

Leukaemia Section

Review

del(6p) (loss of JARID2 and DTNBP1) in myeloid malignancies

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Abstract

Review on 6p deletion in myeloid malignancies. The neighbor genes JARID2 and DTNBP1: possible relation and clinical relevance.

Keywords

Chromosome 6; Deletion 6p; Myeloid malignancies; JARID2; DTNBP1

Clinics and pathology

The deletion of 6p as isolated anomaly in the karyotype is a very rare event in myeloid disorders. To date only 16 cases have been reported: 2 cases with myelodysplastic syndrome (MDS), 3 cases with myeloproliferative neoplasms (MPN) and 11 cases with acute myeloid leukemia (AML). The anomaly was determined by conventional cytogenetics predominantly as terminal deletion (11 cases) and more rarely as interstitial deletion. The terminal deletions affected most frequently the region 6p23-6pter (7 cases), while the interstitial deletions occurred between the bands 6p12 and 6p25 and the deleted segments are variable in size.

Disease

Acute myeloid leukemia

Epidemiology

The deletion of 6p is found in 11 cases with AML (0.06 % of all AML cases with an abnormal karyotype): 1 case with M1 French-American-British (FAB) phenotype (Morris and Fitzgerald, 1985), 5 cases with M2 (Golomb et al, 1978; Yamasaki et al, 1996; Voskova et al, 2004; Igbal et al, 2006), 1 case with M3 (Nakase et al, 2000), 1 case

with M4 (Haase et al, 1995) and 3 cases with AML-NOS (Clavio et al, 2001; Kern et al, 2002; Stark et al, 2004). The sex ratio is balanced M:F=1.2:1. The age is documented in 6 cases: 20, 35, 53 (M2), 70 (M3), 73 (M4) and 52 (AML-NOS). The average age is 52.6 year (range 20-73).

Cytogenetics

Six cases are with terminal deletions with breakpoints located respectively in 6p21 (1 case), 6p22 (1 case), and 6p23 (4 cases). Three cases are presented with interstitial deletions and the deleted segments are variable in size (6p21-23, 6p21-25 and 6p12-23). In two cases the clones with 6p- are associated with unrelated clones carrying other cytogenetic anomalies including inv(3)(q21q26), del(7q), +8 and +13. In one case is found a secondary clone with 6p- and t(8;20)(q11;p11).

Disease

Myeloproliferative neoplasms

Epidemiology

Two cases with terminal deletions del(6)(p23) are reported: one (76-year-old male) with idiopathic myelofibrosis (Reilly et al, 1997) and another with essential thrombocytemia (Ganget et al, 2009).

Disease

Myelodysplastic syndromes

Epidemiology

Three cases are described: two cases (3 and 62-year-old-female) with MDS-MOS (GFCH, 1988; Chen et al, 2000) and one case (62-year-old female) with RAEB-2 (Refractory anaemia with excess blasts) (Meloni-Ehrig et al, 2010).

Cytogenetics

Two cases are with interstitial deletions del(6)(p22p25) and del(6)(p23p25) and one with a terminal deletion del(6)(p21). The 6p- in one case is associated with constitutional +21 and in another with t(9;22)(q34;q11) in a secondary clone.

Genes involved and proteins

Inactivation of a tumor suppressor gene(s) (TSG) as a result of a 6p deletion is possibly linked to the molecular pathogenesis of the 6p- anomaly. In the region 6p12-25 where the deletions have been observed a number of genes are identified that may act as putative TSG, including CDKN1A (6p21.2) FKBP5 (6p21.31), DAXX (6p21.32), MHC class I genes, MPC1, TRIM27 (6p22.1), CASC15, ID4, JARID2 (6p22.3), NOL7 (6p23), DUSP22 (6p25.3). Almost all of them are involved in the pathogenesis of different solid tumors. The minimal deleted region(s) (MDR) at 6p reported in myeloproliferative disorders may point out which of these genes possibly play a role in 6p- associated myeloid malignances. Using high-resolution SNP microarrays, Puda et al, 2012 provided evidence that a region of 1.1Mb containing only the JARID2 gene - member of the polycomb repressive complex 2 (PRC2) is frequently deleted during leukemic transformation of chronic myeloid malignances (MDS and MPN). Three additional MDRs at 6p have been found with high-resolution genotyping in a large series of secondary AML by Milosevic et al, 2012. One of these regions (6p22.3:14130000-1580000) also co-insides with the genome location of the JARID2 gene (6p22.3:15245975-15522042). Both studies indicated that JARID2 gene is involved as a TSG in the pathogenesis of the 6p- associated myeloid malignances. In the cases in which larger segments are deleted than the MDR where JARID2 is mapped, involvement of other genes in the pathogenesis of 6p- associated myeloid malignances, especially those that have been shown to play a role in oncohematological diseases (CASC15, ID4 and DUSP22) (Contreras et al., 2016; Zhou et al., 2017; Melard et al., 2016), can also be assumed.

