvation and chemotherapeutic treatment (Su et al., 2009). Other tumor suppressor miRNAs are: miR-122, normally downregulated in hepatocellular carcinoma, whose overexpression induces apoptosis and cell cycle arrest through targeting of BCLW (Chemistry, 2010); miR-198, which inhibits migration and invasion in a c-MET dependent manner (Akao et al., 2011); miR-125b, which suppresses tumor cell growth in vitro and in vivo and induces cell cycle arrest at G1/S acting as a tumor suppressor gene through the suppression of LIN28B (Bates et al., 2010), a promoter of cell proliferation and metastasis through regulation of c-MYC and E-Cadherin (Ai et al., 2010).

miRNAs in hematological malignancies

Similarly to what has been reported in solid tumors, also in hematological malignancies the miRNome is frequently de-regulated with respect to the normal cell counterpart. Physiologic variations in miRNA expression occur during normal hematopoesis, and affect differentiation and commitment of the multipotent hematologic progenitor (MPP). Hematologic tumors represent abnormal blocks in hematopoesis. Interestingly, the aberrations of the miRNome occurring in these tumors can be explained, at least in some instances, as the result of the block of differentiation leading to the development of the malignancy. In other cases, the cause of the observed de-regulation has not been clarified, but the role of the de-regulated miRNAs in the acquisition of the malignant phenotype has been understood, based on the nature of the targeted genes.

miRNAs in leukemias

Chronic lymphocytic leukemia (CLL) is the most frequent leukemia of the adult in the Western world. Chromosomal aberrations recur in human CLL and harbor diagnostic and prognostic implications. Occurring in about 65% of cases, the 13q14 deletion is the most frequent chromosomal aberration observed in human CLL. Based on the analysis of a large number of CLL cases with monosomic 13q14 deletion, a minimal deleted region (MDR) has been defined. This MDR includes a long ncRNA, called DLEU2 (deleted in leukemia 2), strongly conserved among vertebrates, and the first exon of the DLEU1 gene, another ncRNA (Miglizza et al., 2001; Chai et al., 2010). The miR-15a/16-1 cluster is located in intron 4 of DLEU2, and genetic alterations affecting DLEU2 mRNA expression would also affect miR-15a/16-1 cluster expression (Calin et al., 2002). Therefore, the expression of miR-15a/16-1 is reduced in the majority of CLL patients carrying the 13q deletion (Calin et al., 2002). Interestingly, the same miRNA cluster is involved in cases of familial CLL, since a germ-line mutation in the sequence of pre-miR-16-1 (which leads to a reduced miR-16 expression both in vitro and in vivo), has been identified associated with the deletion of the normal allele in leukemic cells of two CLL patients, one of which has a family history of CLL and breast cancer (Calin et al., 2005). A similar point mutation, adjacent to the miR-16-1 locus has been described in the CLL prone New Zealand Black mouse strain model (Raveche et al., 2007). One of the most frequent molecular hallmarks of the malignant, mostly non-dividing B-cell of CLL, is the up-regulation of the antiapoptotic BCL2. It has been demonstrated that both miR-15a and miR-16 directly target BCL2 in CLL both in vitro and in vivo (Calin et al., 2005; Ambs et al., 2008), therefore suggesting that the miR-15a/16-1 cluster enacts a tumor suppressor function. Clinicians are aware that CLL is characterized by recurrent and common chromosomal aberrations, which harbor prognostic implications. Some of the most frequent of these abnormalities are the 13q deletion, the 17p deletion and the 11q deletion. While CLL patients with the 13q deletion experience the indolent form of the disease (characterized by IGVH mutated and low levels of the prognostic surrogate marker ZAP70), those with the 17p or the 11q deletion (alone or in association with the 13q), experience an aggressive form of the disease (characterized by IGVH unmutated and high levels of ZAP70) (Chiorazzi et al., 2005). Recently, a new molecular network explaining the role of these chromosomal aberrations and their prognostic implications for human CLL has been described. According to this model, the miR-15a/16-1 cluster (located at 13q), directly targets the pro-apoptotic TP53 (located at 17p), which in turn transactivates the miR-34b/34c cluster (located at 11q), directly targeting ZAP70 (Fabbri et al., 2011). Also, TP53 is able to transactivate the miR-15a/16-1 cluster, creating a feed-forward regulatory loop (Fabbri et al., 2011). These findings identify for the first time some of the molecular effectors connecting these three recurrent chromosomal aberrations in CLL and can explain both their prognostic implications and the observed levels of ZAP70 according to the degree of aggressiveness of the disease. Recently, Klein et al. (Danilov et al., 2010) generated two groups of transgenic mice models: one mimicking the MDR and the other containing a specific deletion of the miR-15a/16-1 cluster. Although the same spectrum of clonal lymphoproliferative disorders was observed in both animal models, the disease was more aggressive in the MDR group than in the miR-15a/16-1 group, suggesting that additional genetic elements in the 13q14 region may affect the severity of the disease. The oncogene TCL1 (T-cell leukemia/lymphoma 1A) is over-expressed in the aggressive CLL (Herling et al., 2006; Barlev et al., 2010), and is regulated by miR-29b and miR-181b (Costinean et al., 2006). Furthermore, miR-181a directly targets BCL2 (Ebert et al., 2007), suggesting a central role of miR-181 family and of the miR-15a/16-1 cluster in regulating BCL2 expression in CLL. Stamatopoulos et al. (Stamatopoulos et al., 2009) found that downregulation of miR-29c and miR-223 are
predictive of treatment-free survival (TFS) and overall survival (OS). Low expression of miR-223, miR-29b, miR-29c, and miR-181 family are associated with disease progression in CLL cases harboring the 17p deletion, whereas patients carrying the trisomy 12 abnormality and high expression of miR-181a experience a more aggressive variant of CLL (De Martino et al., 2009). Interestingly, the miR-29 family has been demonstrated to control key epigenetic mechanisms (such as the expression of all three main DNA methyltransferases) both in solid tumors and in hematological malignancies (Calin et al., 2007; Garzon, 2009), therefore suggesting the involvement also of miRNA-mediated epigenetic factors in the pathogenesis and prognosis of human CLL.

Also miR-155 is up-regulated in CLL versus normal CD19+ B lymphocytes, suggesting that this miRNA might act as diagnostic biomarker of CLL (Marton et al., 2008).

