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Gene Section
Review

RARA (Retinoic acid receptor, alpha)

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Abstract

Review on RARA with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords

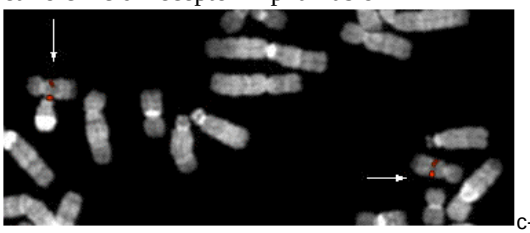
RARA; Retinoic acid receptor, alpha; Acute promyelocytic leukaemia; M3-AML

Identity

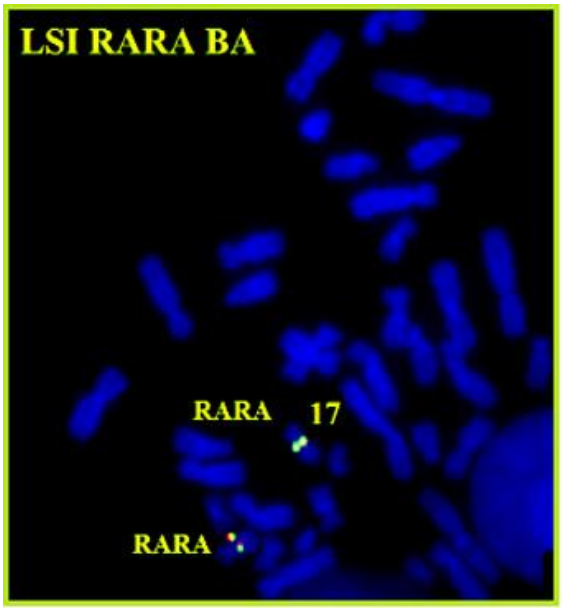
HGNC (Hugo): RARA

Location: 17q21.2

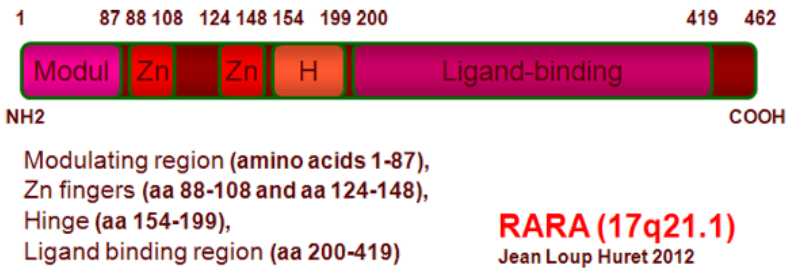
Other names: RAR, NR1B1, Nuclear Receptor Subfamily 1 Group B Member, Nucleophosmin-Retinoic Acid Receptor Alpha Fusion



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



RARA (Retinoic acid receptor, alpha) Hybridization with LSI RARA Dual Color, Break Apart Rearrangement Probe (Abbott Molecular, US), showing the RARA gene on 17q21.2 (red-green or a fused yellow signal - Courtesy Adriana Zamecnikova.



RARA protein and domains.

DNA/RNA

Description

9 exons; total gene sequence: 7450 bp.

Transcription

2.8 and 3.6 kb transcripts.

Protein

Description

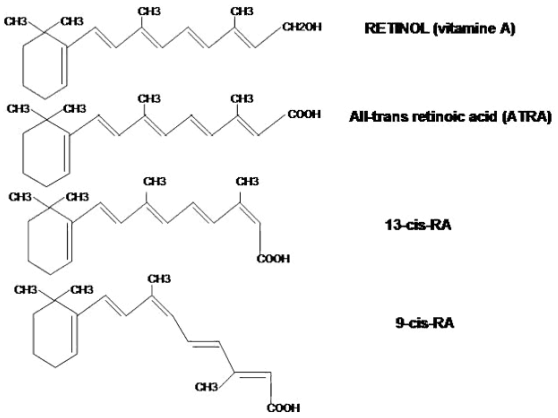
462 amino acids - 6 evolutionarily conserved domains - 5 functional domains : N-terminal A/B domain (transcriptional regulation AF1), C (DNA binding domain, contains 2 zinc fingers motifs, necessary for binding to RARE DNA sequence), D (cellular localization signal), E (ligand-binding domain, transcriptional regulation AF2) and F (function not well understood today)..

