Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Leukaemia Section

Mini Review

t(11;17)(q23;q21)

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Clinics and pathology

Disease

Specifically observed in acute promyelocytic leukemia (APL), or M3 ANLL; in the vast majority of cases, M3 ANLL is characterized by a t(15;17)(q25;q21); the t(11;17) represents a rare variant translocation with characteristic clinicopathologic features concerning presentation, response to treatment with all-trans retinoic acid (ATRA) and prognosis.

Phenotype / cell stem origin

Promyelocytic (M3) acute leukaemia; a number of patients express an unusual morphologic spectrum intermediate between M2 and M3 AML.

Epidemiology

Less than 1% of morphologic M3 ANLL.

Clinics

High incidence at diagnosis of disseminated intravascular coagulation; poor response to ATRA at induction therapy, in contrast with the classical M3 ANLL with t(15;17).

Cytology

High rate of normal or dystrophic promyelocytes in peripheral blood and in bone marrow; no intracytoplasmic Auer rods; myeloperoxydase reaction positive; immunocytochemical detection with an anti-PLZF shows a distinct punctate nuclear distribution of the protein, suggesting its compartmentalization in the nucleus.

Prognosis

Distinctly worse prognosis than M3 ANLL with t(15;17), mainly because the patients fail to respond to the maturation effect of ATRA.

Cytogenetics

Cytogenetics, molecular

Fusion of distal PLZF probe with RARa on 17q21.

Probes

Whole chromosome 11 and 17 paintings; or painting with unique sequence probes for PLZF and RARa.

Additional anomalies

No recurrent additional anomalies are known.

Variants

3 related translocations observed in M3 ANLL; the first is the common translocation (15;17) and the two others are extremelly rare; all these translocations involve a breakpoint at 17q21, in RARa, which fuses with different partners:
1- t(15;17)(q22;q21), fusion with PML in 15q22;
2- t(5;17)(q32;q21), fusion with NPM1 in 5q32, encoding for a RNA processing protein;
3- t(11;17)(q13;q21), fusion with NUMA in 11q13, involved in the control of mitosis.

Genes involved and Proteins

PLZF

Location: 11q24

DNA / RNA

Krüppel-like zinc finger gene.

Protein

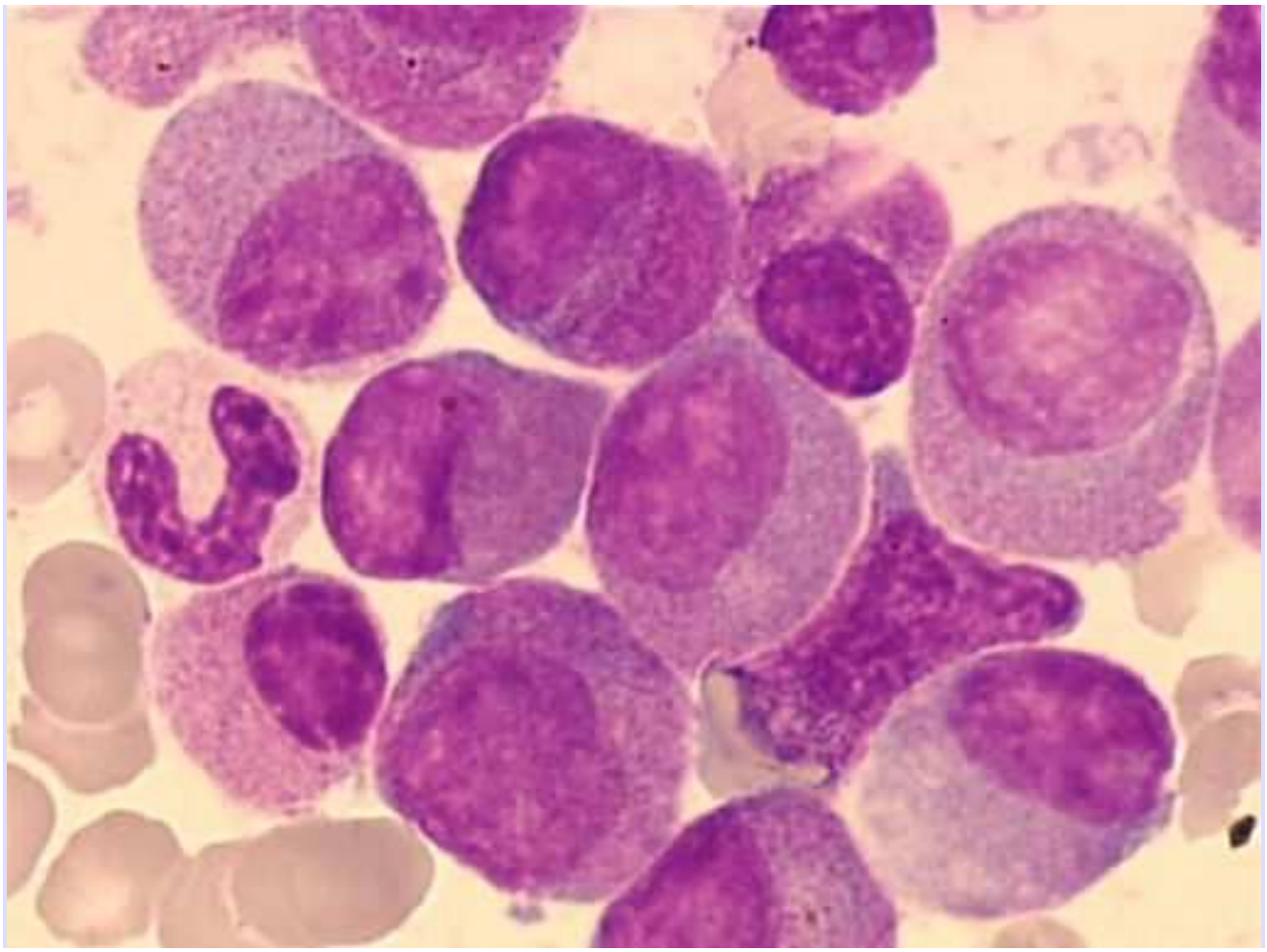
Transcription factor associated with myeloid maturation.

