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Leukaemia Section

Mini Review

t(X;11)(q24;q23) MLL-SEPTIN6

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Clinics and pathology

Disease

All the described cases were diagnosed as having acute myeloid leukemia (AML), classified as FAB- M2 (5 cases), M4 (4 cases), M1 (1 case) and M5 (1 case), indicating that AML with the MLL-SEPTIN6 fusion gene have a tendency to differentiate into the myeloid lineage. All the patients were infants and young children aged 0 to 29 months, suggesting that AML with t(X;11)(q24;q23) is a subgroup of infant leukemia.

Phenotype/cell stem origin

Suggested involvement of a pluripotent stem cell or a myeloid progenitor cell.

Etiology

No known prior exposure; putative association with in utero exposure to recurrent genetic insults.

Epidemiology

Involvement of the SEPTIN6 gene on Xq24 in MLL rearrangements occurs very rarely, with only 13 cases (7 males, 6 females) having been documented in the literature. In addition, 3 AML cases with chromosomal translocation t(X;11)(q24;q23) (3 males aged 0 to 6 years), which also potentially could be found to involve MLL and SEPTIN6 genes have been described confirming the recurrent nature of this translocation.

Clinics

Hepatosplenomegaly (3 cases), massive and diffuse adenopathy (2 cases), lympadenophaty (2 cases), CNS involvement in 2 cases as well as chloroma, scalp nodules, mucosal and cutaneous pallor, bluish cutaneous nodules and petecchiae were described. Notably, in 2 of the patients bilateral and right exophthalmus was described. Peripheral blood leukocytosis (WBC $13.4x10^9$/L to $608x10^9$/L; mean $223x10^9$/L), anemia and thrombocytopenia were reported in the majority of patients.

Prognosis

From the 4 patients treated with chemotherapy one is alive (13+ months), 3 patients died 1 to 8 months from diagnosis; 8 patients received bone marrow transplantation, among them 2 of the patients died after 9 and 11 months, 6 patients are alive (one months to 7 years) indicating the prognosis is rather poor.

Cytogenetics

Cytogenetics morphological

Chromosomal rearrangements of 11q23 and Xq24 resulting in MLL-SEPT6 fusions are often complex and sometimes cryptic associated with 11q insertions. In addition, molecular detection of MLL-SEPTIN6 transcripts in cases with normal cytogenetics and in patients with chromosomal Xq22 breakpoints indicates the difficulty in precise chromosomal breakpoint definition.

Additional anomalies

+6 (2 cases), del(11)(q13), i(10)(q10), add(X)(p11) described in single cases.

Variants

At least four different types of chromosomal rearrangements have been described that can generate the MLL-SEPT6 fusion.

Genes involved and proteins

Note

MLL and SEPTIN6 reside on their respective chromosome loci in reverse orientation, that is, the orientation of the MLL gene is centromere-to-telomere

and the orientation of the SEPTIN6 gene is reversed, telomere to centromere at Xq24. This may explain why the MLL/SEPTIN6/Xq24 rearrangement is often associated with complex translocations and with 11q insertions.

MLL (Mixed lineage leukemia gene, ALL1, HRX, and HRTX)

Location
11q23

DNA/RNA
The MLL genomic structure consists of at least 36 exons spanning a region of ~89 kb. The mRNA of ~11.9 kb encodes a massive nuclear protein of 3969 amino acids with a molecular weight of nearly 430 kDa.

Protein
Multi-domain protein characteristic of several domains with assigned activities including an N terminus with DNA binding motifs; AT-hook motifs, 4 cysteine-rich zinc fingers, a transactivation domain, and a highly conserved C-terminal domain with histone methyltransferase activity. Nuclear protein; a major regulator of class I homeobox (HOX) gene expression; functions as a positive regulator of gene expression in early embryonic development and hematopoiesis regulation.

SEPTIN6

Location
Xq24

DNA/RNA
The SEPT6 gene, belongs to the evolutionarily conserved family of genes of septins consisting of 12 exons. Four types of transcripts: 2.3 kb, 2.7 kb, 3.1 kb and 4.6 kb coding for three isoforms. SEPT6 is ubiquitously expressed in tissues; in the human, several alternatively spliced SEPTIN6 transcripts are differentially expressed in adult and fetal tissues.