The Philadelphia chromosome (reciprocal translocation t(9;22)) is the hallmark of the chronic myeloid leukemia (CML), generating the chimeric protein BCR-ABL1, which is able to activate the miR-17-92 cluster, together with the oncogene c-MYC, during the early chronic phase, but not in blast crisis CML CD34+ cells (Nagel et al., 2007). These findings suggest that the miR-17-92 cluster contributes to early phase CML pathogenesis, harboring CML diagnostic biomarker properties. ABL1 is also a direct target of miR-203, whose over-expression inhibits cancer cell proliferation in an ABL1-dependent manner (Bueno et al., 2008). Moreover, it has been shown that Philadelphia positive CMLs, often present a reduced expression of miR-203 because of its promoter hyper-methylation, while no methylation can be detected in other hematological malignancies that do not carry ABL1 alterations (Bueno et al., 2008). Finally, down-regulation of miR-10a has been observed in about 70% of CMLs, with an inverse correlation with the expression of the oncogene USF2 (upstream stimulatory factor 2) (Agirre et al., 2008). Overall, high levels of miR-17-92 cluster and low expression of miR-203 and miR-10a seem to be part of the diagnostic signature of human CML. More recently, miR-451 has emerged as another key player in CML. Indeed this miRNA can target BCR-ABL1, which in turn can inhibit miR-451 expression, creating a regulatory loop, whose disruption might have therapeutic implications in the disease (Lopotova et al., 2011). Another gene which inhibits cell growth and is frequently down-regulated in CML is CCN3 (also known as NOV or nephroblastoma overexpressed gene). A possible mechanism of its down-regulation in CML has been recently identified and is mediated by miR-130a and miR-130b, which are up-regulated by BCR-ABL1 in CML, and directly target CCN3, contributing to leukemic cell proliferation (Suresh et al., 2011).

Up-regulation of the miR-17-92 cluster has been described also in B- and T-cell acute lymphocytic leukemia (ALL) (Zanette et al., 2007; Nagel et al., 2009). Recently, the miR-17–92 cluster has been correlated with the development of mixed lineage leukemia (MLL)-rearranged acute leukemia (Chemistry, 2010). Up-regulation of this cluster was observed not only in MLL-associated AML, but also in ALL, and is possibly due to both DNA copy number amplification at 13q31 and to direct upregulation by MLL fusions (Chemistry, 2010). Interestingly, a specific miRNA signature of 4 miRNAs is able to distinguish the two forms of acute leukemias (ALL from AML (acute myeloid leukemia)) with an accuracy rate of 98%. Indeed, higher expression of miR-128a and miR-128b was found in ALL compared to AML, whereas down-regulation of let-7b, miR-223 indicates ALL vs AML (Science, 2007). At the moment, the leukemogenic mechanism of miR-128b is still poorly understood. Zhang et al., have identified a miRNA signature in children with ALL complicated by central nervous system (CNS) relapse (Ai et al., 2009). The high-risk-of-relapse signature is composed of over-expression of miR-7, miR-198, and miR-663, and down-regulation of miR-126, miR-345, miR-222, and miR-551a. MiR-16 has a prognostic significance in ALL. Indeed, Kaddar et al., found that low expression of miR-16 is associated with a better ALL outcome (Kaddar et al., 2009).

In AML with normal karyotype high levels of miR-10a, -10b, members of let-7 and miR-29 families, and down-regulation of miR-204, identify NPM1 (nucleophosmin-1) mutated versus unmutated cases (Calin et al., 2008). Recently, Ovcharenko et al., confirmed that miR-10a expression is highly characteristic for NPM1 mutated AML, and may contribute to the intermediate risk of this condition by interfering with the TP53 machinery, partly regulated by its target MDM4 (murine double minute 4) (Ovcharenko et al., 2011). Over-expression of miR-155 is associated with FLT3-ITD+ status, although there is evidence that this up-regulation is actually independent from FLT3 signaling (Calin et al., 2008). The fusion oncoprotein AML1/ETO (generated by the t(8;21) translocation), is the most frequent chromosomal abnormality in AML, and causes epigenetic silencing of miR-223, by recruiting chromatin remodeling enzymes at an AML1-binding site on the pre-miR-223 gene (Fazi et al., 2007). By silencing miR-223 expression, the oncoprotein inhibits the differentiation of myeloid precursors (promoted by high levels of miR-223), therefore actively contributing to the pathogenesis of this myeloproliferative disorder. A central role in the pathogenesis of AML is also played by miR-29b, a direct regulator of the expression of all three DNA methyltransferases (Calin et al., 2007; Garzon et al., 2009b). Re-expression of miR-29b induces de-methylation and re-expression of epigenetically silenced TSGs, such as ESRI (estrogen-receptor alpha), and p15 (INK4b) (Garzon et al., 2009b). Moreover, restoration of miR-29b in AML cell
lines and primary samples, suppresses the expression of OGs such as MCL1, CXXC6, and CDK6, which are direct targets of miR-29b (Garzon et al., 2009a). Abnormal activation of the proto-oncogene c-KIT contributes to leukemogenesis. Gao et al., found that miR-193a is silenced by promoter hyper-methylation in AML, and since this miRNA directly targets c-KIT, this epigenetic silencing is responsible, at least in part, for the aberrant up-regulation of the oncogene in AML (Cheng et al., 2011). Indeed, restoration of miR-193a expression by de-methylating agents, reduces the expression of c-KIT and induces cancer cell apoptosis and granulocytic differentiation (Cheng et al., 2011). Similarly, also miR-193b directly targets c-KIT in AML (Cheng et al., 2011). By using a novel approach based on the integration of miRNA and mRNA expression profiles, Havelange et al., found a strong positive correlation between miR-10 and miR-20a and HOX-related genes, a significant inverse correlation between genes involved in immunity and inflammation (such as IRF7 and TLR4) and a panel of 4 miRNAs (namely, miR-181a, -181b, -155, and -146), and a strong direct correlation between miR-23, -26a, -128a, and -145 and pro-apoptotic genes (such as BIM and PTEN) (Havelange et al., 2011). Also miR-100 has been described as an OG in AML, by targeting the TSG RBSP3 (CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase-like) (Cao et al., 2011). Also in AML, miR-17/20/93/106 have been shown to promote hematopoietic cell expansion by targeting sequestosome 1-regulated pathways in mice (Meenhus et al., 2011). Down-regulation of miR-29a and miR-142-3p has been observed in AML with respect to controls (Bian et al., 2011), and miR-29a contributes to counteract leukemic proliferation by directly targeting the proto-oncogene SKI (Teichler et al., 2011).

miRNAs in lymphomas

De-regulation of miRNAs has been reported also in non-Hodgkin lymphomas (NHL) and in Hodgkin’s disease (HL). The first evidence of an involvement of miRNAs in lymphomagenesis was provided by Eis et al. who observed that the final part of the B-cell integration cluster (BIC) non-coding RNA (ncRNA), where miR-155 is located (Chen and Meister, 2005), was able to accelerate MYC-mediated lymphomagenesis in a chicken model (Bashirullah et al., 2003). Subsequently, high levels of BIC/miR-155 were described also in pediatric Burkitt’s lymphoma (BL) (Metzler et al., 2004), in diffuse large B-cell lymphoma (DLBCL) (Lawrie, 2007; Hoefigt et al., 2008), and in HL (Kluiver et al., 2008; Abdurakhmonov et al., 2008; Van Vlierberge et al., 2009). In a B-cell specific miR-155 transgenic (TG) mouse model the onset of an acute lymphoblastic leukemia/high-grade lymphoma at approximately 9 months of age was observed (Costinean et al., 2006). In these TG mice, the B-cell precursors with the highest miR-155 expression were at the origin of the leukemias (Costinean et al., 2009).

Indeed, miR-155 directly target SHIP (Src homology 2 domain-containing inositol-5-phosphatase), and C/EBPbeta (CCAAT enhancer-binding protein beta), two key regulators of the interleukin-6 signaling pathway, therefore triggering a chain of events that promotes the accumulation of large pre-B cells and acute lymphoblastic leukemia/high-grade lymphoma (Costinean et al., 2009). Also miR-155 knockout (KO) mice models have been generated, showing that the loss of miR-155 switches cytokine production toward Th2 differentiation (de Yebenes and Ramiro, 2010), and also compromises the ability of dendritic cells (DC) to activate T cells, because of a defective antigen presentation or abnormal co-stimulatory functions (de Yebenes and Ramiro, 2010).

As observed in leukemias, also in NHLs, a specific signature of 4 de-regulated miRNAs (namely miR-330, -17-5p, -106a, and -210) can differentiate among reactive lymph nodes, follicular lymphomas (FL), and DLBCL (Hoefig et al., 2008). Noteworthy, miR-17-5p, and miR-106a belong to two paralogous clusters located on chromosome 13 and X, respectively, with a well established oncogenic role both in solid and hematological malignancies (Chang et al., 2008). The miR-17-92 cluster is located in a region frequently amplified in malignant B-cell lymphomas (Abbott et al., 2005), and is overexpressed in over 60% of B-cell lymphoma patients (Allawi et al., 2004). In murine pluripotent cells from MYC-transgenic mice, over-expression of this miRNA cluster accelerates lymphomagenesis (Allawi et al., 2004), whereas in miR-17-92 TG mice models a higher than expected rate of lymphoproliferative disorders and autoimmunity and premature death was observed (de Yebenes and Ramiro, 2010). These effects are at least in part due to the direct targeting of the PTEN and BIM, which controls B-lymphocyte apoptosis (de Yebenes and Ramiro, 2010). The miR-106a-363 polycistr ison is also overexpressed in 46% of acute and chronic human T-cell leukemias (Landais et al., 2007), claiming a role in leukemogenesis. Interestingly, both miR-106b-25 and miR-17-92 paralogous clusters interfere with the transforming growth factor-beta (TGF-beta) signaling (Petrocca et al., 2008), which is inhibited in several tumors (Derynck et al., 2001). Moreover, Ventura et al. have shown that the miR-17-92 and miR-106b-25 double knockout mouse model has a more severe phenotype than the miR-17-92 single knockout mouse model (Ventura et al., 2008), suggesting that both clusters are implicated in the control of apoptosis in malignant lymphocytes. Interestingly, miR-17-5p and miR-20a (which belong to the miR-17-92 cluster) are induced by the proto-oncogene and transcription factor c-MYC (Nakamoto et al., 2005), and in turn the cluster directly targets E2F1, a c-MYC transactivated transcription factor promoting cell-cycle progression (Nakamoto et al., 2005). Therefore, the miR-17-92 cluster tightly regulates c-MYC-driven cell-cycle progression. From a more translational perspective, it
has been also demonstrated that over-expression of the miR-17-92 cluster also significantly increases the resistance to radiotherapy in human mantle cell lymphoma cells (Ahn et al., 2010), revealing a role for this cluster as a theranostic biomarker. MiR-34a is negatively regulated by c-MYC (Abdurakhmonov et al., 2008). In c-MYC over-expressing B-lymphocytes miR-34a confers drug resistance by inhibiting TP53-dependent bortezomib-induced apoptosis (Sotillo et al., 2011). Finally, down-regulation of miR-143 and miR-145 has been described in B-cell lymphomas and leukemias (Akao et al., 2007), and re-expression of these miRNAs in a Burkitt lymphoma cell line demonstrated a dose-dependent growth inhibitory effect, mediated in part by miRNA-induced downregulation of the oncogene ERK5 (Akao et al., 2007).

In HL, Navarro et al. identified a distinctive signature of 25 miRNAs able to distinguish HL from reactive lymph nodes, and 36 miRNAs differentially expressed in the nodular sclerosis and mixed cellularity subtypes of HL (Navarro et al., 2007). Interestingly, 3 miRNAs (namely, miR-96, -128a, and -128b) are selectively downregulated in HL cells with Epstein–Barr virus (EBV) infection, but only one of these miRNAs is part of the signature of 25 de-regulated miRNAs in HL versus reactive lymph nodes, suggesting that EBV might not be relevant for HL pathogenesis (Navarro et al., 2007). Down-regulation of miR-150 and over-expression of miR-155 frequently occur in HL cell lines (Gibcus et al., 2009). Since HL develops in the lymph node germinal center, and high levels of miR-155 have been described in the germinal center also during normal lymphopoiesis, it can be postulated that the observed over-expression of miR-155 in HL might result from an abnormal block of lymphocyte differentiation at the germinal center level. Van Vlierberghe et al., have compared miRNA profiles of microdissected Reed-Sternberg cells and Hodgkin cell lines versus CD77+ B-cells (Van Vlierberghe et al., 2009). In this study a profile of 12 over and 3 under-expressed miRNAs was identified (Van Vlierberghe et al., 2009), showing only a partial overlap with Navarro’s profile. This discrepancy might be due to the different procedure used to collect HL cells. Finally, also in HL miRNA expression profile can predict prognosis. Indeed, low levels of miR-135a are associated with a higher relapse risk and a shorter disease-free survival (Gallardo et al., 2009). A possible molecular explanation for this effect is that miR-135a directly targets the kinase JAK2 (Janus Kinase 2). Therefore, low levels of miR-135a are associated with higher expression of JAK2, which leads to up-regulation of the antiapoptotic BCL-XL, therefore leading to reduced apoptosis and increased cell proliferation (Gallardo et al., 2009).