RARa

Location: 17q21

Protein

Nuclear receptor with DNA binding and transcriptional properties.



In patients with t(11;17)(q23;q21), t(5;17)(q35;q21), and t(11;17)(q13;q21) where RARa is fused to the PLZF (promyelocytic leukemia zinc finger), NPM (nucleophosmin) and NuMA (nuclear mitotic apparatus) genes respectively, chromosome 17 and RARa but not PML are involved. Patients were initially reported as having M3 morphology. Interestingly, the t(11;17)(q23;q21) PLZF/RARa subgroup showed a clearly morphological differences with predominance of cells with regular nuclei, many granules, usually no Auer rods, increased number of pseudo Pelger-Huet cells and a strong MPO activity. These particular characteristics could allow the definition of a separate morphological entity among APL. Patients with t(5;17)(q35;q21) are too rares to draw any morphological correlation - Courtesy Georges Flandrin, CD-ROM AML/MDS G.Flandrin/ICG. TRIBVN.

Results of the chromosomal anomaly

Hybrid gene

Description

The translocation involves a breakpoint in the zinc finger region of PLZF, with fusion of two zinc fingers to the RARa B region to form a 5' PLZF - 3' RARa fusion gene; the reciprocal 5' RARa - 3' PLZF gene fuses seven zinc fingers to the RARa region; RARa's breakpoint occurs in intron 2, as is in classical t(15;17).

Transcript

Both 5' PLZF -3' RARa and 5' RARa - 3' PLZF transcripts are detected by RT-PCR, and both fusion partners would be implicated in leukemogenesis; four chimeric transcripts are produced, due to alternative splicing of PLZF gene and to transcription of either A1 or A2 domain of RARa gene.

Fusion protein

Description

1- As a result of the alternative splicing of PLZF gene, two forms of PLZF-RARa protein can be detected:
a) PLZF(A)-RARa (735 amino acids; 81 kDa) composed of the N-term part of PLZF including POZ domain and two of the nine zinc fingers, fused to the DNA and ligand binding domains of RARa.
b) PLZF(B)-RARa (858 amino acids; 93 kDa) differing from form A by the inclusion of a 123 amino acid prolin rich segment of PLZF; PLZF-RARa protein is an abnormal retinoic acid receptor with reduced and modified DNA-binding and transcriptional activities.
2- Two forms of RARa-PLZF protein are also detected, due to involvement of alternative promoters of the RARa gene: RARa(A1)-PLZF (277 amino acids; 31 kDa) and RARa(A2)-PLZF (274 amino acids; 31 kDa), composed of A1 or A2 transcriptional activation

domain of RARa linked to the seven C-terminal zinc fingers of PLZF.

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