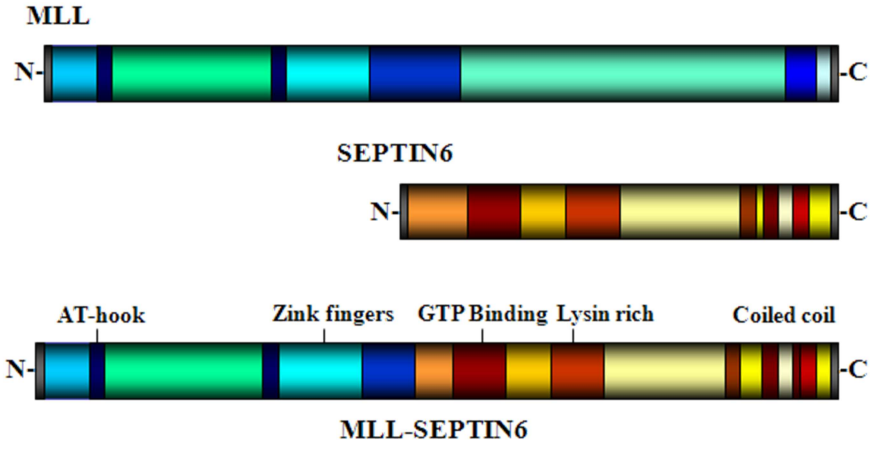
Protein
434 amino acids; 49717 Da.

SEPT6 is a GTP-binding protein with a central conserved ATP-GTP binding motif, a lysin rich region, a variable N-terminal extension domain and a C-terminal coiled coil. May function in heteropolymeric complexes; roles in GTPase signaling, cell division, cytokinesis, cytoskeletal filament formation, cell polarity, and oncogenesis.
Septins, a family of conserved GTP-binding proteins, are characteristically found in the heteropolymeric filaments and associate with cellular membranes, microtubules and actin filaments which are assembled from asymmetrical heterotrimers, composed of SEPT2, SEPT6 and SEPT7 that associate head-to-head to form a hexameric unit. Mammalian septins localize in the cytoplasm and assemble into heteromeric complexes composed of three or more septin subunits.

Result of the chromosomal anomaly

Hybrid gene

Note
5' MLL - SEPTIN6 3'
The MLL genomic breakpoints in MLL-SEPT6 AML patients in all cases occurred in the MLL 8.3 kb breakpoint cluster region (BCR) and seem to occur preferentially in the telomeric half (between introns 7 and 11) of the MLL BCR. In the majority of reported cases 5' MLL sequences joined in-frame with SEPTIN6 downstream of SEPT6 exon 1. In rare cases, out-of-frame fusion between MLL exon 7 and SEPT6 exon 2, with splicing of MLL exon 6 have been described.
The breakpoint junctions in the SEPT6 intron 1 mapped to the vicinity of GC-rich low-complexity repeats, Alu repeats, and a topoisomerase II recognition sequence raising the possibility that the non-homologous DNA end-joining pathway may be involved in the in the generation of MLL-SEPT6 rearrangements in infant acute myeloid leukemia and a putative association with in utero exposure to topoisomerase II inhibitors has been hypothesized.



Schematic representation of MLL-SEPTIN6 fusion protein.

Transcript
5'-MLL/SEPTIN6-3' chimeric transcript.

Fusion protein

Note
The MLL-SEPT6 chimeric protein consists of the AT-hook DNA-binding, the DNA methyltransferase, the and repression domains of MLL and almost the entire open reading frame of SEPT6 including the central conserved ATP-GTP binding motif.

Expression / Localisation
MLL fusion genes express in- frame chimeric proteins residing in the nucleus.

Oncogenesis
MLL is fused with a partner gene in MLL-related leukemias leading to the aberrant activation of target genes, including HOX genes. The phenotype depends on the fusion partner, indicating that each fusion partner is critical for the leukemogenesis. Among partner genes, septins are the protein family most frequently involved in rearrangements with MLL, suggesting that SEPTIN family members are particularly vulnerable to form MLL translocations. MLL fusions with several different SEPTIN family members (SEPT2, SEPT5, SEPT9, and SEPT11) are preferentially associated with myeloloblastic rather than lymphoblastic leukemogenesis suggesting an important common pathway to leukaemogenesis in AML with these translocations.
The observation that overexpression of SEPT6 itself does not lead to the myeloid immortalization of murine hematopoietic progenitors in vitro, whereas the overexpression of MLL-SEPT6 does indicate that the fusion partner-mediated homooligomerization of MLL-SEPT6 through its intact GTP-binding domain and coiled-coil region in the nucleus is essential to immortalize hematopoietic progenitors. However, MLL-SEPT6 rearrangment induced lethal myeloproliferative disease with long latency in mice, but not acute leukemia in experimental models. These findings suggest that secondary genotoxic effects on DNA repair and/or cell-cycle regulation are required for oncogenesis in MLL-SEPT6 associated leukemias.

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