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Gene Section
Review

TP53 (Tumour protein p53 (Li-Fraumeni syndrome))

Thierry Soussi

Sorbonne Université, UPMC Univ Paris 06, F- 75005 Paris, France; INSERM, U1138, Centre de Recherche des Cordeliers, Paris, France; Department of Oncology-Pathology, Karolinska Institutet, Cancer Center Karolinska (CCK) R8:04, Stockholm SE-171 76, Sweden. thierry.soussi@ki.se

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Abstract

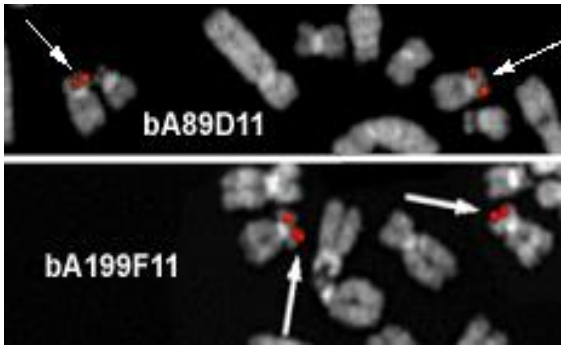
Review on TP53, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
TP53; TP53 pathway; stress; homeostasis; apoptosis; growth arrest; senescence; DNA repair; warburg effect, autophagy; stem cell maintenance; skin cancer; melanoma; lung cancer; breast cancer; colorectal cancer; prostate cancer; gastric cancer; hepatocellular carcinoma, cervical cancer; esophageal carcinoma; bladder cancer, pancreatic cancer; head and neck squamous cell carcinoma; ovarian carcinoma; osteosarcoma; glioblastoma; chronic lymphocytic leukaemia; follicular lymphoma; diffuse large b-cell lymphoma; burkitt lymphoma; myelodysplastic syndromes; acute myeloid leukaemia; Li-Fraumeni syndrome.

Identity

Other names: BCC7, LFS1, P53, TRP53
HGNC (Hugo): TP53

Location: 17p13.1
Location (base pair): HG18 (7536593 to 7503822); HG 19 (7595868 to 7563097); HG38 (7692550 to 7659779)



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics

Note
For complete information and data, see: **the novel TP53 website** and **UMD TP53 Mutation Database**

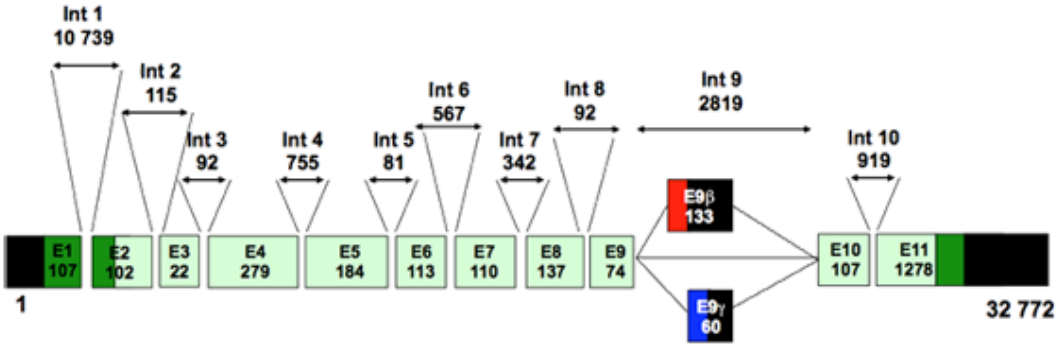


Diagram of the TP53 gene. Exons are represented by boxes with numbers and sizes inside. Intron sizes (not drawn to scale) are also indicated. Translated exons for the canonical TP53 protein (393 aa) are shown in light green, in red for isoforms beta and in blue for isoforms gamma.

DNA/RNA

Description

The TP53 gene spans a region of 32,772 bp. The protypical TP53 gene is composed of 11 exons. Two novel alternatively spliced exons localized in intron 9 have been identified (exons 9β and 9γ).

To solve some confusing situation on TP53 nomenclature, an international consortium has joined forces with the Locus Reference Genomic (LRG) consortium to provide a stable reference sequence and a coordinate system for permanent and unambiguous reporting of disease-causing variants in genes related to any pathology. The TP53 nomenclature can be reached at http://ftp.ebi.ac.uk/pub/databases/lrgex/LRG_321.xml.

Transcription

The transcription of the TP53 is highly complex and can vary between tissue and/or cellular context. Different p53 mRNA variants are expressed through the use of alternative splicing and an internal promoter in intron 4.

Protein

Description

At least, 12 TP53 isoforms are expressed but the full-length protein (TP53 p1 or TP53α is always the major species detected in every tissue. The p1 protein contains from N-term to C-term, two transactivationg domains (TAD1, 1-40 and TAD2, 41-61), a proline rich domain (63-97), a specific DNA binding domain (102-292), 3 nuclear localization signals (305-322), a tetramerization domain that includes a nuclear export signal (325-355) and a negative regulatory domain (360-393).

Shorter C-terminal TP53 isoforms do not contain either the tetramerization domain or the negative regulatory domain. Shorter N-terminal TP53 isoforms do not contain TAD1 (Δ40 TP53 isoforms), TAD1, TAD2 and the proline rich domain (Δ133) or TAD1, TAD2, the proline rich domain and part of the DNA binding domain (Δ160)

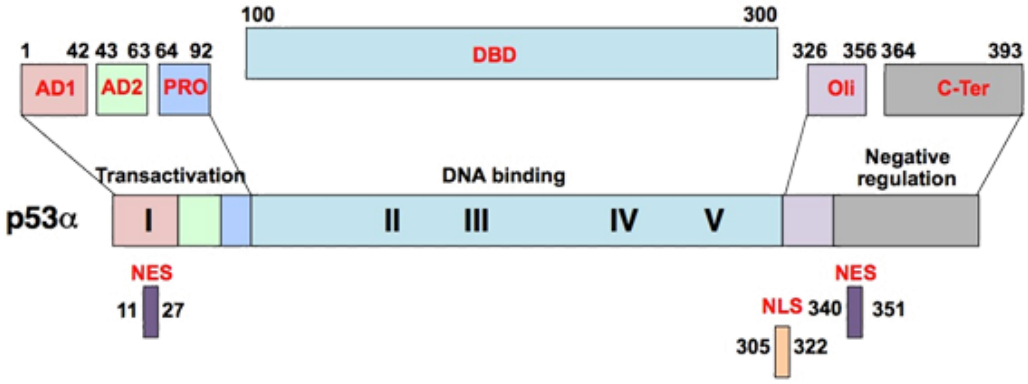
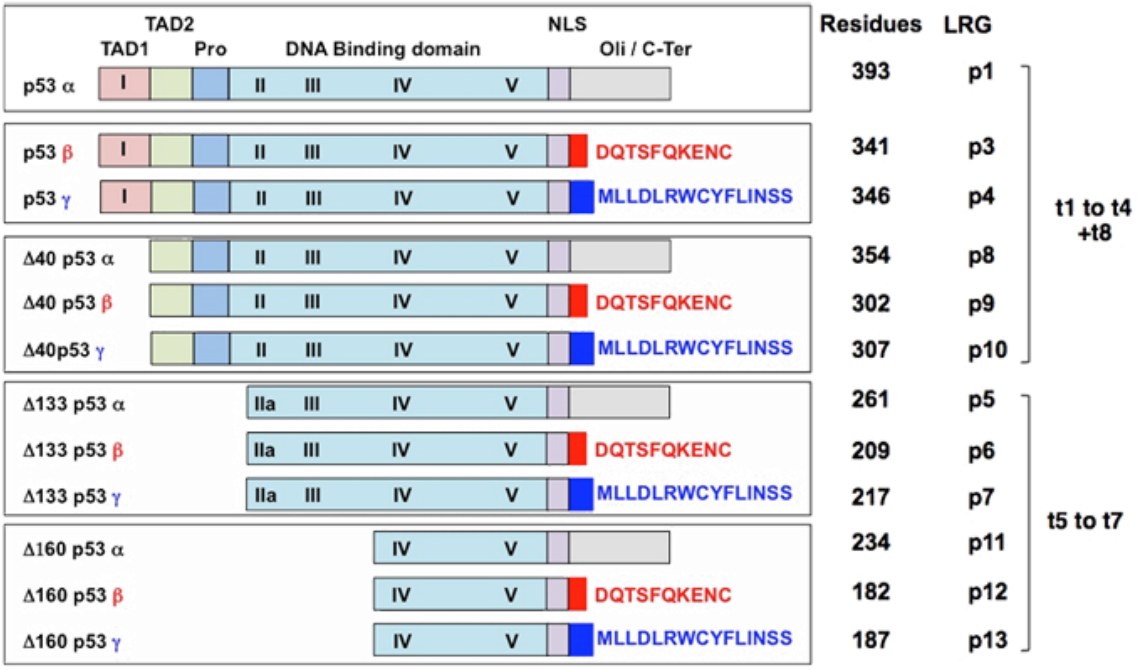
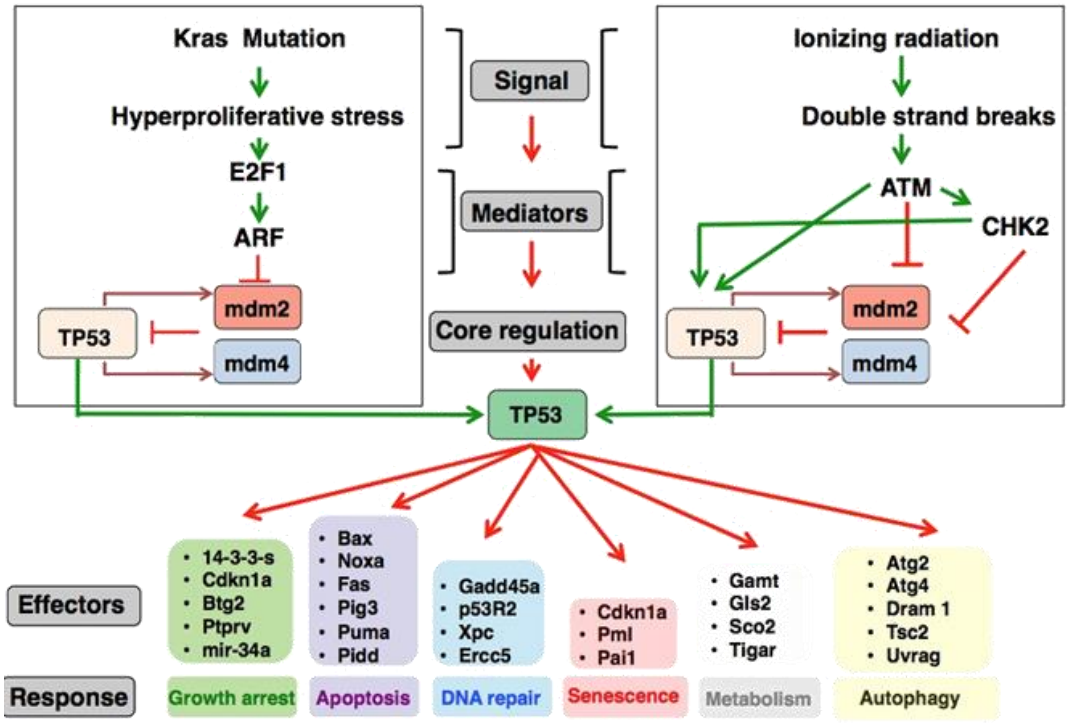