Expression

RARA is expressed in hematopoietic cells.

Localisation

Nuclear localisation.



Retinoid structures.

Function

Ligand-dependent transcription factor activated by all-trans retinoic acid (ATRA), specifically involved in hematopoietic stem 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. The gene response to RARA binding is modulated by a series of co-repressors and co-activators.

Retinol (vitamin A) is strictly furnished by the nutrition. The active retinol product is the retinoic acid (RA) which plays a great role as modulator of proliferation and differentiation in numerous tissues. In target cells retinol is oxidized as retinal with the help of an alcohol dehydrogenase. Then retinal is oxidized as ATRA by a retinal dehydrogenase (ALDH1A2 or RALDH). ATRA gives rise to 9-cis-RA, 11-cis-RA and 13-cis-RA, via an isomerase. All these isoforms are members of the retinoids, acting in different tissues after linkage with specific nuclear protein receptors. There are two families of RA receptors, the RARs (retinoic acid receptor α, β, and γ: RARA, RARB, RARG) and the RXRs (retinoid X receptor α, β and γ: RXRA, RXRB, RXRG). RARA (RARα) is involved essentially in hematopoiesis, while RARγ (RARG) is assigned to the skin. To be activated RARs can bind to ATRA or 9-cis-RA while RXRs bind only to 9-cis-RA (Allenby G et al., 1993).

Wild type RARA binds to DNA by its C domain, as a heterodimer with a related retinoid X receptor (RXR). The site of binding is a specific DNA sequence, the RA response element (RARE). The RARE domain is located in the promoter of target genes, it is composed classically of two direct repeats of a consensus sequence 5'-PuG(G/T)CA-3', separated by 1, 2 or 5 base pairs named respectively DR1, DR2 and DR5 (Umesono K et al., 1991). In the absence of ligand the AF2 domain of the RARA protein associates with corepressors NCOR2 (also called SMRT: silencing mediator of retinoid thyroid hormones) and/or N-CoR (nuclear corepressor) which are members of a multiprotein repressor complex. In this complex SMRT and N-Cor associate with the Sin3 proteins (SIN3A and SIN3B) which then links to histone deacetylases HDAC1 and/or HDAC2. Histone deacetylation would produce a local structural modification of the chromatin with an arrest of transcription initiation (Beato M et al., 1995; Pazin MJ and Kadonaga JT, 1997; Melnick A and Licht JD, 1999).

Transport of the ligands ATRA and 9-cis-RA, and their link with RAR/RXR heterodimer are facilitated by another family of receptors, CRABP1 and CRABP2 (cellular retinoic acid binding proteins) (Bastie JN et al., 2001).

When the ligand reaches its target it binds to RARA on the AF2 domain and modifies the molecular conformation of the receptor, so that the repressor complex dissociates from the molecule and is replaced by coactivator proteins which can bind at the same site (Chambon P, 1996; Wade PA and Wolffe AP, 1997). These coactivators involve TRIM24 (also called TIF1), PSMC5 (also called TRIP1 or SUG1), NCOA2 (TIF2), NCOA3 (ACTR), NCOA1 (SRC-1), TAF4 (TAFII135), and CREBBP (CBP). PSMC5 has a DNA helicase activity, able to unwind DNA. CREBBP and NCOA3 have an histone acetylase activity, they bind to KAT2B (P/CAF) which is also an histone acetylase. Consequently, when RARA binds to its ligand ATRA, it becomes the member of a multiprotein complex, in association with RXR and a number of coactivators. The result is a local histone reacetylation leading to the modification of

chromatin conformation and stimulation of transcription machinery. The activity of many genes involved in myeloid maturation, including transcription factors, may be potentially triggered by this coactivator's complex, resulting in the arrest of cell growth, terminal differentiation and production of mature granulocytes.

Homology

RARA shares homology with RARB and RARG, 9-cis RA receptors (RXRs) and receptors for thyroid and steroid hormones and for vitamine D3 (VDR)

Implicated in

Top note

In oncogenesis, RARA has been primarily implicated in acute promyelocytic leukaemia (APL) induction, via the expression of the PML/RARA fusion gene. Apart from its fusion with PML, RARA gene may be seldom fused by translocation, with a great variety of genes (Chen Z et al., 1996; Redner RL, 2002; Adams J and Nassiri M, 2015; Yan W and Zhang G, 2016) and all these fusion genes contain the RARA C-terminal B through F domains, encoding DNA binding, retinoid X receptor (RXR) heterodimerization, ligand binding, and co-repressor and co-activator interaction functions of RARA, leading invariably and specifically to the development of an APL. In all the variant translocations the functional activity of PML is not altered showing the crucial role of RARA in the leukemogenesis process. On other part it was observed recently that RARB or RARG, instead of RARA, could exceptionally fuse with various genes, giving rise to an APL responding poorly to ATRA therapy (Osumi T et al., 2018; Miller CA et al.; 2018; Chen X et al., 2019)

t(15;17)(q24;q21) / acute promyelocytic leukemia (APL) --> PML / RARA

The translocation fuses the promyelocytic leukaemia gene (PML) at 15q24 with RARA (Kakizuka A et al., 1991; de Thé H et al., 1991).

Disease

Typical APL (or M3 AML, FAB classification), approximately 98% of APL cases; arrest of the white blood cells maturation at the promyelocytic stage giving an accumulation of 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 is impaired by intravascular disseminated coagulopathy; long term prognosis is favorable with treatment combining ATRA and/or arsenic trioxide (ATO) plus anthracycline chemotherapy (Wang Z-Y and Chen Z, 2008; Testa U and Lo-Coco F, 2016).

Treatment: More than 90% of complete remission with ATRA plus ATO. Additional gene(s) alterations, involving mainly FLT3, KRAS or CMYC, are considered as progression factors (de Thé H, 2018).

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. Rarely the t(15;17) is not detectable cytogenetically, resulting from a cryptic molecular insertion; if the insertion is too small, FISH analysis may be negative and the molecular analysis only will be able to detect the PML-RARA transcripts.

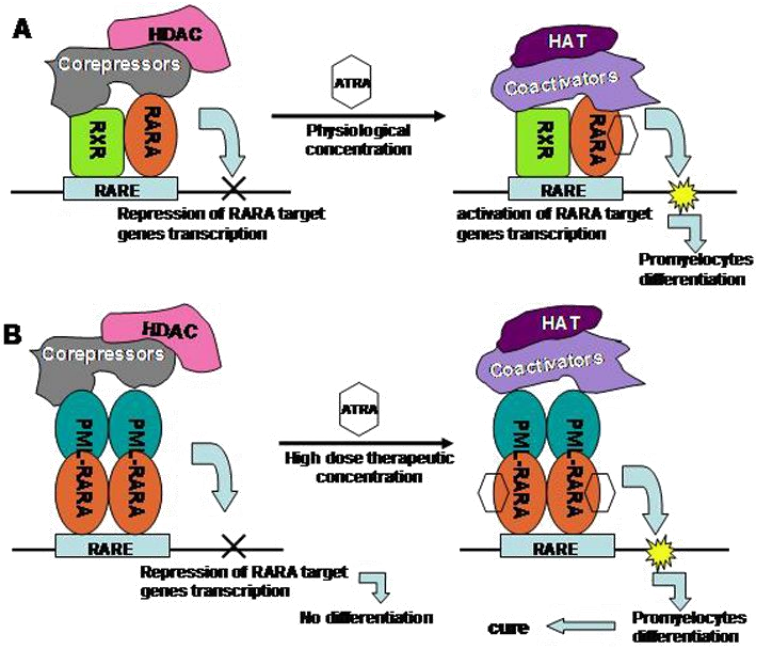
Hybrid/Mutated gene

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.

The breakpoint in RARA gene is always located in intron between A and B domains. PML gene is composed of approximately 53.000 bp with 9 exons; the PML protein is member of a multiprotein complex composing the matrix-associated nuclear bodies, which are dynamic nuclear components of 0.1 to 1.0 m in size. PML works as a tumour suppressor gene, the protein is implicated in a wide variety of cellular functions: apoptosis, differentiation, genome stability (Bernardi R and Pandolfi PP, 2007; Hsu K-S and Kao H-Y, 2018). There are 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-RARA transcripts; in the 3 types of proteins the coiled-coil domain of PML, which is an element of the ring-B box-CC/tripartite domain, is conserved; V form would be linked to ATRA with a decreased sensitivity and S form would be associated to an excess of secondary chromosome changes.

Abnormal protein

106 Kda fusion protein; role in the leukemogenic process through two main pathways: 1) interference with the signalling pathway controlled by RARA and involved in differentiation and maturation of myeloid precursors (mainly dysregulation of retinoid-inducible genes responsible for in myeloid differentiation). 2) disruption of the PML nuclear bodies (PML-NBs) which control the P53 pathway and many other cellular functions involved in genome stability, apoptosis, cellular senescence, differentiation, angiogenesis.



Molecular pathogenesis of APL.

In contrast with wild type RARA which only forms heterodimers with RXRA, the fusion protein PML/RARA can form homodimers through the coiled-coil domain of PML, which is the critical domain for the transformation of PML/RARA into an oncoprotein (Lin RJ and Evans RM, 2000; Occhionorelli M et al., 2011).
The homodimer can link to the DNA, independently from RXR. The expression of PML/RARA homodimer is sufficient ex vivo to operate the cellular transformation, however the PML/RARA homodimer is quasi always linked in vivo to RXRA which is necessary to an efficient DNA binding.
It results in a dominant negative control of both native PML and RARA functions (de Thé H et al., 1991; Melnick A and Licht JD, 1999; Occhionorelli M et al., 2011). Binding of the homodimer, by the RARA domain of PML-RARA, with DNA sites located in the promoter region of target genes, and multimerisation owing to the coiled-coil domain of PML, enhances the recruitment of co repressor proteins and of histone deacetylases (HDACs), leading to a gene repression via DNA methylation (Di Croce L et al., 2002; Martens JH et al., 2010; Occhionorelli M et al., 2011).
The classical consequences are a block of myeloid differentiation at the promyelocytic stage. A second activity of PML-RARA is to disrupts the PML nuclear-bodies involved in many cellular regulations, particularly TP53 activation, leading to an increase of progenitors self renewal (Bernardi R and Pandolfi PP, 2007; Nasr R et al., 2008).

t(11;17)(q23;q12) / acute promyelocytic leukemia --> ZBTB16 / RARA

Described in Chen Z et al., 1994; Licht JD et al., 1995; Melnick A and Licht JD, 1999; Sainty D et al., 2000. ZBTB16 is also named PLZF, ZNF145.

Disease

Variant acute promyelocytic leukemia (APL) form with atypical cytologic aspects: intermediate morphology between M2 and M3, less or not bilobed promyelocyte nucleus, no Auer rods, the hypogranular form is predominant with coarse granules, absence of faggot cells, increased number of hypogranular pseudo-Pelger neutrophils and increased CD56 expression; generally no response to ATRA therapy; however some cases achieved a remission with a treatment combining ATRA and chemotherapy or ATRA and G-CSF; worse prognostic than APL with t(15;17), whatever the treatment. Found in less than 1% of APL cases.

Cytogenetics

In some cases the translocation may be cryptic.

Hybrid/Mutated gene

Native ZBTB16 (zinc finger and BTB domain containing 16) has 7 exons, 3 alternative transcripts; encodes a 673 amino acids zinc finger protein, containing one N-terminal POZ-BTB domain (Pox virus and Zinc finger domain also called Broad Complex, tramtrack, Bric a Brac), one RD2 domain and 9 C-terminal zinc finger motifs. The native protein is involved as transcriptional

repressor in a number of pathways during development (Liu et al., 2016). The t(11;17) results in two reciprocal transcripts, encoding in the same reading frame ZBTB16/RARA and RARA/ZBTB16 proteins. ZBTB16/RARA contains the same RARA domains as in PML/RARA.
Resistance to ATRA therapy is caused by the insensibility to ATRA of the corepressors-ZBTB16-/RARA complex, in which N-CoR/SMRT co repressor proteins maintain there link with the ZBTB16 part of ZBTB16/RARA, even with therapeutic levels of ATRA.

t(5;17)(q35;q12) / acute promyelocytic leukemia --> NPM1 / RARA

Described in Corey SJ et al., 1994; Redner RL et al., 1996; Rush EA et al., 2013. The translocation fuses the nucleophosmin gene (NPM1) with RARA. It is the second most frequent variant translocation after the t(11;17)(q23;q21). Apart from NPM1/RARA two other translocation / fusion gene involve NPM1 in haematological neoplasms: t(2;5)(p23;q35) NPM1/ALK fusion in anaplastic large cell lymphoma and t(3;5)(q25;q35) NPM1/MLF1 fusion in MDS and AML. Down or up regulation of NPM1 caused by mutations lead also to solid tumors (Grisendi S et al., 2006).

Disease

Exceptional; expresses overall similar morphologic and immunophenotypic features as classical APL; respond to ATRA treatment.

Hybrid/Mutated gene

NPM1 encodes a nucleolar phosphoprotein mainly involved in ribosomal particles assembly and regulation of centrosome duplication. It is also implicated in the regulation of stability and activity of various tumor suppressor proteins, including TP53. It plays a crucial role in cell growth regulation and genomic stability. According to the physiological or physiopathological conditions NPM1 should be considered either as an oncoprotein or as a tumor suppressor (Grisendi S et al., 2006). The t(5;17) produces both NPM1/RARA and, inconstantly, RARA/NPM1 transcripts. Only NPM1/RARA protein is responsible for APL disease. As for PML/RARA and ZBTB16/RARA fusion genes the breakpoint in RARA occurs in the second intron so that its B-F domain is fused to the N-terminal domains of NPM1, in the same reading frame. The analysis of the initial published case (Redner RL et al., 1996) showed two different breakpoint in NPM1, generating two transcripts of 2.3 kb and 2.4 kb. Both coded two proteins of 520 and 563 amino acids respectively, with the same level of expression. These two fusion proteins had a RA-dependent transcriptional activity.

t(11;17)(q13;q12) / acute promyelocytic leukemia --> NUMA1 / RARA

Described in Wells RA et al., 1996, 1997, the third variant translocation to be described. Only one case reported to date, in a 6-month old male infant.

Disease

Presentation as a quite classical APL who expressed, however, multiple unexpected cutaneous lesions but peripheral blood smears and cellular immunophenotype were typical of APL. Respond to ATRA treatment and there was no relapse at 3 years after autologous bone marrow transplantation.

Hybrid/Mutated gene

The NUMA1 gene (nuclear mitotic apparatus) located at 11q13, encodes NuMA, a high molecular weight (238 kDa) coiled-coil protein component of the nuclear matrix at interphase and associated with the spindle poles during mitosis. It is involved in the processes of mitosis and in the nuclear reconstructing after mitosis. NUMA1 is composed of a large coiled-col interstitial domain of approximately 1500 amino acids involved in homo-heterodimerization, encompassed with two globular C-terminal and N-terminal domains. The C-terminal domain contains a nuclear localization signal (NLS), a microtubule binding domain (MT), a LGN binding sequence and 4 phosphorylation sites. This complex domain is necessary for localization to the nucleus and mitotic spindle functioning. The N-terminal domain is required for post mitotic nuclear reassociation. Both N- and C-terminal domains contain DNA-binding S/TPXX motifs (Melnick A and Licht JD, 1999; Radulescu AE and Cleveland DW, 2010).
The t(11;17)(q13;q21) gave rise to a 2286 amino acids NUMA1/RARA fusion protein, linking in the same reading frame the B-F domain of RARA to the N-terminal globular and the coiled coil domains of NUMA1. No alternative RARA/ NUMA1 protein could be detected. NUMA1/RARA plays a role of dominant negative RA receptor. It is able to bind to quite the same RARE sites as PML/RARA, equally as a homodimer or a heterodimer with RXR but more stable as a RXR heterodimeric complex (Dong S et al., 2003).

der(17) / acute promyelocytic leukemia --> STAT5B / RARA

The STAT5B/RARA fusion gene is a rare event, no more than 12 cases were published in 2018. It results probably from a variable rearrangement of 17q, interstitial deletion, duplication, inversion or other more complex rearrangement, undetectable by conventional and molecular cytogenetic.