miRNAs in body fluids as tumor biomarkers

MiRNAs have been successfully detected in blood and other human fluids. It has been shown that they circulate wrapped in circulating microvesicles called "exosomes" (Bar et al., 2008), and therefore are extremely stable and resistant to degradation (Aumiller and Forstemann, 2008; Kroh et al., 2010). In 2010, Weber et al. determined miRNA expression in 12 different types of body fluids (amniotic fluid, breast milk, bronchial lavage, cerebrospinal fluid (CSF), colostrum, peritoneal fluid, plasma, pleural fluid, saliva, seminal fluid, tears and urine) collected from healthy individuals, and showed that the highest concentrations of miRNAs were found in tears and the lowest in CSF, pleural fluid and urine (Black et al., 2010). The ability to detect miRNAs in body fluids has generated interest in their possible role as tumoral biomarkers. Several studies have demonstrated that miRNAs can indeed be successfully employed both as cancer diagnostic and prognostic biomarkers both in solid and in hematological malignancies. Table 2 summarizes some of these studies.

miRNAs in body fluids as tumor biomarkers in solid tumors

Diagnostic biomarkers

The first evidence that circulating miRNAs can be effectively used to diagnose cancer was provided by Mitchell et al. in 2008 (Bar et al., 2008). They found that higher levels of miR-141 in the serum of 25 patients affected by prostate cancer, compared with 25 healthy control donors identify patients affected by cancer with a sensitivity of 60%, and a specificity of 100% (Bar et al., 2008). Subsequently, Taylor et al. showed that a signature of 8 circulating miRNAs (enclosed in tumor-derived exosomes of endocytic origin) can be used as diagnostic biomarker of ovarian cancer (Chang et al., 2008). Moreover, in a comparison of 152 patients affected by NSCLC versus 75 healthy donors, Chen et al., identified higher levels of miR-25, and miR-223 in the serum of patients affected with cancer (Aumiller and Forstemann, 2008). Interestingly, these Authors also demonstrated that circulating miRNAs resist treatments with HCl, NaOH, and repeated freeze and thaw cycles, therefore acting as stable, reliable biomarkers (Aumiller and Forstemann, 2008). Patients affected by pancreatic cancer have higher concentrations of circulating miR-210 (Bar et al., 2008), -200a, and -200b (Chemistry, 2010), suggesting that these miRNAs might be used to successfully screen for pancreatic cancer. High levels of circulating miR-29a, -92 and -17-3p have been found in patients affected by colorectal cancer (Anand et al., 2010).
### Table 2. MiRNAs detectable in body fluids and their diagnostic and prognostic significance for cancer patients.

**Legend:** The column “Biomarker property” should be read as each letter (or in parenthesis letters) referred to the miRNA reported in the column “miRNA”, according to the sequence order in which these miRNAs are reported. D= Diagnostic biomarker; P= Prognostic biomarker; (D,P)= Diagnostic and Prognostic biomarker. OSCC= Oral Squamous Cell Carcinoma; HCC= Hepatocellular Carcinoma; DLBCL= Diffuse Large B-Cell Lymphoma.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Expression in cancer</th>
<th>Biomarker property</th>
<th>Body fluid</th>
<th>miRNA</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>High</td>
<td>D, D, D</td>
<td>Blood</td>
<td>200a, 200b, 210</td>
<td>Ho, Weber</td>
</tr>
<tr>
<td>Prostate</td>
<td>High</td>
<td>(D,P), P</td>
<td>Blood</td>
<td>141, 375</td>
<td>Mitchell, Brase</td>
</tr>
<tr>
<td>Colorectal</td>
<td>High</td>
<td>(D,P), D, D</td>
<td>Blood</td>
<td>29a, 92, 17-3p</td>
<td>Ng, Huang</td>
</tr>
<tr>
<td>OSCC</td>
<td>High</td>
<td>D</td>
<td>Blood</td>
<td>31</td>
<td>Liu</td>
</tr>
<tr>
<td>Breast</td>
<td>High</td>
<td>(D,P),D,(D,P)</td>
<td>Blood</td>
<td>21, 195, let-7a</td>
<td>Asaga, Heneghan</td>
</tr>
<tr>
<td>Lung</td>
<td>High</td>
<td>D,D</td>
<td>Blood</td>
<td>25, 223</td>
<td>Lu</td>
</tr>
<tr>
<td>HCC</td>
<td>Lower ratio</td>
<td>D</td>
<td>Blood</td>
<td>92a/638</td>
<td>Shigoka</td>
</tr>
<tr>
<td>Lung, Gastric</td>
<td>High</td>
<td>D,D,D</td>
<td>Pleural effusion</td>
<td>24, 26a, 30d</td>
<td>Xie</td>
</tr>
<tr>
<td>Bladder</td>
<td>High</td>
<td>D,D,D</td>
<td>Urine</td>
<td>126, 182, 199a</td>
<td>Hanke</td>
</tr>
<tr>
<td>OSCC</td>
<td>High</td>
<td>D</td>
<td>Saliva</td>
<td>31</td>
<td>Liu</td>
</tr>
<tr>
<td>OSCC</td>
<td>Low</td>
<td>D</td>
<td>Saliva</td>
<td>200a, 125a</td>
<td>Park</td>
</tr>
<tr>
<td>Bladder</td>
<td>Higher ratio</td>
<td>D</td>
<td>Urine</td>
<td>126/152 and 182/152</td>
<td>Hanke</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>High</td>
<td>(D,P), (D,P), D</td>
<td>Blood</td>
<td>21, 155, 210</td>
<td>Lawrie</td>
</tr>
</tbody>
</table>

Interestingly, miR-92 is not elevated in the plasma of patients with irritable bowel disease, suggesting a role for this miRNA in the differential diagnosis between this benign condition and cancer. Moreover, the increased levels of circulating miR-29a and -92 occur already in presence of pre-cancerous conditions such as colon adenomas (Anand et al., 2010), revealing that the de-regulation of these two miRNAs is an early event in colon carcinogenesis and their increased plasma concentration might be helpful for the very early (even pre-cancerous) phase of colorectal tumorigenesis. In breast cancer, Asaga et al. showed that serum concentrations of miR-21 correlates with the presence and extent of breast cancer (Asaga et al., 2011), whereas Heneghan et al., showed that circulating miR-195 differentiates breast cancer from other malignancies and is a potential biomarker for the detection of non-invasive and early stage disease (Henegan et al., 2010). Finally, in oral squamous cell carcinoma (OSCC) high levels of circulating miR-31 differentiate patients from healthy controls and the concentration of this miRNA decreases after surgical resection of the tumor (Anand et al., 2010), suggesting that miR-31 might be helpful also for the early detection of OSCC recurrence. In addition to blood and plasma, miRNAs can be detected also in other body fluids and have diagnostic biomarker properties. High levels of miR-31 (Anand et al., 2010), and lower levels of miR-200a and -125a (Addo-Quaye et al., 2009) have been identified in the saliva of OSCC patients. An increased expression of miR-126, -182, and -199a has been described in the urine of patients affected by bladder cancer with respect to healthy controls (Hanke et al., 2010), whereas the ratio miR-126/miR-152 and miR-182/miR-152 is higher in patients affected by bladder cancer versus carriers of urinary tract infections, with a sensitivity of 72% and 55%, respectively, and a specificity of 82% (Hanke et al., 2010). Similarly, in the blood of patients with hepatocellular carcinoma (HCC), Shigoka et al. found that the ratio of miR-92a/miR-638 is lower than healthy controls, suggesting a possible role of this non-coding RNA parameter in the diagnosis of HCC. Also in malignant pleural effusions of patients affected by lung cancer and gastric carcinoma, higher levels of miR-24, -26a, and -30d compared to controls were reported (Dai et al., 2010). Prognostic biomarkers In addition to their role as diagnostic biomarkers, miRNA can also act as prognostic and theranostic in several human solid tumors. Low levels of circulating let-7a are associated with node positive breast cancer, compared to negative node disease (Henegan et al., 2010), whereas higher levels of miR-21 can be detected in patients with advanced breast cancer with respect to early stage disease (Asaga et al., 2011). Similarly, circulating miR-29a expression differs in early stage versus advanced colorectal cancer (Anand et al., 2010). In prostate cancer, higher serum levels of miR-375 and -141 are found in patients with...
advanced disease (Brase et al., 2011), whereas higher circulating miR-21 was found in hormone refractory prostate cancer, with respect to benign prostatic hyperplasia, localized prostate cancer and hormone dependent prostate cancer (Bo et al., 2011).

miRNAs in body fluids as tumor biomarkers in hematological malignancies

Diagnostic biomarkers
Higher levels of circulating miR-21, -155 and -210 have been described in patients affected by diffuse large B-cell lymphoma (DLBCL), compared to controls (Lawrie, 2008). Interestingly, the same group had previously shown that the expression of miR-155 in primary DLBCLs distinguishes between the activated B-cell phenotype (ABC) (higher expression of miR-155), than in the germinal center B-cell-like phenotype (GCB) (lower expression of miR-155) (Chen and Meister, 2005; Lawrie, 2007). Since, the 5-year survival rates of the ABC and the GCB subtypes of DLBCL are 30% and 59%, respectively (Kovanen et al., 2003), miR-155 expression in DLBCL has a prognostic value. A correlation between miR-155 and NFkB expression was found in DLBCL cell lines and patients (Abu-Elnaeel et al., 2008). In addition to miR-155, high levels of miR-21 and miR-221 are also associated with ABC-DLBCL and severe prognosis (de Yebenes and Ramiro, 2010). It would be interesting to investigate whether the expression of circulating miR-155 correlates with the expression of this miRNA in primary DLBCL, since it would indicate that miR-155 is a diagnostic biomarkers not only to put the diagnosis of DLBCL, but also of subtype of DLBCL.

Prognostic biomarkers
In DLBCL, increased serum levels of miR-21 are associated with a longer relapse-free survival (Lawrie, 2008), indicating that circulating miR-21 harbors prognostic implications in patients affected by DLBCL. Overall, miRNAs can be detected in body fluids and increasing evidence shows that their expression in these fluids allows the diagnosis of cancer histotype and, in some cases histologic subtype. Finally, specific signatures of de-regulated miRNAs in body fluids harbor prognostic implications. These discoveries cast a new light on the translational implications of research in the miRNA field, by suggesting that these non-coding RNAs could be detected non-invasively and provide key diagnostic and prognostic clinical information.

miRNAs in invasion, angiogenesis and metastasis

In the last few years several studies have pointed out a critical role of miRNAs in tumor angiogenesis and metastasis. By regulating these processes miRNAs have emerged as crucial players, thus allowing primary tumor cells to invade adjacent tissues and reach through the systemic circulation distant sites in which they can finally proliferate as secondary tumors. Depending on their role in the modulation of these processes, miRNAs can be subdivided into two groups: the anti-angiogenic and the pro-angiogenic ones.

Poliseno et al. demonstrated that the miR-221/miR-222 family has anti-angiogenic properties as it inhibits the angiogenic activity of stem cell factor SCF by targeting its receptor c-KIT in endothelial cells (Poliseno et al., 2006).

Since miR-21 plays a crucial role in cancer progression Sabatel et al. pondered whether it could also be involved in angiogenesis (Sabatel et al., 2011). Their in vitro and in vivo study revealed that miR-21 is a negative regulator of endothelial cell migration and tubulogenesis. Angiogenesis inhibition would occur through the targeting of RhoB, a small GTPase which is responsible for the assembly of actin stress fibers (Aspenstrom et al., 2004). However, it seems that miR-21 has a dual role in the regulation of angiogenesis. Liu et al. in fact found that the overexpression of miR-21 in prostate cancer cell line increases the expression of HIF-1α and VEGF through the AKT and ERK pathway, thus acting as a pro-angiogenic miRNA (Ayala de la Pena et al., 2011). Other miRNAs are known to be positive regulators for angiogenesis. For example, in vascular endothelial cells miR-130a downregulates the expression of the antiangiogenic homeobox genes HOXAS and GAX in response to mitogens, proangiogenic and proinflammatory factors (Aumiller and For stemann, 2008).

