Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

RARA (Retinoic acid receptor, alpha)

Franck Viguié

Laboratoire de Cytogénétique - Service d'Hématologie Biologique, Hôpital Hôtel-Dieu, 75181 Paris Cedex 04, France (FV)

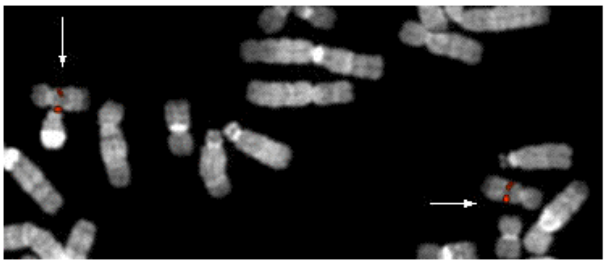
Published in Atlas Database: October 2000

Online updated version : http://AtlasGeneticsOncology.org/Genes/RARAID46.html
DOI: 10.4267/2042/37670

Identity

HGNC (Hugo): RARA

Location: 17q12



c-RARA (17q21) in normal cells: PAC 833D9 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

9 exons; total gene sequence: 7450 bp.

Transcription

2.8 and 3.6 kb transcripts.

Protein

Description

462 amino acids - 5 functional domains A/B (transcriptional regulation), C (DNA binding domain, contains 2 zinc fingers), D (cellular localization signal), E (ligand-binding domain) and F (function?).

Expression

In hematopoietic cells.

Localisation

Nuclear.

Function

Ligand-dependent transcription factor specifically involved in hematopoietic cells differentiation and maturation = receptor for all-trans retinoic acid (ATRA) and 9-cis RA which are intracellular metabolites of vitamine A, active in cellular differentiation and morphogenesis.
After linking with ATRA, RARA binds with a high affinity as a heterodimer with RXR (retinoid X receptor protein) to the RARE domain (retinoic acid response elements), a DNA sequence common to a number of genes and located in their promoter.
The gene response to RARA binding is modulated by a series of co-repressors and co-activators.

Homology

with RARB and RARG (retinoic acid receptors beta and gamma), 9-cis RA receptors (RXRs) and receptors for thyroid and steroid hormones and for vitamine D3.

Implicated in

t(15;17)(q22;q12) / 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 microspeckeled 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-RARAtranscripts; 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).

t(11;17)(q23;q12) / acute promyelocytic leukemia -->PLZF-RARA

Disease

Variant acute promyelocytic leukemia (APL) form with atypical cytologic aspects (intermediate morphology between M2 and M3, no Auer rods) and no response to ATRA therapy; less than 1% of APL cases.

t(5;17)(q35;q12) / acute promyelocytic leukemia --> NPM-RARA

Disease

Exceptional; probable response to ATRA.

t(11;17)(q13;q12) / acute promyelocytic leukemia --> NuMA-RARA

Disease

Exceptional: probable response to ATRA.

t(11;17)(q23;q12) / M5 acute non lymphocytic leukemia --> MLL-RARA

Disease

1 case to date; not to be confused with the t(11;17)(q23;q12) mentioned above; not found in APL; belongs to the MLL/11q23 leukemias.

References

de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature. 1990 Oct 11;347(6293):558-61

Kakizuka A, Miller WH Jr, Umesono K, Warrell RP Jr, Frankel SR, Murty VV, Dmitrovsky E, Evans RM. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. Cell. 1991 Aug 23;66(4):663-74

Nervi C, Poindexter EC, Grignani F, Pandolfi PP, Lo Coco F, Avvisati G, Pelicci PG, Jetten AM. Characterization of the PML-RAR alpha chimeric product of the acute promyelocytic leukemia-specific t(15;17) translocation. Cancer Res. 1992 Jul 1;52(13):3687-92

Casini T, Grignani F, Pelicci PG. Genetics of APL and the molecular basis of retinoic acid treatment. Int J Cancer. 1997 Feb 7;70(4):473-4

Grimwade D. The pathogenesis of acute promyelocytic leukaemia: evaluation of the role of molecular diagnosis and monitoring in the management of the disease. Br J Haematol. 1999 Sep;106(3):591-613

Melnick A, Licht JD. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. Blood. 1999 May 15;93(10):3167-215

This article should be referenced as such:

Viguié F. RARA (Retinoic acid receptor, alpha). Atlas Genet Cytogenet Oncol Haematol. 2000; 4(4):195-196.