Diagram of TP53α, the major TP53 protein expressed in normal cells. TAD1: transactivation domain 1; TAD2: transactivation domain 2; Pro: proline- rich domain; DBD: DNA binding domain; NES: nuclear exclusion signal: NLS: nuclear localization signal; Oli: oligomerization domain; C-ter: carboxy-terminus domain. I to V correspond to the five highly conserved domains of the protein.



Domains in the various TP53 isoforms. TAD1: transactivation domain 1; TAD2: transactivation domain 2; Pro: proline- rich domain; NES: nuclear exclusion signal: NLS: nuclear localization signal; Oli: oligomerization do- main; C-ter: carboxy-terminus domain.
The LRG nomenclature used for TP53 protein (p1 to p13) and RNA (t1 to t8) is also shown on the right.



Pathway i) the stress signals activate the pathway; ii) the upstream mediators detect and interpret the upstream signals; iii) the core regulation of TP53 is disrupted leading to TP53 accumulation and activation; iv) the downstream events, mainly transcriptional activation or protein-protein interaction v) The final outcome.

Response	Gene
Apoptosis	APAF1 ; BAX - FAS - - MIR34A - PMAIP1 ; TP53AIP1 - PERP -PIDD1 - TP53I3 - BBC3 - SIVA1 ; TNFS10
Growth arrest	YWHAZ ; BTG2 ; CDKN1A - GADD45A ; MIR34A ; MIR34B / MIR34C ; Prl13; PTPRVP ; RPRM
Senescence	CDKN1A ; SERPINE1 ; PML l
DNA repair	Dbd2; ERCC5 ; FANCC ; GADD45A ; XRCC5 ; MGMT ; MLH1 ; MSH2 ; RRM2B ; PAPD7 ; XPC
Metabolism / Anti oxydant	ADORA2B ; ALDH4A1 ; PRKAB1 ; GAMT ; GLS2 ; SLC2A1 (-);SLC2A4 (-);GPX1 ; IGFBP3 ; LPIN1 ; PARK2 ; VCAN (-); PRKAB1 ID:44100 ; PRKAB2 ; ten; SCO1 ; SESN1 ; SESN2 ; TIGAR ; TP53INP1 ;
Autophagy	ATG10 ; ATG2B ; ATG4A ; ATG4C ; ATG7 ; CTSD ; DDIT4 ; DRAM1 ; RBFOX3 ; LAPTM4A ; STK11 ; PIK3R3 ; PRKAG2 ; BBC3 ; ACD ; TSC2 ; ULK1 ; ULK2 ; UVRAG ; VAMP4 ; VMP1
Tumour micro environment	ADGRB1 ; CX3CL1 ; ICAM1 ; IRF9 ; ISG15 ; SERPINB5 ; CCL2 ; NCF2 ; SERPINE1 ; TLR1 - TLR10 ; PRSS55 ; ULBP1 ; ULBP2
Invasion metastasis	CDKN1A ; MIR34A ; MIR200C
Stem cell biology	CDKN1A ; MIR145 ; MIR34A ; MIR34B / MIR34C ; NOTCH1
TP53 regulation	CARD16 ; MDM2 , PIRH-2; TP63 , TP73
Unknown*	APOBEC3H; HRAS ; TNFAIP8 ; ZMAT3

This list is not exhaustive. Several TP53 responses overlap and include identical genes. Adapted from Bieging et al. with modifications.
* Genes induced by TP53 without any clear relation to a specific pathway

TP53 is modified by numerous post-translational modifications phosphorylation, acetylation, ubiquitination, sumoylation, neddylation, methylation, ADP ribosylation, and glycosylation. Acetylation of multiple residues is essential for TP53 activation and DNA transcriptional activity.

Function

The transcription factor TP53 is at the centre of a network that integrates and transmits multiple signals generated during various stress events to ensure cell and tissue homeostasis. This network also includes the two other members of the TP53 family, TP63 and TP73 as well as the two negative regulators, MDM2 and MDM4 (MDMX).
The p53 response can be conveniently divided into two sets of pathways acting upstream and downstream the core regulation of TP53.
The upstream pathways (stress signal detection and integration)
Multiple type of stress such as DNA damage, hypoxia, nucleotides pool depletion, viral infection, oncogene activation or oxidative stress can elicit a TP53 response. For each stress, a different panel of mediators is recruited.
In most cases, the goal of this step is the disruption of the TP53-MDM2 interaction leading to an accumulation and an activation of the TP53 protein.
Subsequent post translational modifications (phosphorylation and acetylation principally) modulate TP53 activity depending of the type and the intensity of the damage and the cellular context.
For DNA damage, the ATM and CHEK2 kinase will phosphorylate TP53, MDM2 and MDM4 to release the negative regulation of the regulatory proteins.
For ribosomal stress, free ribosomal proteins will bind and sequester MDM2, relieving its inhibitory
For oncogene activation (hyperproliferative stress), the P16-ARF protein will sequester MDM2 in the nucleolus and relieve its inhibitory activity.
The core regulation of TP53
In normal tissues, TP53 protein levels are maintained at a very low level predominantly by the action of specific E3 ligases such as MDM2 and the ubiquitin proteosome pathway.
Other E3 ligases such as Pirrh2, RFWD2 or TRIM24 target TP53 and able to regulate its stability.
TP53 translation is also highly regulated and enhanced after various types of stress.
TP53 mRNA includes two Internal Ribosome Entry Sites (IRESs) elements.
The first IRES is located in the 5'UTR of the full-length isoform, the second is located into the protein-coding region and mediates the translation

of a ΔN-p53 isoform.

The downstream pathways (effectors activation and TP53 response)
Several thousand genes have been shown to be activated by TP53 upon various types of stress. Different sets of genes are associated with a specific response. Initially, apoptosis, growth arrest and senescence have been considered to be the main response to TP53 activation.
More recent studies have emphasized the importance of TP53 in other cellular responses such as DNA repair, metabolism and regulation of the Warburg effect, autophagy and regulation of stemm cell maintenance.
Although growth arrest, apoptosis and senescence were originally associated with the tumour suppressor activity of TP53, their importance has recently been challenged. Several mouse models defective for these three T53 activities lack any predisposition to develop neoplasia.
TP53 also has cytoplasmic transcription-independent functions (apoptosis and autophagy) via a direct interaction with pro- and anti-apoptotic factors in mitochondria.

Expression

Widely expressed.

Localisation

Nucleus

Mutations

Germinal

Germline TP53 mutations are associated with Li-Fraumeni (LFS) and Li-Fraumeni-like syndromes (LFL), characterized by a familial clustering of tumours, with a predominance of soft tissue and bone sarcomas, breast cancers, brain tumours, and adrenocortical carcinomas, diagnosed before the age of 45 years.
TP53 germline mutations have also been observed in families at high risk of breast cancer, albeit at very low frequency.
A founder mutation TP53 (NG_017013.2:g.21852G#62A, p.R337H) is detected in 0.3% of the general population in southern Brazil. This mutation is associated with an increased risk of childhood adrenal cortical carcinoma (ACC) but is also common in Brazilian LFS/LFL families.
The frequency of TP53 de novo germline mutation ranges between 7 and 20%.

Somatic

Mutation of the TP53 gene can be found in 50% of human cancer.
More than 80% of TP53 mutations are missense mutations that lead to the synthesis of a stable oncogenic protein that accumulates in the nucleus of tumour cells. The frequency of TP53 alterations range from less than 5% in cervical carcinoma to 90% in ovarian carcinoma or Small Cell Lung Cancer (SCLC) but these numbers must be taken with caution due to several factors such as the subtype of the cancer (lung or breast cancer), the stage of the tumour (prostate carcinoma or chronic lymphocytic leukaemia) and exogenous features such as viral or bacterial infection.
Two international consortiums have reported the sequencing of more than 10.000 tumour genomes and confirmed that the TP53 gene is the most frequently mutated gene in human cancer. TP53 mutations are strongly associated with tumours with high chromosomal instability.
Cancer specific driver genes can be noticed: APC in colorectal carcinoma (violet); VHL in kidney cancer (green) or PTEN and PIK3CA in endometrial carcinoma (green and red)
Molecular epidemiology studies demonstrate a link between exposure to various types of carcinogens, specific mutational events in the TP53 gene and the development of specific cancers.
Lung cancer
TP53 mutations in lung cancer are mostly GC to TA transversions, with a rate of transition mutations lower than in other cancers. There is a strong correlation between the frequency of these GC to TA transversions and lifetime cigarette smoking. This high frequency of GC to TA transversions has not been detected for other cancers such as colon, breast, ovary or brain cancer, which are not directly associated with smoking. This observation is compatible with the role of exogenous carcinogens such as benzo(a)pyrene in lung cancer. After metabolic activation, one of the derivative products of benzo(a)pyrene, the prime carcinogen in cigarette smoke, binds predominantly to guanine and gives rise to specific G-C to T-A transversions. Exposure of cells to benzo(a)pyrene lead to the formation of adducts at codon 157, 248 and 273 in the p53 gene. These positions are the major mutational hotspots in human lung cancer but not in other cancers. The p53 gene is one of the targets of carcinogens found in tobacco.
Liver cancer
There is a strong association between infection with hepatitis B virus and hepatocellular carcinoma. Aflatoxin B1 has been considered to be a significant etiological factor for liver cancer in Western Africa and Asia. Aflatoxins are compounds produced by fungal strains (such as Aspergillus flavus for aflatoxins B1) that are known food contaminants in these countries. Aflatoxins are highly carcinogenic in experimental animals, producing liver tumours in newborn mice, rats, fish, ducks and monkeys.
Worldwide epidemiological studies showed that a specific mutation at codon 249 (c.747G>T, p.R249S) is specifically found in liver cancer from countries in which food was contaminated by

