Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

LYL1 (lymphoblastic leukemia derived sequence 1)

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Published in Atlas Database: December 2006

Online updated version: http://AtlasGeneticsOncology.org/Genes/LYL1ID51ch19p13.html
DOI: 10.4267/2042/38405

Identity

Hugo: LYL1 (lymphoblastic leukemia derived sequence 1)
Location: 19p13.2

DNA/RNA

Note: DNA size: 3.83 kb; mRNA size: 1492 bp; Exons: 4.

Description

Location of the LYL1 gene, identified by Non-random chromosomal translocation t(7;19)(q35;p13) associated with T-cell acute lymphoblastic leukemia (T-ALL), was mapped to the short arm of chromosome 19 (19p13) by in situ hybridization.

Transcription

Expression levels of LYL1 are comparatively higher in normal bone marrow, spleen, lung, thymus and spinal cord tissues. Ectopic transcription is observed in T-lymphoblastic and myeloblastic leukemic cells.

Protein

Description

LYL1 encodes a basic helix-loop-helix (bHLH) protein, with 267 amino acids and molecular weight of 28628 Da.

Localisation

Subcellular location is potentially intracellular (nucleus). However, ectopic protein staining was observed in cytoplasm of myeloid leukemia cells with immunohistochemistry.

Function

Recent studies show that LYL1 is required for fetal and adult hematopoietic stem cell function and B-cell differentiation. Overexpression of LYL1 is implicated in the pathogenesis of T-ALL as well as myeloid malignancies (see below, disease implications). The LYL1 protein is a transcription factor (TF), structurally and functionally similar to another bHLH protein TAL1/SCL which is also implicated in T-ALL. Expression of both LYL1 and TAL1/SCL are regulated by the Ets and GATA factors; However, ectopic expression of SCL but not Lyl1 can rescue haematopoietic differentiation in SCL(-/-) ES-cells, providing a molecular explanation for the vastly different phenotypes of SCL(-/-) and Lyl1(-/-) mouse embryos.
Efficient DNA binding of LYL1 requires dimerization with proteins. Specific in vivo association was observed between the bHLH and LIM proteins (LMO1 and LMO2). LYL1 readily forms heterodimeric complexes with E2A and may function as a dominant-negative preventing the activation of E2A responsive genes. LYL1 interacts also with p105 the precursor of NF-KappaB1 p50.

Homology

The bHLH region of LYL1 and TAL1/SCL proteins show 82% amino acid identity, suggesting that these two proteins share at least some target genes and biologic functions. However, LYL-1 and TAL1diverge largely outside the bHLH region and display a distinct expression pattern in hematopoietic cells. Mouse Lyl-1 protein is 78% identical to human LYL1.

Implicated in

t(7;19)(q35;p13) ⟶ TCRB /LYL1 in T-cell acute lymphoblastic leukemia, other T-ALL, acute myeloblastic leukemia (AML) or myelodysplastic syndrome (MDS)

Disease

The LYL1 gene was originally identified at the chromosomal translocation t(7;19)(q35;p13) associated with T-ALL. However, over-expression of LYL1 has been reported in T-ALL cases without apparent chromosome aberration. Recent studies on leukemia cell lines and patient samples suggested its involvement in myeloid malignancies. Using real-time quantitative RT-PCR assay, the authors found that the expression of LYL1 was at a significantly higher level than normal bone marrow cells in the majority of cases of acute myeloblastic leukemia (AML) or myelodysplastic syndrome when compared to normal bone marrow. This study also showed that LYL1 was highly expressed in most AML cell lines and in CD34(+) AML cells.

Prognosis

Expression of LYL1 is associated with unfavorable prognosis in T-ALL cases. LYL1(+) cases have a gene expression signature corresponding to that of the most immature normal T-cell precursors (CD4/CD8 double-negative cells), which express CD34 but not CD4, CD8, or CD3. Less favorable outcomes were observed in subgroups defined by gene expression profiles characteristic of TAL1(+) or LYL1(+) samples, which resemble late cortical and early pro-T thymocytes, respectively.

Cytogenetics

The LYL1 gene was originally identified at the breakpoint of the translocation t(7;19)(q35;p13) in cases of T-ALL. It is the LYL1 gene but not protein that is structurally altered following t(7;19), resulting in its head-to-head juxtaposition with the T-cell antigen receptor beta gene (TCR-beta). The translocation resulted in truncation of the LYL1 gene and production of abnormal-sized RNAs, bringing LYL1 gene under the regulatory control of TCR-beta, and thus resulting in its ectopic expression. In addition to the t(7;19)(q35;p13), other translocations are t(1;19)(p34;p13), t(1;19)(p32;p13), t(9;19)(q34;p13), t(9;19)(q32;p13), t(10;19)(q24;p13), t(11;19)(p13;p13), t(15;19)(q22;p13) etc; it is not known if all of the translocations lead to enhanced expression of LYL1.

Hybrid/Mutated Gene

The TCR-beta locus at 7q35 spans 685 kb (64-67 variable genes TRBV, 2 clusters of diversity, joining and constant segments).

Oncogenesis

As discussed above, the LYL1 gene was first identified at t(7;19)(q35;p13) associated T-ALL. However, over-expression of LYL1 has been reported in T-ALL cases without apparent chromosome aberration. LYL1, TAL1 and TAL2 constitute a discrete subgroup of helix-loop-helix proteins, each of which can potentially contribute to the development of T-ALL. Specific in vivo association between the bHLH and LIM proteins is implicated in human T cell leukemia. LYL1 can readily form heterodimers with E2A and NF-KappaB1 p105 protein. It is possible that LYL1 may function as a dominant-negative preventing the activation of the tumor suppressors like E2A. Ectopic expression of LYL1 may also be involved in myeloid leukemia.

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This article should be referenced as such:
Meng Y, Minden MD. LYL1 (lymphoblastic leukemia derived sequence 1). Atlas Genet Cytogenet Oncol Haematol.2007; 11(2):99-101.