JARID2 and DTNBP1 in close proximity: It is interesting to note that JARID2 is located in very close proximity to the DTNBP1 gene (Dysbindin) (genome location chr 6: 15522801-15663058). The distance between JARID2 and DTNBP1 is only 759 bp and remains constant in mammals (approximately 1 kb). Both genes have divergent patterns of gene expression, conservative gene structures and are implicated in embryonic development and morphogenesis (JARID2: heart and liver development, neural tube formation, differentiation of embryonic stem cells; DTNBP1: regulation of dendritic spine morphogenesis and neurite

outgrowth). These data suggest that both genes are with coordinate transcription and are functionally linked.

The Neighbor Genes JARID2 and DTNBP1: Possible Relation and Clinical Relevance

Both genes are characterized by a variety of functions:

JARID2 (Jumonji, AT Rich Interaction Domain 2) facilitates PRC2 recruitment to its target genes and in this way stimulates PCR2 mediated lysine 27 di/trimethylation of histone H3 (H3K27me2/3). It is required for PCR2-repressive activity in different cell types, including in embryonic stem (ES) cells. It also represses the expression of CCND1 (cyclin-D1) by activating methylation of Lys 9 of histone H3 (H3K9me) (through EHMT1 (GLP1) and EHMT2 (G9a) histone methyltransferases) and via interaction with GATA4 and NKX2-5 represses the transcription of NPPA (natriuretic peptide A).

DTNBP1 (Dysbindin) is one of the candidate susceptibility genes for schizophrenia. As a component of the Biogenesis of Lysosome-related Organelle Complex-1 (BLOC-1) it is required for the normal biogenesis of the endosomal-lysosomal system. It appears to promote neuronal transmission influencing glutamatergic release and modulates prefrontal cortical activity via the dopamine D2 pathway. It is involved also in actin cytoskeleton reorganization, neurite outgrowth and regulation of cell surface exposure of DRD2. In association with the BLOC-2 complex it facilitates the transport of TYRP1 (Tyrosinase related protein 1).

Actin cytoskeleton

The detailed consideration of the functions of the two genes indicated that the merging entity, which possibly binds them functionally, is the actin cytoskeleton reorganization. In dendritic spines dysbindin assembles a protein complex with WASF2 (WAVE2) and ABI1, which activates the actin nucleators ACTR2/ ACTR3 (ARP 2/3) enabling de novo rapid actin polymerization (Ito et al, 2010). WAVE2-Arp2/3 induced actin polymerization is associated with the formation of the cell cytoskeleton, including bundled or branched filamentous structures, such as filopodia and lamellipodia that are responsible for the cell motility and adhesion. On the other hand actin polymerization (as well as depolymerization) are important for the regulation of the G-actin homeostasis. Actin depolymerization (or its down regulation by decreased dysbindin expression) will increase the cytoplasmic G-actin (monomeric form) which will lead to translocation of G-actin from the cytoplasm to the nucleus via IPO9 (importin 9) (Dopie et al, 2012). In turn, the increased nuclear actin will enhance transcriptional activity, because it is a component of the transcription initiation complex of RNA polymerases II (Hofmann et al, 2004) and is bound also to the heterogenous