aflatoxin B1. In countries which do not consume contaminated food (including Europe and the USA), TP53 mutations are scattered along the central part of p53, as for the other types of cancer. In vitro and in vivo analysis showed a specific binding of aflatoxin B1 to codon 249 of the TP53 gene.

Bladder cancer

Aristolochic acid (AA), a common ingredient in many Chinese herbs, is a powerful nephrotoxin and human carcinogen associated with chronic kidney disease and upper urinary tract urothelial carcinomas including bladder cancer. AA exposure is also associated with Balkan endemic nephropathy (BEN) similarly characterized by kidney failure and a high frequency of transitional cancer of urothelial tracts including bladder, renal pelvis and ureters.

TP53 mutation from patients exposed to AA display a high frequency A:T-to-T:A transversions, a mutational signature associated with AA which forms a covalent adduct with adenine that leads to this transversion.

Skin cancer

Ultraviolet (UV) light induces specific DNA damage such as cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4)pyrimidine photoproducts (64PPs) at dipyrimidine sites, where two pyrimidine (Py) bases are juxtaposed in tandem in the nucleotide sequence of DNA. If left unrepaired, this lesion leads to specific types of mutation: base substitutions of cytosine (C) → thymine (T) at dipyrimidine sites and CC → TT tandem base substitutions. These two types of mutation are called UV signature and their detection suggests past exposure to UV. In skin cancer such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), the frequency of TP53 is high (70 to 80%) with more than 15% of tandem mutations (less than 1% for other cancer types).

Colorectal or brain cancer

The cytosine-guanine (CpG) dinucleotide is a hotspot for pathological mutations in the human genome. This hypermutability is due to its role as the major site of cytosine methylation with the attendant risk of spontaneous deamination of 5-methylcytosine (5mC) to yield C → T and G → A transitions. Most TP53 hotspots for mutations in colorectal or brain cancer are located at CpG sites with a mutation spectrum compatible with 5-methylcytosine deamination. These hotspot codons, CGN at positions 175, 248 or 273, encode arginine residues important for TP53 structure and/or activity. It is interesting to note that arginine can also be encoded by AGG and AGA that have the same frequency of usage in human but are not targeted by methylation. It has not yet been determined whether or not there is a specific selection to keep CGN in the TP53.

Implicated in

Skin cancers (non melanoma)

Disease

Non melanoma skin cancers are the most common form of cancer, globally accounting for at least 40% of human cancer. About 80% are basal-cell cancers (BCC) and 20% squamous-cell cancers (SCC). Most skin cancer cases are caused by exposure to ultraviolet radiation from the sun.

Prognosis

Patients with primary cutaneous SCC or BCC have a very good prognosis.

Oncogenesis

The hedgehog signalling pathway (HH pathway) is the primary target in BCC with mutations in PTCH1, SMO or SFU. TP53 mutations are found in 60% of BCC. In SCC, the frequency of TP53 mutation varies between 40 to 80% depending on the aggressivity of the tumour or the seuqnecing methodology. Deep sequencing allows the detection of multiple subclones with different TP53 mutations.

The pattern of TP53 mutations in skin cancer is highly related to UV exposure.

Skin cancers (Melanoma)

Disease

Case per year (thousands) 132; death per year (thousands) 31. Melanoma is a skin tumours characterized by the malignant growth of melanocytes. The incidence is continuing to increase worldwide and UV exposure is a known risk factor for melanoma. Epidemiologic data suggest that gender and genetics may influence the distribution of melanoma on the body surface and histopathologic characteristics of the lesion.

Oncogenesis

The MAPK pathway is the primary target in melanoma with mutations in BRAF1 (50%) or NRAS (20%). TP53 gene mutations are rare in melanoma (5%) but the apoptotic function of the protein is often impaired. Melanoma often loses , a cell-death effector that acts with cytochrome c and CASP9 to mediate p53-dependent apoptosis. It may contribute to the low frequency of TP53 mutations observed in this highly chemoresistant tumour type. Alteration of CDKN2A in 30% of melanoma could also contribute to TP53 deficiency.

Lung cancers

Disease

Case per year (thousands) 1,825; death per year (thousands) 1,590 (Worldwide ranks, cases / deaths: 1/1). There are 2 main types of lung cancer: about 10% to 15% are small cell lung cancer (SCLC) and 85% to 90% arenon-small cell lung cancer (NSCLC). There are several subtypes of NSCLC, Adenocarcinoma (50%), Squamous cell carcinoma (30%); Large cell carcinoma (15%) and other

(includes carcinoid and neurodendocrine tumours) (5%).

Oncogenesis

In SCLC, recent studies using Novel Generation Sequencing showed that TP53 mutations can be found in 95% of the cases. In NSCLC, the frequency of TP53 mutations varies among the subtypes. The frequency of TP53 mutations is the highest in squamous cell carcinomas (70 to 80%) and lower in adenocarcinomas (50%). Lung cancer from smokers shows a distinct, unique TP53 mutation spectrum with G to T transversions at codons 157, 158, 179, 248, and 273, which is uncommonly observed in lung cancer from non-smokers or in cancer unrelated to tobacco smoking such as colorectal or brain tumours.

Breast cancer

Disease

Case per year (thousands) 1,677; death per year (thousands) 522 (Worldwide ranks, cases / deaths: 2/5). Breast carcinoma is a heterogeneous disease with multiple subtypes defined either histologically or more recently via gene expression.

Oncogenesis

In Triple Negative Breast Cancer (TNBC, 10-15% of breast cancer with low or lack of expression of estrogen (ER) and progesterone (PR) receptors, lack of human epidermal growth factor receptor 2 (HER2) over-expression and a worse prognostic), the frequency of TP53 is high (80%).

Molecular profiling studies have identified four major subtypes of breast cancer: luminal A, luminal B, basal like, and HER2. The frequency of TP53 alteration in these subtypes ranges from 12% in luminal A, 30% in luminal B, 70% in HER2 to more than 80% in basal like. There is a partial overlap between TNBC and Basal like.

Colorectal cancers

Disease

Case per year (thousands) 1,360; death per year (thousands) 693 (Worldwide ranks, cases / deaths: 3/4). CRC is a heterogeneous disease classically divided into three sub-types

(i) Chromosomal instability (CIN) characterized by microsatellite stable tumours (MSS), loss of heterozygosity and major chromosomal changes in tumour-suppressor genes and oncogenes (60% of CRC)

(ii) The CpG island methylator phenotype (CIMP) which causes transcriptional silencing by methylation of CpG-rich regions in the promoter of tumour-suppressor genes (10 to 15% of CRC).

(iii) Microsatellite instability (MSI) is characterized by the accumulation of frame shift mutations in microsatellite sequences due to a deficiency in mismatch repair (MMR) genes (10 to 15% of CRC)

Cytogenetics

MSI tumour are generally characterized by diploid or near-diploid cells

Oncogenesis

The most frequently mutated genes in CRC are KRAS, APC and TP53.

Prostate cancer

Disease

cases per year (thousands): 1,112; deaths per year (thousands): 307 (Worldwide ranks, cases / deaths: 4/8). Prostate carcinoma is characterized by a high genetic and clinical heterogeneity with multiple subclones.

Oncogenesis

TP53 mutations are infrequent in primary disease and are mostly found in patients with metastatic disease

Gastric cancer

Disease

cases per year (thousands): 952 ; deaths per year (thousands): 723 (Worldwide ranks, cases / deaths: 5/3). Risk factors for gastric cancer include: Helicobacter pylori gastric infection, advanced age, male gender, diet including dry salted foods, atrophic gastritis, pernicious anemia, cigarette smoking, Menetrier's disease , and familial polyposis. Adenocarcinoma histology accounts for 90% to 95% of all gastric malignancies. The prognosis of patients with gastric cancer is related to tumour extent and includes both nodal involvement and direct tumour extension beyond the gastric wall. Tumour grade may also provide some prognostic information.

Oncogenesis

TP53 is the most frequently mutated gene in gastric carcinoma with a frequency ranging between 40 and 60%.

Liver cancer

Disease

cases per year (thousands): 782 ; deaths per year (thousands): 746 (Worldwide ranks, cases / deaths: 6/2). Most patients with HCC (70 to 90%) have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), Alcoholism, and nonalcoholic steatohepatitis (NASH). Additional risk factors include intake of aflatoxin-B1 contaminated food (China and West Africa), diabetes, obesity, certain hereditary conditions such as hemochromatosis, and some metabolic disorders.

Cytogenetics

Losses of 1p, 4q, 5p, 5q, 8q, 13q, 16p, 16q, and 17p in 20 to 50% of cases.

Oncogenesis

Somatic mutations in the TERT (coding for telomerase reverse transcriptase) promoter is the most frequent genetic alteration in hepatocellular carcinoma (HCC).
These mutations created a potential binding site for ETS transcription factors and are predicted to increase promoter activity and TERT transcription. Mutated genes in HCC are TP53, beta-catenin (CTNNB1) and ARIDA1. TP53 mutations are more frequent in patients associated with HBV infection compared to those associated with alcoholism.
The frequency and the pattern of TP53 mutations in HCC show a high geographical variation depending on HBV infection prevalence or aflatoxin consumption.
In areas of high aflatoxin exposure, 50% of HCC cases bear a specific AGG to AGT point mutation in codon 249 of the p53 tumour suppressor gene. A second mutation at codon 157 is also frequent albeit at lower frequency. Exposure of cells to aflatoxin B1 leads to the formation of adducts at codon 249 in the p53 gene.

Cervical cancer

Disease

Cases per year (thousands): 527 ; deaths per year (thousands): 265 (Worldwide ranks, cases / deaths: 7/10). Almost all cervical cancers are caused by HPV (human papilloma virus). There are more than 100 types of HPV, of which at least 13 are cancer-causing (also known as high-risk type) including HPV16 and 18.

Oncogenesis

The UBE3A (E6) oncoprotein produced by the high-risk type of HPV stimulates ubiquitinylation and proteasome-dependent degradation of the tumour suppressor p53 via the formation of a trimeric complex comprising E6, p53, and E6-AP. TP53 mutation is therefore very infrequent in cervical cancer.

Oesophagus cancers

Disease

Case per year (thousands) 455; death per year (thousands) 400 (worldwide ranks 8/6) There are two main types of esophageal carcinoma, squamous cell carcinoma and adenocarcinoma. Most adenocarcinomas arise in Barrett esophagus that develops in response to chronic gastroesophageal reflux.

Oncogenesis

The frequency of TP53 mutation is high in both types, ADC and SCC, and can reach 70%. TP53 mutations are an early event in ADC as it can be found in Barrett esophagus.

Bladder cancer

Disease

Case per year (thousands) 429; death per year (thousands) 165 (worldwide ranks 9/12).

Prognosis

Highly variable, according to the stage and the grade.

Cytogenetics

-9, -11 or del(11p), del(17p) and LOH at 17p, del(13q), frequent other LOH, aneuploidy, polyploidy, complex karyotypes.

Oncogenesis

TP53 mutation are found in 40 to 50% of bladder carcinoma. Three variants are particularly frequent in bladder cancer: c.853G>A; p.E285K, c.839G>C; p.R280T and c.839G>A; p.R280K.

Pancreatic cancer

Disease

Case per year (thousands) 338; death per year (thousands) 330 (worldwide ranks 12/7); Pancreatic cancers are divided into two major subtypes: adenocarcinoma (95% of cases), and rare endocrine tumours often designated as neuroendocrine tumours.

Prognosis

Pancreatic cancer is one of the most deadly of all types of cancer.

Oncogenesis

KRAS mutation is the most frequent genetic variation in pancreatic adenocarcinoma (95%) followed by TP53 mutation (60-70%) and CDKN2A deletion (50%).

Head and neck squamous cell carcinoma

Disease

Head and neck cancer encompasses malignant tumours arising within the upper aerodigestive tract. The major etiologic agents are tobacco and alcohol consumption and for some cases human papilloma virus (HPV) infection. More than 90% of head and neck cancers are squamous cell carcinomas, which originate from the mucosal surfaces of the lip and oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.

Oncogenesis

TP53 mutation can be found in about 60 to 70% of HPV positive HNSCC cancers. The frequency is lower in HPV negative tumours (less than 10%)

Ovary carcinoma

Disease

Case per year (thousands) 238; death per year (thousands) 152 (worldwide ranks 18/13). Based on histopathology, immunohistochemistry, and molecular genetic analysis, at least five main types of ovarian carcinomas are identified: high-grade serous carcinomas (HGSCs; 70%), endometrioid carcinomas (EC; 10%), clear-cell carcinomas (CCC;

10%), mucinous carcinomas (MC; 3%), and LGSC (<5%). These tumours account for 98% of ovarian carcinomas.

Oncogenesis

In HGSC, the frequency of TP53 mutation reaches 95% and is the most frequent genetic alteration in this subtype.

sarcoma

Disease

Osteosarcoma is a primary bone malignancy with a particularly high incidence rate in children and adolescents relative to other age groups.

Oncogenesis

Mutation of RB1, located at chromosome 13q14.2 and TP53 are frequent in osteosarcoma. Deletion or rearrangement of the TP53 gene can reach 20% and are not found in other cancer types.

Brain Tumours

Disease

Case per year (thousands) 256; death per year (thousands) 189 (worldwide ranks 17/11) Glioblastoma (GBM), also known as glioblastoma and grade IV astrocytoma, is the most common and most aggressive form and represent 15% of brain tumours. There are two subtypes of GBM: de novo (new or primary) and secondary. De novo tumours are the most common (90%) and are very aggressive. Secondary GBM (10%) typically start as low-grade or mid-grade astrocytoma and eventually transform into malignant, rapidly growing GBM.

Oncogenesis

TP53 mutation is an early and frequent (over 60%) event in secondary glioblastomas while it is rare in primary glioblastomas (less than 10%). Primary glioblastomas display a high frequency of mdm2 amplification which is mutually exclusive to TP53 mutations. Isocitrate dehydrogenase 1 (IDH1) mutations are frequent in secondary glioblastomas (60-70%) and seems to co-occur with TP53 mutations.

Chronic lymphocytic leukaemia (CLL)

Disease

Chronic lymphocytic leukaemia (CLL) represents the most common leukaemia in the Western world; it accounts for ~40% of all adult leukaemia's.

Prognosis

TP53 mutations are associated with a poor response to therapy.