However FISH with a commercial RARA dual colour or break apart probe is able sometimes to give informations, mainly in case of deletion of the 3'-RARA sequences. In the first published case (Arnould C et al., 1999) der(17) resulted from a duplication of the 17q21.3-q23 segment.

Disease

Male predominance, only two female cases reported. Clinical and cytological data compatibles with variant APL or sometimes quite atypical for APL. Very poor response to ATRA and/or ATO therapy. No one long term complete remission could be obtained (Zang C et al., 2018).

Hybrid/Mutated gene

The STAT5B gene (signal transducer and activator of transcription 5B) is located at 17q21.2, it contains 19 exons and a total of 5090 coding nucleotides. It is a member of the STAT family, it encodes a 92 kD S STAT5B protein which contains STAT proteins conserved domains: a N- terminal coiled coil domain, a DNA binding domain, a SH2 domain and a C-terminal transactivation domain. STAT5B is a signal transducer and activator of transcription, acting in the janus kinase (JAK)-STAT signaling pathway. It is activated by tyrosine-phosphorylation, permitting homo- or heteridimerization. Located inactive in the cytoplasm, the protein is rapidly translocated to the nucleus after dimerization and binds to DNA to activate its target genes (Del Rosario AM et al., 2012). The STAT5B/RARA fusion protein is composed of the N- terminal coiled-coil domain necessary for dimerization, the DNA binding domain, the SH2 and a part of the SH3 domains of STAT5B, fused in the same reading frame to the B to F domains of RARA.

No alterne RARA/ STAT5B protein is produced. Like PML/RARA, STAT5B /RARA binds to RARE as a homodimer or heterodimer with RXR. It works as a competitive inhibitor of transcriptional activity of RARA-RXR. This inhibition depends essentially on the presence of the coiled coil domain of STAT5B.

When this domain is absent, in transfection experiments with modified STAT5B /RARA protein, STAT5B/RARA expresses the same transcriptional activity as wild type RARA (Dong S and Tweardy DJ, 2002; Huret JL, 2010).

t(X;17) (p11;q21) / acute promyelocytic leukemia --> BCOR / RARA

Described in Yamamoto Y et al., 2000. Only two cases reported to date, the first in a 45-year-old man with a 45,-Y, t(X;17)(p11;q21) karyotype.

Disease

First case clinical presentation as a variant APL, with 83% of promyelocytes in a hypercellular bone marrow and a coagulopathy, but with unusual rectangular and round cytoplasmic inclusion bodies in promyelocytes.

Patient responded to ATRA therapy but was resistant to ATO.

Hybrid/Mutated gene

The BCOR gene (BCL6 co repressor) located at Xp11.4 encodes a 180 kDa nuclear protein which is a component of a polycomb complex acting as a transcription suppressor.

The BCOR/RARA fusion protein has a self association capacity through its BCOR-S region and ankyrin-repeat domain.

It can also form a heterodimer with RXR to bind with RARE, acting as a dominant negative factor of RARA transcription.

der(17) / acute promyelocytic leukemia --> PRKAR1A / RARA

Described in Catalano A et al., 2007. Only one case published in a 66-year-old man.

Karyotype showed only a trisomy 22. RARA break apart FISH showed a deletion of the 5'-RARA probe on a der(17).

A dual colour PML/RARA FISH showed a split of the RARA signal on der(17) and normal PML signals. Later on FISH with RARA and PRKAR1A probes confirmed the split of RARA and the PRKAR1A/RARA fusion on the der(17).

Disease

The patient was investigated for fatigue and anorexia. No signs of coagulopathy were observed, hypercellular bone marrow contained 83% of hypergranular promyelocytes, but without Auer rods or fagot cells. Patient responded well to ATRA and ATO.

Hybrid/Mutated gene

PRKAR1A (protein kinase A regulatory subunit1) is located at 17q24.2.

The protein is involved in the regulation of cAMP-dependent PRKA enzymatic activity. PRKAR1A/RARA binds to a number of RARE sequences, either as a homodimer or as a heterodimer with RXR.

