Leukaemia Section
Short Communication

inv(3)(q21q26) RPN1/MECOM / t(3;3)(q21;q26)
RPN1/MECOM / ins(3;3)(q26;q21q26)
RPN1/MECOM

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Abstract
Review on inv(3)(q21q26) RPN1/MECOM, with data on clinics, and the genes implicated.

Identity
Note
The three chromosome anomalies are variants of each other, and they share identical features.

Clinics and pathology

Disease
inv(3) and t(3;3) have been documented in de novo AML (in all FAB subtypes except M3), t-AML, s- AML, myelodysplastic syndrome (MDS), chronic myelogenous leukaemia (CML), more often in accelerated phase or blast crisis, and in other myeloproliferative disorders. AML with inv(3)(q21q26) or t(3;3)(q21q26) are part of the new WHO 2008 classification in the AML subgroup with recurrent genetic abnormalities.

Phenotype/cell stem origin
Hematopoietic stem cell with multilineage potential is implicated.

Epidemiology
inv(3)(q21q26) and t(3;3)(q21;q26) are the most common 3q abnormalities in AML (32%). The frequency of these rearrangements is estimated to range between 1.4% and 1.6% of AML in adults with no difference between sexes. These rearrangements are slightly more common in patients aged 60 years or younger, and extremely rare in pediatric AML.

Clinics
Patients may present a normal platelet count, however marked thrombocytosis may occur in 7% to 22% of patients.

Cytology
Blasts express CD13, CD33, CD117, HLA-DR, CD56, CD34 and CD38; CD7 is aberrantly expressed in some cases, whereas the other lymphoid markers are uncommon; blasts may also express megakaryocytic markers such as CD41 or CD61. Blasts present morphologic and cytochemical features of any AML subtypes other than M3. Multilineage dysplasia is frequently associated with dysmegakaryopoiesis (characterized by small monolobate or bilobate megakaryocytes that can be increased in number). In peripheral blood, morphological abnormalities may be observed: hypogranular neutrophil, pseudo-Pelger anomaly, macrothrombocytes, circulating micromegakaryocytes.
Prognosis

Patients with inv(3)(q21q26) or t(3;3)(q21:26) present an aggressive course with short OS and poor response to conventional therapy (CR is estimated at 31%). Studies describe an unfavourable 5-year survival rate (OS: 5.7%) with a median survival of 10.3 months. OS is shorter, if additional monosomy 7 is present. There is no difference in survival between inv(3) and t(3;3).

Cytogenetics

Note

inv(3)(q21q26) are the most frequent abnormalities, ins(3;3)(q26;q21q26) are less frequent.

Additional anomalies

In AML, the most frequent additional anomaly is monosomy 7 (66% of cases), deletion 7q may occur in 3%, deletion 5q in 6%; complex karyotype is observed in 21% of cases, and monosomal karyotype in 68%. In CML, inv(3) or t(3;3) can be an additional anomaly to t(9;22)(q34;q11), but t(9;22) has also been found additional to inv(3).

Genes involved and proteins

MECOM

Location 3q26,2

Note Alias EVI1.

DNA/RNA

EVI1 has 16 exons, and five alternative mRNA 5'-ends: EVI1-1A, EVI1-1B, EVI1-1C, EVI1-1D and EVI1-3L.

Protein

EVI1 encodes a nuclear zinc finger protein that is a transcriptional regulator involved in cell proliferation, differentiation, and apoptosis.

RPN1

Location 3q21

DNA/RNA

RPN1 has 10 exons.

Protein

RPN1 encodes a transmembrane glycoprotein, localized in the rough endoplasmic reticulum.

Result of the chromosomal anomaly

Hybrid gene

Description

inv(3)(q21q26) or t(3;3)(q21q26) lead to a juxtaposition of the region surrounding the RPN1 gene in 3q21 with the EVI1 gene in 3q26. Breakpoints occur about 900 kb located 5' and 3' to the EVI1 gene with the t(3;3) and the inv(3) respectively. Breakpoints in the RPN1 gene area span over 235 kb and are either located 3' or centromeric to the RPN1 gene.
inv(3)(q21q26) RPN1/MECOM

Recently, studies have described a role for G2DHE, GATA2 distal hematopoietic enhancer, that is located 160 kb 3′ to the RPN1 gene on 3q21. In 3q21q26 rearrangements, G2DHE is juxtaposed to EVI1 and is thought to induce EVI1 gene transcription instead of GATA2 and thus promote leukemogenesis.

To be noted

Note

AML with inv(3) or t(3;3) are associated with NRAS mutations (28%), FLT3-ITD mutations (less than 20%), and rare NPM1 mutations.

EVI1 overexpression has been described without 3q21q26 rearrangement and conversely, there are extremely rare cases of 3q21q26 rearrangement without EVI1 overexpression.

Recently, Groschel et al. have observed that 98% of myeloid malignancies with inv(3) and t(3;3) present mutations in gene activating RAS/RTK signalling pathways.

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