Cytogenetics

CLL patients have acquired chromosomal abnormalities such as: deletion 13q; deletion 11q; trisomy 12 and deletion 17p

Oncogenesis

TP53 mutations are infrequent in the early phase of the disease and are mostly found in patients in progressive disease or with relapse/refractory disease.

CLL is one of the few cancers where TP53 status is used to for therapeutical decision.

Non-Hodgkin lymphoma

Disease

Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are the two most common non-Hodgkin lymphomas (NHLs).

Prognosis

TP53 mutation is an independent marker of poor prognosis in patients with diffuse large B-cell lymphoma (DLBCL) treated with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) therapy

Oncogenesis

Both FL and DLCBL are characterized by a high frequency of mutations in genes associated with chromatin modification such as KMT2D /MLL2.

Frequency of TP53 mutation in DLBCL range between 20 and 80%.

This large range is due to the heterogeneity of the various cohorts as TP53 mutations are more frequent in patients with refractory DLBCL.

Burkitt lymphoma

Disease

Burkitt lymphoma (BL) is an uncommon form of aggressive lymphoma.

Three subtypes of Burkitt lymphoma are recognized: the endemic form, occurring primarily in Africa and associated with the Epstein-Barr virus (EBV); the sporadic form, representing less than 3 % of all non-Hodgkin lymphomas (NHL); and the immunodeficiency-associated form, occurring primarily in HIV-infected patients.

Oncogenesis

BL is characterized by chromosomal translocations leading to the overexpression of myc.

The most common rearrangement is t(8;14)(q24;q32), which accounts for most cases and involve MYC and .

Other frequently mutated genes are ID3, ARID1A, SMARCA4 and TP53 which is inactivated in 40 to 50% of BL.

Myelodysplastic syndromes

Disease

Myelodysplastic syndromes (MDS) describe a heterogeneous group of bone marrow disorders that predominate in the elderly. These patients present with a dysplastic bone marrow morphology and variable cytopenias, and they have an increased risk of transformation to acute myeloid leukaemia (AML)

Oncogenesis

The frequency of TP53 mutation in MDS is low but associated with a poor prognosis.

Acute myeloid leukaemia

Disease

Acute myeloid leukemia (AML) is a biologically heterogeneous disease that can be classified into 3 distinct groups: secondary AML (s-AML) represents transformation of an antecedent diagnosis of myelodysplastic syndrome (MDS) or myelo-proliferative neoplasm (MPN), therapy-related AML (t-AML) develops as a late complication in patients with prior exposure to therapies, and de novo AML arises in the absence of an identified exposure or prodromal stem cell disorder.

Oncogenesis

The most frequently mutated gene in AML are FLT3, NPM1 and DNMT3A. The frequency of TP53 mutation does not exceed 10% in de novo AML. In t-AML or s-AML, the frequency of TP53 mutation can reach 30% and is associated with a poor prognosis.

Li-Fraumeni syndrome (LFS)

Disease

Autosomal dominant condition, cancer-prone disease, Li-Fraumeni syndrome (LFS) is defined by the existence of a proband with early onset sarcoma and a first degree relative with cancer before 45 years, plus another first/second degree relative with cancer at before 45 years or sarcoma at any age.

Other extended criteria have been proposed to provide better guidelines for TP53 genetic testing:

Birch definition : (1) a proband with any childhood cancer or sarcoma, brain tumour, or adrenocortical carcinoma diagnosed before age 45 years and (2) a first- or second-degree relative with a typical Li-Fraumeni cancer (sarcoma, breast cancer, brain tumour, adrenocortical carcinoma, or leukaemia) at any age and (3) a first- or second-degree relative with any cancer before age 60 years.

Eels definition: Two first- or second-degree relatives with Li-Fraumeni-related malignancies (sarcoma, breast cancer, brain tumour, leukaemia, adrenocortical tumour, melanoma, prostate cancer, pancreatic cancer) at any age.

Chompret definition: A proband who has (1) a tumour belonging to the Li-Fraumeni tumour spectrum (soft-tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumour, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer) before age 46 years and (2) at least one first- or second-degree relative with a Li-Fraumeni tumour (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumours or a proband with multiple tumours (except multiple breast tumours), 2 of which belong to the Li-Fraumeni tumour spectrum and the first of which occurred before age 46 years or A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumours, irrespective of family history.

Prognosis

Most common cancer in Li-Fraumeni children (before the age of 10 years) are: soft tissue sarcoma, brain tumours and adrenocortical carcinomas; osteosarcoma predominates in adolescents; afterwards, female breast cancer, soft tissue sarcomas and brain tumours prevail, and other less frequent cancers such as leukemias or colon carcinomas are also observed. Multiple primary cancers are quite characteristic of Li- Fraumeni syndrome but may also be representative of Bloom's syndrome. Cancers in this disease, as in other cancer-prone diseases, often occur early in life: 50% of patients aged 30 years have had a cancer (i.e. penetrance is 50%, according to this disease definition), and penetrance is 90% at age 60 years.

Oncogenesis

Approximately 70% of families with LFS have a mutation in the TP53 gene. Most of these variants are missense mutations similar to those found in colorectal carcinoma with a high frequency of mutations at CpG dinucleotides.

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