Identity

The translocation, well known as t(15;17)(q22;q21) or t(15;17)(q22;q12), should be re-named t(15;17)(q24;q21), since PML sits in 15q24, and RARA in 17q21.

Disease and pathology

Phenotype / cell stem origin

t(15;17) is quasi pathognomonic of M3 ANLL (acute promyelocytic leukaemia, or APL).

Epidemiology

Found in 10% of adult ANLL; annual incidence: 1/10^6, similar to the incidence of the t(8;21); any age, but frequent in the young adult; sex ratio 1M/1F.

Clinics

WBC and platelets may be lower than in other ANLL; coagulopathy.

Cytology

Large cells with myeloperoxidase positive cytoplasmic granulations (microgranular forms are called variant M3 ANLL, and are often hyperleucocytic); bundles of Auer rods.

Treatment

One of the rare leukaemia where treatment is an emergency, as intra vascular coagulation is prominent, causing a high rate (10 to 40%) of early mortality, mainly due to cerebral haemorrhage; with the recent differentiation therapy using all trans-retinoic acid (with combined chemotherapy), CR is obtained in 80-90% of cases; this is the only cancer which, to date, can be treated by differentiation therapy.

Prognosis

Early death rate still at 15-20%; combination of retinoic acid and chemotherapy prolonged survival significantly: survival at 1 yr and at 3 yrs are stable at 70%, instead of a 30 to 40 % 3 yr survival previously.
t(15;17)(q22;q21) is associated consistently with AML M3. This chromosomal abnormality first appeared to be confined to the characteristic or morphologically typical M3 AML or "hypergranular promyelocytic leukaemia", defined by bone marrow replacement with highly granulated blast cells. The nuclear size and shape is irregular and highly variable; they are often kidney-shaped or bilobed. The cytoplasm is completely occupied by densely packed or even coalescent large granules, staining bright pink, red or purple by MGG. In some cells the cytoplasm is filled with fine dust-like granules. Characteristic cells containing bundles of Auer rods ("faggot cells") randomly distributed in the cytoplasm, although frequent, are not present in all cases. Auer rods in M3 are usually larger than in other AML and they may have a characteristic morphology at the ultrastructural level. In some cases, the cytoplasmic granules are so large and/or numerous that they totally obscure the cell, rendering the nuclear cytoplasmic limit indistinct. In M3 AML, MPO is always strongly positive in all blast cells, with the reaction product covering the whole cytoplasm and often the nucleus too - Courtesy Georges Flandrin, CD-ROM AML/MDS G.Flandrin/ICG. TRIBVN.

Cytogenetics

Cytogenetics, morphological

Although primary anomaly in most cases, t(15;17) can also occur in rare occurrences at acutisation (of promyelocytic type, of course) of a CML with the usual t(9;22).

Additional anomalies
+8 in 1/3 of cases; del (7q); del(9q) rare.

Variants
1- True variants, i.e. three way complex t(15;Var;17) exist; they demonstrated that the crucial event lies on der(15), which receives the end part of chromosome 17.
2- Related translocations, rarely observed, involve a commun breakpoint in 17q21, within RARa, fused with different partners, in: t(11;17)(q23;q21), fusion with PLZF, t(5;17)(q32;q12), fusion with NPM1, and t(11;17)(q13;q21), fusion with NUMA.

Genes involved and Proteins

PML
Location: 15q22
DNA / RNA
Numerous splices in 3’.
Protein
Nuclear protein; contains zinc fingers and a leucine zipper; transcription factor.

RARa
Location: 17q12-21
Protein
Wide expression; nuclear receptor; binds specific DNA sequences: HRE (hormone response elements); ligand and dimerization domain; role in growth and differentiation.

Results of the chromosomal anomaly

Hybrid gene
Description
Variable breakpoint in PML between intron 3 and exon 7a; constant breakpoint in intron 2 of RARa.
Transcript
5' PML - 3' RARa transcript is found in all cases, and 5' RARa - 3' PML transcript is detected in 2/3 of cases.

Fusion protein
Description
Variable, as breakpoints in PML are variable; e.g.: 932 amino acids; 103 kDa; N-term PML, with the DNA binding and the dimerization domains fused to most of RARa with the DNA and retinoid binding regions.

Oncogenesis
Abnormal retinoic acid receptor with a dominant effect over RARa, antagonizing differentiation.

References


This article should be referenced as such: