

Leukaemia Section

Mini Review

t(X;21)(p22;q22)

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Clinics and pathology

Disease

Acute myeloid leukemia with maturation (AML M2) in one case only.

Phenotype/cell stem origin

CD13+, CD33+, CD34+, and CD117+ blast population consistent with AML-M2 by FAB subtype.

Etiology

Unknown.

Epidemiology

Single case involving 74 year old male.

Clinics

A 74-year-old Caucasian male patient with progressive weakness and fatigue without any 'B symptoms'.

Evolution

Despite intensive induction chemotherapy with Ara-C, Mitoxantrone, Topotecan and Mylotarg, no remission was obtained. The patient developed prolonged pancytopenia and remained transfusion-dependent.

Prognosis

The patient died five months after diagnosis from an episode of febrile neutropenia.

Genes involved and proteins

PRDX4

Location
Xp22.

DNA/RNA

About 24.4 kb in size and contains 7 exons.

Protein

PRDX4 is one of six peroxiredoxin-family genes, all of which are highly conserved in eukaryotes and prokaryotes and are ubiquitously expressed, being highest in pancreas, liver, heart and lowest in small intestine, thymus, spleen, and brain, and undetectable in peripheral-blood leukocytes. They use redox-active cysteines to reduce peroxides. In contrast to the intracellular localization of other family members, PRDX4 exists uniquely in the plasma, where the reduced form binds as a homodimer to heparan sulfate on endothelial cell surfaces. PRDXs are also implicated in a number of cellular functions such as cell proliferation and differentiation, enhancement of natural killer cell activity, protection of free radical sensitive proteins, hemoglobin metabolism, and intracellular signaling. PRDX4 plays a regulatory role in the activation of the transcription factor NF-κB by modulating IκB -α phosphorylation in the cytoplasm, and thus it is an immediate regulator of H₂O₂-mediated activation of NF-κB. In addition, PRDX1 or PRDX2 null mice have hemolytic anemia and several malignancies including lymphoma, indicating the essential role of these genes in erythrocyte antioxidant defense and in tumor suppression.

RUNX1/AML1

Location
21q22.

DNA/RNA

Transcription from telomere to centromere.

Protein

Contains the RUNT binding domain at 5' portion and

the transactivation domain at 3' portion. Forms heterodimers; widely expressed; nuclear localization; a transcription factor and critical regulator of hematopoietic-cell development.

Result of the chromosomal anomaly

Hybrid gene

Description

AML1 is fused to PRDX4 in-frame. Two in-frame AML1-PRDX4 fusion transcripts were detected with alternative splicing of exon 6 of AML1. One was the fusion between exon 5 of AML1 and exon 2 of PRDX4; the other was between exon 6 of AML1 and PRDX4.

Transcript

No PRDX4-AML1 fusion transcript was detected.

Fusion protein

Description

Contains the RUNT binding domain of AML1 at 5' portion and two highly conserved cysteine residue motifs of PRDX4 in 3' portion. The first exon of the

PRDX4 gene codes for a signal peptide that allows the secretion of the PRDX4. The first exon is lost as a result of the translocation.

Oncogenesis

The hybrid gene could function with a dominant-negative effect on the normal AML1. The hybrid gene contains two cysteine residue motifs of the PRDX4 at the 3' portion, but not the signal peptide which allows the secretion of PRDX4, thus resulting in loss of at least one function of PRDX4 due to non-secretion. Recently, microarray studies on leukemia samples showed PRDX4 was down-regulated in APL with t(15;17) compared with all other AML samples.

References

Zhang Y, Emmanuel N, Kamboj G, Chen J, Shurafa M, Van Dyke DL, Wiktor A, Rowley JD. PRDX4, a member of the peroxiredoxin family, is fused to AML1 (RUNX1) in an acute myeloid leukemia patient with a t(X;21)(p22;q22). *Genes Chromosomes Cancer*. 2004 Aug;40(4):365-70

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