However, only the interaction of RXR with PRKAR1A/RARA is critical for leukemic transformation (Qiu JJ et al., 2010).

t(4;17)(q12;q21) / acute promyelocytic leukemia --> FIP1L1 / RARA

Described in Kondo T et al., 2008, Zamecnikova A, 2015. Seventh variant translocation to be described, three APL cases published, however the FIP1L1/RARA fusion was previously reported in one case of juvenile myelomonocytic leukaemia (Buijs A and Bruin M, 2007).

Disease

The first patient, a 90-year old woman, responded to ATRA therapy.

Hybrid/Mutated gene

RARA breakpoint was, as expected, up side of exon 3 and it fused with exon 15 or exon 13 of FIP1 motif.

der (2)t(2;17)(q32;q21) / acute promyelocytic leukemia --> NABP1 / RARA

Described in Won D et al., 2013; Zamecnikova A, 2018.

Disease

Only one case described to date, a 59-year old man who achieved complete remission with ATRA followed by chemotherapy and allogenic bone marrow stem cells transplantation.

Hybrid/Mutated gene

NABP1 (nucleic acid binding protein 1) also named OBFC2A (oligonucleotides / oligosaccharide binding fold containing 2A) is located at 2q32.3, it is involved in DNA damage response and genome stability. In the NABP1/RARA fusion gene exon 5 of the NABP1 gene is fused with the exon 3 of RARA.

t(3;17)(26;q21) --> TBL1XR1 / RARA

Described in Chen Y et al., 2014; Zamecnikova A, 2018.

Disease

Fusion gene detected in a patient with a complex translocation t(3;17)(q26;q21), t(7;17)(q11.2;q21). Three cases known to date. Response to ATRA therapy.

Hybrid/Mutated gene

TBL1XR1/RARA (transducin beta-like 1 X-linked receptor 1) also known as TBLR1 (transducin beta-like protein 1-related protein). The TBL1XR1protein contains a LisH domain which is necessary for homo or heterodimerization, it could be involved in the TBL1XR1/RARA homodimerization.

t(1;17)(q42;q21) --> IRF2BP2 /RARA

Described in Yin CC et al., 2015 ; Shimomura Y et al., 2016 ; Jovanovic JV et al., 2017 ; Zamecnikova A, 2017 ; Mazharuddin S et al., 2018.

Disease

Four cases described in 2018, all with clinical, cytological and immunophenotypic features compatibles with APL. Two patients at least responded to ATRA therapy.

Hybrid/Mutated gene

Breakpoint in IRF2BP2 (interferon regulatory factor 2 binding protein 2) exon 2 and in RARA intron 2.

t(7;17)(q11;q21) --> GTF2I / RARA

Described in Li J et al., 2015.

Disease

One case reported in a 35-year-old APL man which did not respond to ATRA therapy.

Hybrid/Mutated gene

The t(7;17) unbalanced translocation resulted in a fusion between exon 6 of GTF2I and common exon 3 of RARA. GTF2I protein (general transcription factor 2I) is a members of the transcription factor 2I family.

It contains a leucine zipper for homodimerization and a DNA binding domain. There are 4 human GTF2I isoforms which are expressed in various tissues.

Prognosis

In APL, resistance to ATRA was studied on GTF2I/RARA-transfected HL60 cells. It showed that the resistance was associated to the interaction between GTF2I/RARA and the RING finger protein 8 (RFN8) (Yan W et al., 2019).

t(3;17)(q26;q21) --> FNDC3B / RARA

Described in Cheng CK et al., 2017.

Disease

One case in a 36-year-old man. Cytology and immunophenotype were compatible with APL and patient responded to ATRA followed by chemotherapy and a complete remission was obtained at day 30, however patient relapsed at 8 months.

Hybrid/Mutated gene

At the karyotypic level the translocation was the same as the t(3;17)(26;q21) which produce the TBLR1XR1/RARA fusion. DNA sequencing showed the FNDC3B/RARA fusion between exon 24 of FNDC3B and exon3 of RARA. Two reciprocal RARA-FNDC3B transcripts were detected. FNDC3B (fibronectin type III domain containing 3B) is implicated in protein interactions, particularly it has a role in granulocytic differentiation and it was involved in an APL-like leukaemia without RARA intervention (Wang HY et al., 2016)

t(3;17)(q12;q21) --> TFG / RARA

Described in Chong ML et al., 2018.