rebound nucleoproteins and HAT1 (histone acetyltransferase) during transcriptional elongation (Obrdlic et al, 2008). In the opposite mechanism increased actin polymerization (including caused by increased dysbindin expression) will result in a decreased level of nuclear G-actin and respectively in a decreased activity of the RNA polymerases - a process that would allow suppression of the gene transcription by polycomb 2 mediated histone H3 lysine 27 trimethylation (Le et al, 2016). It could be concluded that a coordinated transcription of both neighbor genes JARID2 (member of the repressor complex of polycomb 2) and DTNBP1 are responsible for the transition from an active transcriptional status to gene repression, and that one of the mechanisms which possibly modulates this process is dysbindin expression. It seems that an interconnection exists between polycomb 2 complex and the cytoplasmic/nuclear actin axis. The fact that the core unit of the cytosolic polycomb 2 complex Ezh2 (structurally resembles the nuclear Ezh2 complex) controlled the cytoplasmic actin polymerization in various cell types and human prostate cancer cells conforms to this assumption (Su et al, 2005; Bryant et al, 2008).

The data presented above could highlight the genome alterations in schizophrenia, the mechanisms related to the high incidence of malignances in Wiskott-Aldrich syndrome and the pathogenesis of the 6p- associated myeloproliferative disorders.

It has been found that schizophrenia is associated with both insufficiency of key regulators of actin polymerization as dysbindin (Weickert et al., 2004), Arp2/3 (Datta et al., 2016), CYFIP1 (Pathania et al., 2014) and regulators of Rho-family GTPases (Hill et al., 2006; Hayashi-Takagi et al., 2010) and deregulation of the actin homeostasis manifested by increased G-actin, decreased F-actin and decreased ratios of F-actin/total actin as a result of reduced actin polymerization in the anterior cingulate cortex of schizophrenic patients (Bhambhani et al., 2017). These findings indicated that the reduced actin polymerization in schizophrenia could create an increased level of nuclear monomeric actin leading to prolonged transcription of certain gene sets as a result of genome imbalance between activators and suppressors. The same genome imbalance as a consequence of defective actin polymerization in highly divided tissues, such as the hematopoietic tissue, could be a prerequisite for leukemogenesis. First, genes with prolonged transcription will be at risk of damage and involvement in chromosomal rearrangements. Second, the normal order of the expression of the genes will be impaired, which would affect the functioning of the signaling pathways. The noted prerequisite for leukemogenesis will explain the high incidence of malignances (including MDS and AML) in the

Wiskott-Aldrich syndrome (Salavoura, et al., 2008), because this complex X-linked disorder is also associated with aberrant actin polymerization as a result of the insufficiency of the key regulator of the actin cytoskeleton in the hematopoietic cells known as WASp.

The pathogenesis of 6p- associated myeloid malignances is related with the deletion of both genes JARID2 and DTNBP1. JARID2 is a cofactor of PRC2 (polycomb repressive complex 2) regulating its targeting to chromatin allowing methylation of lysine 27 on histone H3 - a process that plays a very important role not only in the differentiation of the embryonic stem cell (evidenced by their impaired differentiation in its absence) (Landeira et al, 2010), but also in the differentiation of the precursor and stem cells of the hematopoietic system (Kinkel et al, 2015). Therefore, deletion of JARID2 would result in PRC2 insufficiency and impossibility to repress the gene set coordinating the function of the myeloid precursors. On the other hand, deletion of DTNBP1 leads to an increased level of nuclear monomeric actin and constant activation of the genes that are not suppressed by PRC2. In other words, the gene orchestration responsible for the transition of the precursor cell to the next stages of differentiation is compromised which is manifested in maturation arrest and accumulation of immature cells. This interpretation is confirmed by the fact that the locus of JARID2 (and respectively DTNBP1) is frequently deleted during leukemic transformation of chronic myeloid malignances and that most of the cases with 6p-associated myeloid disorders are MDS and AML. However, there are indications that nuclear monomeric actin is also involved as JARID2 in differentiation of the hematopoietic system (macrophage-like differentiation of HL-60 cells) (Xu et al, 2010) and is included in the chromatin remodeling complex SWI/SNF (Szerlong et al, 2008) that can function as both - transcriptional activator and repressor (Tolstorukov et al, 2013). It is possible that actin may affect genes related to the differentiation of the myeloid series, which would explain the observation that almost half of the 6p-associated AML are with M2 subtype (acute myeloid leukemia with differentiation).

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