

Gene Section

Mini Review

PML (Promyelocytic leukemia)

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Published in Atlas Database: October 2000

Online updated version : <http://AtlasGeneticsOncology.org/Genes/PMLID41.html>

DOI: 10.4267/2042/37669

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Identity

Other names: MYL (myelocytic leukemia)

HGNC (Hugo): PML

Location: 15q24



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

9 coding exons; total gene sequence: 35 kb ?

Transcription

3 main mRNAs 4.6, 3.0 and 2.1 kb; alternative splicing generates at least 16 isoforms of mRNAs, varying in the region coding for the C-terminal part of the protein.

Protein

Description

560 amino acids, 70 KDa (longest isoform); composed successively, from the N- to the C-terminus, by: 1- a proline-rich N-terminus 2- a so-called "tripartite motif", cysteine-histidine rich, composed of a RING finger structure and 2 B box domains, with putative DNA-binding function 3- a coiled-coil motif corresponding to a dimerization interface 4- a basic sequence with a nuclear localization domain, and 5- a serine-proline

rich C-terminal region, of unknown function, variable in length (alternative splicing) and containing phosphorylation sites.

Expression

In a wide variety of tissues. In hematopoietic tissue, expression apparently restricted to myeloid precursors.

Localisation

Nuclear, as part of a multiproteic complex located into multiple subnuclear PML oncogenic domains (PODs).

Function

Unknown to date; putative transcription factor; in conjunction with other proteins included in the PODs, it would play a role as tumor suppressor and in apoptosis.

Homology

With (numerous) other RING finger/B box proteins.

Implicated in

t(15;17)(q22;q21) / acute promyelocytic leukemia (APL) --> PML-RARA

Disease

Typical APL (or M3 ANLL, FAB classification), approximately 98% of APL cases; abnormal promyelocytes with Auer rods and bundles (faggots); disruption of the PODs with a microspeckled pattern; maturation response to all-trans retinoic acid (ATRA) therapy.

Prognosis

Immediate prognosis impaired by intravascular disseminated coagulopathy; long term prognosis is favorable with treatment combining ATRA plus chemotherapy.

Cytogenetics

Variant or complex t(15;17) translocation in 5% of cases, no known prognosis implication; secondary chromosomal abnormalities in 30 to 35% of APL at diagnosis; association with +8 in 17 to 28% of cases; other associations are rare but recurrent: del(7q), del(9q), ider(17)t(15;17), +21.

Hybrid/Mutated gene

The crucial fusion transcript is 5'PML-3'RARA, encoded by der(15) chromosome; the counterpart 5'RARA-3'PML encoded by der(17) is inconstant.

Breakpoint in RARA gene is always located in intron between A and B domains.

Three breakpoint clusters in PML gene: bcr1 (70% of patients), bcr2 (10%) and bcr3 (20%), giving rise respectively to the long (L), intermediate (V) and short (S) length hybrid PML-RAR transcripts; V form would be linked to ATRA decreased sensitivity and S form to association with an excess of secondary chromosome changes.

Abnormal protein

106 Kda fusion protein; role in the leukemogenic process by probable interference with the signalling pathway leading to differentiation and maturation of myeloid precursors (mainly dysregulation of retinoid-inducible genes involved in myeloid differentiation).

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This article should be referenced as such:

Viguié F. PML (Promyelocytic leukemia). *Atlas Genet Cytogenet Oncol Haematol*. 2000; 4(4):193-194.