By using in vitro and in vivo studies Fang et al. found that miR-93 promotes angiogenesis and tumor growth by suppressing integrin-b8 expression and enhancing endothelial activity (Fang et al., 2011). Indeed this miRNA induces blood vessels formation, cell proliferation and migration by targeting the cell death-inducing antigen integrin-b8. The authors cannot exclude that miR-93 may also target other genes involved in tumorigenesis and angiogenesis. Also, the miR-17-92 cluster promotes angiogenesis by inhibiting the expression of antiangiogenic protein thrompospodin-1 (TSP1) and connective tissue growth factor (CTGF) (Dews et al., 2006); miR-378 overexpression in glioblastoma cell line U87 enhanced angiogenesis and tumor growth through its targeting of tumor suppressor proteins SUFU and FUS-1 (Barakat et al., 2007); miR-296 is highly expressed in primary human brain microvascular endothelial cells and contributes to angiogenesis by directly targeting the hepatocyte growth factor-regulated tyrosine kinase substrate (HGS) mRNA, leading to decreased levels of HGS and thereby reducing HGS-mediated degradation of the growth factor receptors VEGFR2 and PDGFR-b (Gabriely et al., 2008).

Also in the regulation of the metastatic process miRNAs can be divided into two categories: pro-metastatic (such as miR-340, miR-92a, miR-10b, miR-
373/520c) or anti-metastatic (such as miR-101, miR-34a, miR-126, miR-148a, miR-335) ones.

In breast cancer reduced miR-340 expression is associate with tumor cell migration, invasion and poor prognosis (Dong et al., 2011).

Of the six mature miRNAs produced by the miR-17-92a cluster, miR-92a is involved in the metastatization process. It has been reported that miR-92a is highly expressed in tumor tissue from ESCC (Esophageal Squamous Cell Carcinoma) patients (Cai et al., 2008). Chen et al. verified whether there is a correlation between the relative expression of miR-92a in tumor and normal tissues and lymph node metastasis in ESCC patients. Not only they found that miR-92a promotes ESCC cell migration and invasion through the inhibition (by direct targeting) of CDH1, which is known to mediate cell-to-cell adhesion, but also that ESCC patients with up-regulated miR-92a are prone to lymph node metastasis and poor prognosis (Bao et al., 2011).

In 2007, Ma et al. reported that miR-10b is highly expressed in metastatic breast cancer cells, when compared with non-metastatic cells. However, when overexpressed in the latter it promotes robust invasion and metastasis. Induced by the transcription factor Twist, miR-10 inhibits the translation of the messenger RNA encoding HOXD10 (homeobox D10), thus increasing the expression of the pro-metastatic gene RHOC and leading to tumor invasion and metastasis (Derby et al., 2007).

Through the transduction of a non-metastatic breast cancer cell line with a miRNA expression library Huang et al. studied which miRNAs could allow the cells to migrate. MiR-373 and miR-520c were found to promote cell invasion and metastasis both in vitro and in vivo through the inhibition of the expression of CD44, a protein involved in cell adhesion (Abdurakhmonov et al., 2008).

As previously reported, miRNAs are known also to have an anti-metastatic role. One of them is miR-101, whose expression decreases during prostate cancer progression, as described by Varambally et al. (Varambally et al., 2008). The authors showed that during this process there’s a negative correlation between the expression of miR-101 and EZH2, a mammalian histone methyltransferase overexpressed in solid tumors (Varambally et al., 2002) and involved in the epigenetic silencing (Yu et al., 2007; Cao et al., 2008) of genes responsible for tumor invasion and metastasis. By performing experiments based on computational analysis the authors showed also that miR-101 targets EZH2. Loss of miR-101, paralleled by increased levels of EZH2 in the tumor, leads to dysregulation of epigenetic pathways and cancer progression.

Another miRNA typically downregulated in tumors (colorectal cancer (Tazawa et al., 2007), pancreatic cancer (Chang et al., 2007), and neuroblastoma (Welch et al., 2007)) is miR-34a. Li et al. observed that in hepatocellular carcinoma miR-34a is also down-regulated (Li et al., 2009) and its expression is inversely correlated with that of the receptor for the hepatocyte growth factor c-MET (Leelawat et al., 2006), involved in cell invasion and metastasis. In their study the Authors demonstrated that miR-34a targets c-MET when ectopically expressed in Hep-G2 cells and observed reduced cell scattering, migration and invasion.

Crk (v-crk sarcoma virus CT 10 oncogene homolog) is a protein that regulates cell motility, differentiation and adhesion (Kobashigawa et al., 2007). High expression levels of this protein are found in several human tumors such as breast, ovarian, lung, brain, stomach and chondrosarcoma (Wang et al., 2007) and knock down of Crk decreases cell migration and invasion (Rodrigues et al., 2005; Wang et al., 2007). Crawford et al. showed that Crk is a functional target of miR-126 in NSCLC tumors and that overexpression of miR-126 induces a decrease in adhesion, migration and invasion (Crawford et al., 2008).

Finally, the list of anti-metastatic miRNAs includes miR-206 and miR-335. In a manuscript published in 2008 Tavazoie and coworkers took under consideration a set of miRNAs whose expression was lost in human breast cancer cells (Tavazoie et al., 2008). Among these they considered miR-206 and miR-335. By restoring their expression through retroviral transduction they found that the ability of these cells to migrate to the lung was lost. MiR-335 exerts its anti-metastatic role by targeting PTPRN2 (receptor-type tyrosine protein phosphatase) (Varadi et al., 2005), MERTK (the c-Mer tyrosine kinase) (Graham et al., 1995), SOX4 (SRY-box containing transcription factor), the progenitor cell transcription factor (van de Wetering et al., 1993; Hoser et al., 2007) and TNC (tenascin C) (Ilunga et al., 2004), which is an extracellular component of the matrix.

**Therapeutic implications of miRNAs in oncology**

The involvement of miRNAs in different aspects of human carcinogenesis, such as cell proliferation, apoptosis, differentiation, angiogenesis, motility and metastasis, has raised the question whether reverting these aberrations of the miRNome can be effectively used for therapeutic purposes. Preclinical data encourage this hypothesis and provide the biological rationale for clinical studies in this direction. Re-expression of miRNAs down-regulated in cancer (e.g. miR-15a and miR-16 in BCL2 positive CLL) and/or silencing of miRNAs up-regulated in the tumor (e.g. miR-155 in lung cancer) may lead to cancer cell apoptosis and exert a therapeutic effect. Before this becomes a reality in patients though, several issues need to be solved. First, there is a need to know the full spectrum of targets and effects that a given miRNA has on a given genome. It has been estimated that a single miRNA cluster (namely, the miR-15a/16-1 cluster) is
able to affect, directly and indirectly, the expression of about 14% of the whole human genome (Calin et al., 2008). Also it is clear that each miRNA is able to target both OGs and TSGs, and that the phenotype induced by the external manipulation of a miRNA is the result of this combined targeting effect on several genes. Therefore, one of the goals of the preclinical research is to fully clarify this aspect before any clinical application can even be taken into consideration. Secondly, it needs to be established how can we reach a tumor-specific delivery of the miRNAs of interest? This question is more general, and involves the whole field of gene therapy, being not limited to the research on miRNAs. The advent of nanoparticles, able to target tumor-specific antigens hopefully will address this concern and allow tumor specificity. Another aspect of relevance consists in determining how the modulation of miRNA expression can integrate the existing anti-cancer therapies (chemo-, radio-, hormonotherapy)? Interestingly, some studies have been published showing that miRNAs can restore sensitivity to current therapeutic options to which the tumors became resistant, and this encourages a certain optimism on therapeutic options to which the tumors became resistant, and this encourages a certain optimism for the years to come, in which the existing treatments (the number of published studies on this regard is still relatively small to allow any safe conclusion). Nonetheless, despite there seems to be still a lot of work ahead, it is promising that in such a relatively small amount of time, from the discovery of their involvement in human cancer, till today so much has been discovered about miRNAs and cancer. The effort devoted by the scientific community in this research field is unprecedented, allowing a certain optimism for the years to come, in which the introduction of these ncRNAs in the clinical practice seems about to become a realistic option.

Conclusion

The involvement of miRNAs in human cancer development and progression has been proven without any doubt by several studies. Other aspects of miRNA research are still under development, such as their role as molecular biomarkers (the published studies still suffer in most cases from a limited number of patients, which questions the statistical power of certain results), the identification of the full spectrum of targets of a given miRNA (in particular, there is a need to critically interpret the plethora of the identified targets in light of the specific genome in which the effect is observed, and in relation to the other identified and validated targets of that same miRNA), and their interaction with the existing treatments (the number of published studies on this regard is still relatively small to allow any safe conclusion). Nonetheless, despite there seems to be still a lot of work ahead, it is promising that in such a relatively small amount of time, from the discovery of their involvement in human cancer, till today so much has been discovered about miRNAs and cancer. The effort devoted by the scientific community in this research field is unprecedented, allowing a certain optimism for the years to come, in which the introduction of these ncRNAs in the clinical practice seems about to become a realistic option.

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MicroRNAs and Cancer

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Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycytemic myelofibrosis

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Clinics

Age and sex
66 years old male patient.

Previous history
No preleukemia. No previous malignancy. No inborn condition of note.

Organomegaly
Hepatomegaly (enlarged liver (+ 20 cm)), splenomegaly, no enlarged lymph nodes, no central nervous system involvement.

Blood

WBC : 46 X 10^9/l
HB : 8.5 g/dl
Platelets : 239 X 10^9/l
Blasts : 15%
Bone marrow : 25%

Cyto-Pathology Classification

Cytology: NA
Immunophenotype: NA
Rearranged Ig Tcr: NA
Pathology: NA
Electron microscopy: NA

Diagnosis
Polycythemia vera. Myelofibrosis: hypocellular bone marrow with marked increase in reticulin fibres. AML M2.

Survival

Date of diagnosis: 01-1980

Treatment

Complete remission: no (March-November 2009: complete hematological remission; molecular remission not reached (JAK-2 positivity in June 2009))

Treatment related death: no

Status: Death. Last follow up: 11-2010 (due to gastrointestinal hemorrhage).

Survival: nearly 30 years.

Karyotype

Sample: Bone marrow biopsy in Dec. 2008
Culture time: 24 and 48 h.

Bandings: Cytogenetic analysis performed in QFQ banding; band level: 400.

Results
46,XY, +9,der(9;18)(p10;q10) in 25/25 cells scored.
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycythemic myelofibrosis

Cambosu F, et al.

Atlas Genet Cytogenet Oncol Haematol. 2012; 16(1)

Polycythemia Vera (PV) is a clonal myeloproliferative disorder characterized by excessive erythrocyte production, which may evolve into myelofibrosis and acute myeloid leukemia. Transformation to myelofibrosis occurs in 15-20% of cases and leukemic transformation in 5-10% of patients. The median survival time is 8-11 years and the median age at diagnosis is over 60 years. Normal karyotype is present at diagnosis in the majority of patients, while during transformation several acquired chromosome anomalies are present as trisomy 9 and gains in 9p.

The activating JAK2 V617F mutation, present in the majority of patients with PV, seems to have a primary role in the pathogenesis of myeloproliferative neoplasms. The JAK2 gene maps to 9p24, so patients carrying gains of 9p have an extra copy of the gene, in its normal or mutated form, leading to a gain of function.

The rearrangement here reported, der(9;18)(p10;q10), is rarely detected in patients with PV, myelofibrosis, essential thrombocythemia and therapy-related AML. Some authors suggest that the simultaneous presence of both JAK2 V617F mutation and this rearrangement could define a subgroup of PV patients with the proliferative phenotype of the disease, at high risk of transformation into postpolycythemic myelofibrosis and potentially acute myeloid leukemia.

We describe a new case of der(9;18)(p10;q10) detected in a patient with AML evolved from post-polycythemic myelofibrosis. The patient was diagnosed with PV in 1980 and died in 2010. He was in good health for several years after diagnosis with bleeding treatment and low dose aspirin, then he showed a progressive worsening of anemia with liver enlargement and splenomegaly. In February 2008 the diagnosis was of myelofibrosis post PV in progression. In December 2008, when the leukemic transformation was evident, the cytogenetic analysis on bone marrow aspirate found the unbalanced translocation leading to der(9;18)(p10;q10), with trisomy of the short arms of chromosome 9 and monosomy of the short arms of chromosome 18. FISH experiments with specific alphoid centromeric probes for chromosome 9 and 18 showed both positive signals on the der(9). Subsequent molecular analysis detected the presence of the JAK2 V617F mutation.

The patient here reported had a classical evolution of the disease, after a very long polycythemic phase with a noteworthy survival time likely correlated to the young age of the patient when PV occurred. Because of the absence of cytogenetic results at diagnosis and during the polycythemic phase, we cannot fully evaluate the significance of der(9;18)(p10;q10) in the natural history of the disease before its evolution. Future reports could make clear this not negligible aspect.