Disease

One case published in a 16-year-old man with a t(3;14;17) complex translocation. Bone marrow hypergranular promyelocytes and immunophenotype diagnosed an APL which responded to ATRA therapy.

Hybrid/Mutated gene

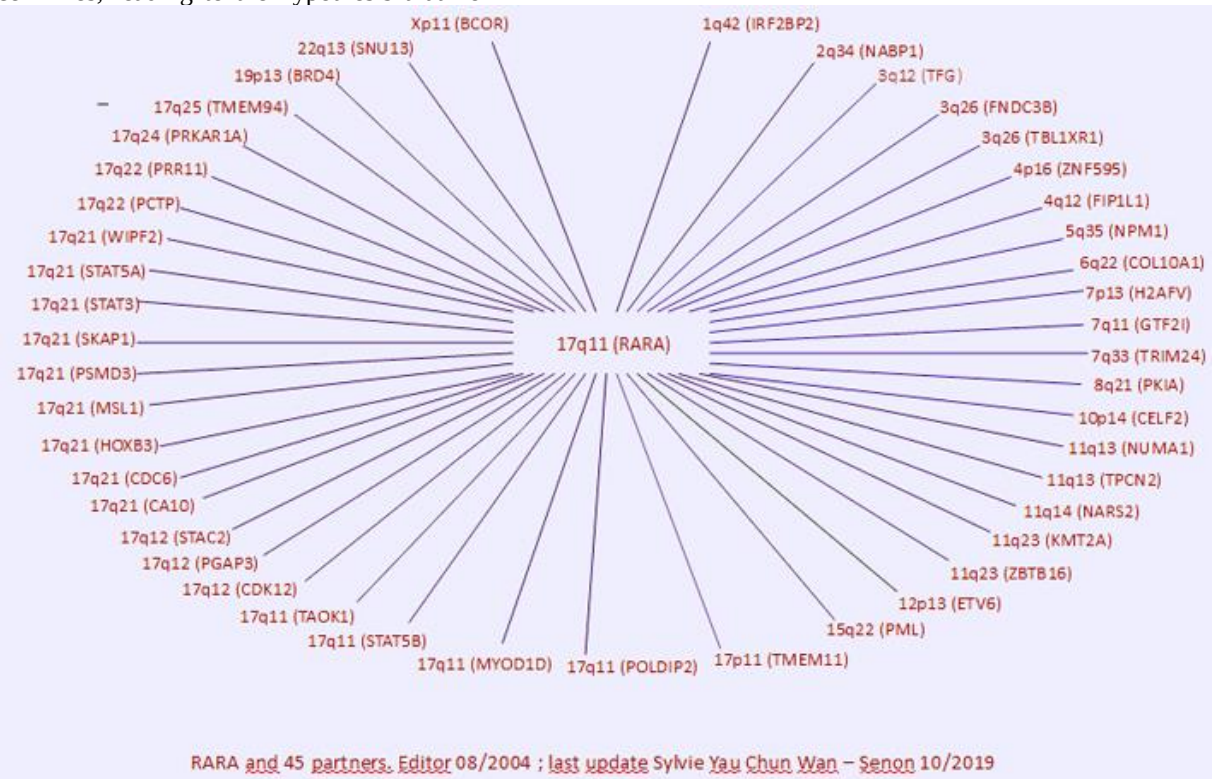
RNA and cDNA sequencing showed a TFG/RARA fusion. TFG (TRK-fused gene) is located at 3q12.2, breakpoints of the fusion gene occurred in TFG exon 7 and RARA exon 3.

Non APL malignancies

Disease

Mutations in the ligand binding domain of RARA, associated with MED12 gene mutations, were frequently observed in breast fibroadenoma and phyllode tumors (Tan J et al., 2015).
A super enhancer (SE) was observed at the RARA locus, in a subset of patients with AML other than APL. This SE was associated with a high RARA expression and evidences of differentiation in AML cell lines, leading to the hypothesis that non-APL AML patients with such a SE could be sensitive to RA therapy (McKeown MR et al.; 2017).
t(11;17)(q23;q12) / M5 acute myeloid leukemia --> KMT2A / RARA: 1 case to date (Shekhter-Levin et al.2000); not found in APL; belongs to the MLL/11q23 leukemias

Breakpoints



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