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Short Communication

1q translocations (unbalanced) in myeloid malignancies

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Clinics and pathology

Disease

BCR-ABL-negative chronic myeloproliferative neoplasms (MPN): essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), myelodysplastic syndromes (MDS) and less frequently in acute myeloid leukemia and other myeloproliferative disorders.

Etiology

Although the underlying mechanism for these chromosomal alterations is unclear, it is possible that chromosomes with large constitutive heterochromatin bands such as chromosome 1 may be at risk of centromeric instability and be predisposed to centromeric fusion with other chromosomes. This possibility is supported by observations that unbalanced chromosome rearrangements frequently involve the fusion of the large constitutive heterochromatin regions of chromosomes. Therefore, it is likely, that larger constitutive heterochromatin chromosomes may be more at risk of centromeric instability and predisposed to chromosome breakage at the centromere (Caramazza et al., 2010; Millington et al., 2008).

Pathology

While the mechanism(s) is not entirely clear, hypomethylation of heterochromatic 1q sequences may be a cause of centromeric instability leading to centromeric DNA decondensation. Immunodeficiency may be a factor involved in centromeric instability, at least in some cases. This is supported by observations of high frequency of centromeric heterochromatin instability and frequent 1q exchanges in some patients with immunodeficiency (Sawyer et al., 1995a; Sawyer et al., 1995b; Polito et al., 1996).

Prognosis

While mechanistically unbalanced 1q abnormalities result in gain of 1q, the prognostic implication may be entirely different, depending on partner chromosomes. Although more case studies are needed, previously published data indicate a possible association of unbalanced 1q rearrangements with a highly proliferative phenotype in myeloproliferative disorders with a propensity of disease transformation.

Genetics

Note

der(Y)t(Y;1)(q11-12;12-25). Myelodysplastic syndromes (MDS), acute myeloid leukemia (AML) (M2, M4 mostly), chronic myelomonocytic leukemia (CMMoL) and less frequently other chronic myeloproliferative disorders (MPD). Most cases involve Yq12 and 1q12 breakpoints. Sole anomaly in the majority of myeloid disorders, may be accompanied by numerical anomalies (+8, +9). Rarely found in lymphoid malignancies as part of complex karyotypes (Manabe et al., 2013; Michaux et al., 1996b).

der(1)t(1;1)(p36;q11-q32). The balanced translocation t(1;1)(p36;q21) involving the DUSP10/PRDM16 genes is associated with myeloid disorders; the unbalanced der(1)t(1;1) involving 1q11-32 breakpoints may be observed in both myeloid and lymphoid proliferations and is frequently associated with a highly complex karyotype (Duhoux et al., 2011; Noguchi et al., 2007).

der(2)t(1;2)(q12;q37). Identified in patients suffering from different acute myeloid leukemia subtypes; less frequently chronic myeloid disorders. Found mostly in complex karyotypes; likely to be a secondary anomaly. The balanced t(1;2)(q12;q37) is occurring in acute myeloid leukemia (Busson-Le Coniat et al., 1999).

der(5)t(1;5)(q12-q25;q13-q35). Found in lymphoid and myeloid malignancies with cytogenetically heterogeneous breakpoints. In both lineages found as part of complex karyotypes, most likely as a secondary anomaly. In myeloid disorders the anomaly seems to confer a poor prognosis with a possible link to previous mutagenic exposure. The balanced t(1;5)(q23;q33) involving the PDGFRB gene is associated with a myeloproliferative disorder and eosinophilia (Johansson et al., 1997).

der(6)t(1;6)(q21-23;p21.3). Found in chronic myeloproliferative disorders and less frequently in AML/MDS. DNA sequences may be overrepresented at 6p as either cryptic duplications or cryptic low-copy gains. The presence of fragile site FRA6C, located in 6p22 suggest, that 6p gains may arise from acquired and/or congenital genomic instability. In addition, the occurrence of translocations involving 6p22 after chemotherapy or radiation therapy indicates, that one or more therapeutic agents might play a role in their origin (Dingli et al., 2005; Busson-Le Coniat et al., 1999).

der(1;7)(q10;p10). Defines a unique clinicopathological subgroup of myeloid neoplasms; found particularly in MDS and AML and less frequently in chronic myeloproliferative disorders. Previous history of chemo- and/or radiotherapies has been described in more than half cases. Sole cytogenetic anomaly in around one-half cases, limited number of additional abnormalities, consisting mostly of trisomy 8. The unbalanced translocation, der(1;7)(q10;p10), leading to allelic imbalance of trisomy 1q and 7q monosomy is associated with high rates of progression to AML in MDS and unfavorable prognosis (Caramazza et al., 2010; Slovak et al., 2009; Sanada et al., 2007).

der(1;9)(q10;p10). Rarely found in patients of essential thrombocythemia with JAK2 V617F mutation that transformed to acute myelogenous leukemia or to myelofibrosis, suggesting the anomaly may play a role in the progression of myeloproliferative neoplasms (Bobadilla et al., 2007).

der(9)t(1;9)(q11;q34). Rare occurrence, found in 3 cases of acute myeloid leukemia, 1 case of polycythemia vera, 1 case with chronic myelomonocytic leukemia and 1 case of multiple myeloma (Suh et al., 2009).

der(9)t(1;9)(q12;q12). Rare, found in 2 patients with polycythemia vera in transformation and in 1 patient with myelofibrosis, which later evolved into acute myelomonocytic leukemia; may be consistently associated with myeloproliferative disorders showing a high propensity to transformation. Sole abnormality in most cases; gain of 9p might play a role for gain of function of the JAK2 gene on 9p24 (Rege-Cambrin et al., 1991).

der(1;10)(q10;p10). Rare anomaly, described in patients with myelodysplastic syndromes (Leon et al., 2011).

der(11)t(1;11)(q12-21;q14-25). Unbalanced form is identified in myeloid and lymphoid malignancies; described mainly in secondary cases as part of highly complex karyotypes (Secker-Walker et al., 1998; Douet-Guilbert et al., 2008). The balanced t(1;11)(q21;q23) and MLL rearrangement is associated with in AML, mainly M4/M5.

der(12)t(1;12)(q11-21;p11-13). Rare abnormality, found in myeloid and lymphoid neoplasm, described in complex karyotypes; most likely as a secondary rearrangement (La Starza et al., 1999; Andersen et al., 2005).

der(1;13)(q10;q10). Uncommon in myeloid malignancies; described in chronic myeloid neoplasms including polycythemia vera and essential thrombocythemia (Flach et al., 2011; Tanaka et al., 2006).

der(1;14)(q10;q10). Detected in chronic and acute myeloid disorders found as a single anomaly in a majority of patients (Fogu et al., 2012).

dic(1;15)(p11;p11). Found in patients with various conditions, including both lymphoid and myeloid neoplasms. Rare, but nonrandom anomaly in MPD, mostly MDS and AML (Michaux et al., 1996a).

der(16)t(1;16)(q11-25;q11-24). Occurs in a wide variation of hematologic malignancies mostly as a part of complex karyotypes; limited number of additional anomalies in myeloproliferative disorders. A rare but nonrandom abnormality in myelodysplastic syndromes, associated with male predominance, suggesting a putative association of this translocation with male gender (Lunghi et al., 2010).

der(18)t(1;18)(q10-25;q11-23). Heterogeneous breakpoints; the anomaly is relatively restricted to myeloid disorders; found mostly in a highly proliferative ET/PV phenotype with a propensity to transform into myelofibrosis and acute leukemia. In particular, the subtype der(18)(q10;q10) seems to be associated with the aggressive phenotype of PV. Found as the sole karyotypic abnormality in the majority of patients. A relatively high incidence of JAK2 mutations in these patients suggests a possible link between JAK2 mutations and disease etiology (Trautmann et al., 1992; Diez-Martin et al., 1991; Gangat et al., 2008; Wan et al., 2001a; Azuma et al., 2010; Alter et al., 2000).

der(1)t(1;19)(q23;p13.1). Cytogenetic appearance identical to t(1;19)(q23;p13.3), a specific aberration in ALL; occasionally described in myeloid neoplasms (MDS and AML) with various 1q21-1q25 breakpoints (Tchinda et al., 2002).

der(20)t(1;20)(q10-21;q11-13). Rare occurrence in myeloid lineages; apparently secondary anomaly, found mostly as part of complex karyotypes (Wan et al 2001b; Raimondi et al., 1999).

Cytogenetics

Cytogenetics morphological

Unbalanced rearrangements, resulting in partial or total trisomy of 1q and loss of genomic sequences from the partner chromosome.
Abnormal clones containing extra copies of 1q may originate by several mechanisms, including whole-arm translocations, unbalanced rearrangements between variable partner chromosomes, 'dicentric' translocations and partial duplications of 1q.

Additional anomalies

Usually appear as a sole chromosomal abnormality during the entire clinical courses or accompanied only by a limited number of additional abnormalities, suggesting that gain of 1q plays a role in the pathogenesis of these rearrangements.

Genes involved and proteins

Note
No specific gene targets at the breakpoints are likely to be involved.
In these rearrangements, the critical region between 1q21 and 1q32 is known to be commonly spanned, but no pathogenetically relevant genes have been demonstrated.

Result of the chromosomal anomaly

Fusion protein

Oncogenesis
The unbalanced nature of these rearrangements indicates that mechanistically, either trisomy of 1q and/or loss of putative tumor suppressors may potentially contribute to disease pathogenesis.
As the gain of 1q that results from these translocations is consistently associated with myeloproliferative disorders, it is likely that certain chromosome 1q regions are pathogenetically relevant to both chronic and advanced phases of MPN.
This finding suggests that the gain of 1q and appears to be one of the progressional steps in these disorders, while the loss of tumor suppressor genes may also contribute to clonal proliferation, analogous to numerical aberrations and chromosome deletions.

To be noted

Note
A relatively high incidence of JAK2 mutations in combination with 1q rearrangements in MPN, suggests a possible link between JAK2 mutations and 1q rearrangements in myeloid malignances, pathologically relevant either at diagnosis or in advanced stages of the disease.

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