Comments

Probes: whole-chromosome painting probes (wcp) and centromeric (CEP) probes of chromosomes 9 (9p11-q11 alpha satellite DNA) and 18 (D18Z1) (Abbott Molecular/Vysis).
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycythemic myelofibrosis

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Weird animal genomes and sex chromosome evolution

Jenny Graves
La Trobe University, Melbourne, Australia (JG) (Paper co-edited with the European Cytogeneticists Association)

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Weird animal genomes and sex chromosome evolution

Jenny Graves
La Trobe University, Melbourne, Australia

Genomes of distantly related mammals, other vertebrates
Sex chromosome origins, evolution, fate
Evolution of X and Y genes

Embryonic diapause: blastocyst goes into suspended animation for up to 11 months.
Premature birth of underdeveloped Young: limb, organ development still going on. Provides opportunities for observation and manipulation of development that are impossible in mouse.

Lactation complex: big changes in milk composition between newborn and 3 months pouch young. Premmies? Control?

There are 26 species of kangaroo.
We chose the tammar wallaby as our model kangaroo. Small, easy to handle, most of the classic work on marsupial physiology is done on this species.
Inter-island crosses like *M. musculus* x *M. spretus* because they are very different.
- Lots of markers: microsatellite (variable numbers of repeats).
- Have loads of phenotypic differences including in reproductive characters like diapausas.
Mono and tammar differ by about 10 interchromosomal rearrangements.

**Carnivorous marsupials (Dasyuridae)**

Tasmanian tiger *Thylacine cynocephalus*

*Dunnart* *Sminthopsis crassicaudata*

*Extinct 1936*

---

**Tasmanian Devil**

Facial Tumour Disease: Tumour cells transmitted by biting

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Atlas Genet Cytogenet Oncol Haematol. 2012; 16(1) 76
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycytemic myelofibrosis

- Sequence all vertebrates (66,000 species)
- Both sexes!
- Map at least one species in group

Genome 10K

Sex and sex chromosomes

Sex determination

<table>
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<tbody>
<tr>
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identity of the testis determining gene?

Jamie Foster, Andrew Sinclair

ZFY is in the wrong place
ZFY is the wrong gene
SRY is the right gene
SOX3 ancestor of SRY

Genes on the X and Y chromosomes

- PAR: Shared by X and Y, Contains 18 genes
- X: 1669 genes, Many different functions, Well conserved in mammals
- Y: Only 27 genes specific to Y, Male-specific functions, Poorly conserved

Sex chromosomes

- Problems at meiosis
- Dosage problems
- Sex-linked diseases
- Sex-reversal syndromes

Why so weird?

- so they work optimally
- evolutionary accident?

Dumb design!

XY evolution

- Once the X and Y were an ordinary pair
- proto-XY: One partner acquires a male-determining gene
- Other male-advantage genes accumulate - recombination suppressed
- Y degraded by deletion, mutation

And degraded and degraded

And could even disappear

The Y is a degraded X

Degeneration of the sex-specific element (Y or W) from an original autosome, with examples of animal species which exhibit this level of differentiation.
Evidence
Human X-Y homology

Y genes in different mammals

Suggests progressive gene loss from Y

Origin of human sex chromosomes

Reptiles and birds
Monotrems
Marsupials
Placental?

Amphibians
Fish

X conservation in placental mammals

Evolutionary blocks on the X
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycythemic myelofibrosis

**Genes on kangaroo Y**
- Microdissect Y, make DNA
- Use to screen BACs
- Map
- Sequence

- 12 new genes
- All on tiny Yp
- 11 have copies on X

**Different Y genes, same rules**

**Relationship between X and Y**

**Origin of human sex chromosomes**

- Reptiles and birds
- Monotrems
- Marsupials
- Placentals
- XY
- XY

**Bird sex**

- male
  - Z
  - Z
- female
  - Z
  - W

**What is the bird sex-determining gene?**

- Male
  - ZZ
  - Z
  - Z

- Female
  - Z
  - W

DMRT1 on Z but not W
Knockdown → ZZ female

Need two doses to make enough male-determining product

**Dose-dependent sex determination**

**Distantly related birds?**

- Emu
  - ZZ: ZW

**Comparative mapping**

- bird ZW = human 9.5
- mammal XY = bird 4.1
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Cambosu F, et al.

Evolution of sex chromosomes

- frogs
- many fish
- turtles
- alligators
- humans
- mice
- kangaroos

Sex in dragons

- microdissect Z,W
- use ZW DNA to screen BAC library
- sequence BACs
- identify orthologous region in chick genome
- read off candidate sex determining genes

Ezaz, Georges, Sarre

Snake ZZ/ZW

# bird ZW

Arthur Georges, U Canberra

Sex chromosome variation in reptiles

Gekko Z= bird Z!!

Bird ZW is ancestral?

Origin of human sex chromosomes

Reptiles and birds

Monotremes

Marsupials

Placentals

Amphibians

Fish

Tetrapods

Marine turtles

No sex chromosomes

Temperature-dependent sex (TSD)

Turtle chromosomes

Painted with chick Z

Platypus sex chromosomes?
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycythemic myelofibrosis

Genes on platypus sex chromosomes
- No homology to human X
- Homology to chicken Z

Origin of human sex chromosomes
- Repiles and birds: TSD, XY, ZW
- Monotremes: XXYXXX
- Marsupials: XY
- Placentals: XY
- Amphibians: ZW
- Fish: ZW

Evolution of vertebrate sex determination
- TSD turtle
- Snakes: XY
- Birds: XY
- Platypus: ZW
- Kangaroo: XXX
- Human: XX

Evolution of the X
- Lots of genes
- Many different functions
- Conserved in mammals (because of XCI?)
Unbalanced rearrangement der(9;18)(p10;q10) and JAK2 V617F mutation in a patient with AML following post-polycytemic myelofibrosis

Cambosu F, et al.

Atlas Genet Cytogenet Oncol Haematol. 2012; 16(1)

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Nice examples of neofunctionalization (SRY, RBMY) and subfunctionalization.
Hope for men! 
Japanese spiny rats have survived loss of Y

Y loss in XO spiny rat
Could it happen in humans?

War of the sex genes
Infertility
-> species divergence

New hominin species?

**Conclusions**

Vertebrate genome is very conserved
Different regions may become sex chromosomes
Biased gene content, degeneration

**This article should be referenced as such:**

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