**Leukaemia Section**

Short Communication

**t(X;11)(q26;q23) / ins(X;11)(q26;q23q23)**

Nuno Cerveira, Manuel R Teixeira

Department of Genetics and Research Center, Portuguese Oncology Institute, Rua Dr Antonio Bernardino de Almeida, 4200-072 Porto, Portugal (NC, MRT)

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**Clinics and pathology**

**Disease**

Pediatric biphenotypic acute leukemia

**Phenotype/cell stem origin**

Suggested involvement of a pluripotent stem cell.

**Etiology**

De novo acute leukemia.

**Epidemiology**

The only case described was a 6-year-old boy who was diagnosed as having biphenotypic phenotype (T/myeloid) acute leukemia (Cerveira et al., 2010). This is the first, and to our knowledge, the only case described in the literature of a rearrangement between the CT45A2 gene located on Xq26.3 and the MLL gene located in 11q23 (Cerveira et al., 2010).

**Clinics**

Fever, asthenia and cutaneous pallor. Peripheral blood analysis revealed anemia (Hb 6.3 g/dl) and bicipotenia. Bone marrow analysis revealed the presence of 51% of blasts with the immunophenotype CD3+, CD13+, CD33+, and CD117+. No blasts were detected in the cerebrospinal fluid (Cerveira et al., 2010).

**Cytogenetics**

In the only case characterized the karyotype was complex showing a cryptic insertion of 11q23, where the MLL gene is located, in Xq22-25 (Cerveira et al., 2010). Based on the chromosome banding and FISH findings, the karyotype was described as 45,XY,add(14)(q24),add(17)(p13)-,-18[8],ish ins(X;11)(q22-25;q23q23)(MLL5'+;MLL5'-,MLL3'+), add(14)(IGH-),der(17)17qter-->17p13::?:18q21-- >18q21::?(BCL2+)/46,XY[12].

**Prognosis**

The patient was treated according to the ELAM 02 protocol (aracytine, mitoxantrone and methotrexate) and entered complete remission after induction chemotherapy. Seven months later he was submitted to allogeneic bone marrow transplantation with umbilical cord hematopoietic progenitors but, after one year, the patient showed evidence of relapse. Treatment with the AML relapse protocol was started, but only partial remission was achieved four months later. The patient underwent a haploidentical transplant with his mother's peripheral blood cell progenitors, but the disease relapsed again and the patient died nine months later. In conclusion, the prognosis seems to be rather poor, but additional cases are needed to support this hypothesis.

**Genes involved and proteins**

**MLL**

**Location**

11q23

**DNA/RNA**

The mixed lineage leukemia protein-1 gene (MLL) is the mammalian homolog of Drosophila trithorax (trx), the founding member of the trithorax group proteins (Cerveira et al., 2011). The MLL gene is approximately 89 kb long and consists of 37 exons.

**Protein**

MLL encodes a 3969 amino acid histone methyltransferase that has been reported to assemble a supercomplex of proteins of varied function involved in transcriptional regulation (Cerveira et al., 2011). Current evidence suggests that MLL binds DNA in a
non-sequence-specific manner, and is a major regulator of class I homeobox (HOX) gene expression. HOX genes are transcription factors involved in the specification of cell fate during development, playing a key role in the regulation of hematopoietic development (Cerveira et al., 2011).

**CT45A2**

**Location**

Xq26.3

**DNA/RNA**

The CT45A2 gene is a member of the Cancer/Testis (CT) gene family cluster localized at Xq26.3 and consists of 5 exons (Chen et al., 2005; Chen et al., 2009). The CT45 gene family comprises six members (CT45A1 to CT45A6) located in Xq26.3 that are near-identical gene copies, suggesting the occurrence of recent gene duplications (Chen et al., 2005; Chen et al., 2009).

**Protein**

CT genes encode a heterogeneous group of immunogenic proteins (CT antigens) that were initially identified as immunogenic tumor antigens and whose expression is almost restricted to the normal testis and a percentage of various tumor types, including melanoma and carcinomas of the bladder, lung and liver (Chen et al., 2005; Chen et al., 2009). The combination of restricted normal tissue expression, spontaneous immunogenicity and frequent tumor expression has made these antigens attractive targets for cancer vaccines. The function of CT proteins function remains to be elucidated (Chen et al., 2005; Chen et al., 2009).

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**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**

5’ MLL - 3’ CT45A2

The insertion of 11q23 material into Xq26.3 contained the 5’ MLL region (exons 1 to 9) in addition to 16 other 11q23 genes (Cerveira et al., 2010). In respect Xq26.3, the insertion occurred in DDX26B intron 8, 550 bp downstream of DDX26B exon 8 and 3,951 bp upstream of the CT45A2 gene, with the insertion of two (CG) and three additional nucleotides (GAA) at the breakpoint junctions, respectively. In addition to the insertion, a large fragment of Xq26.3, encompassing the 3’ region of DDX26B (exons 9-16) and the CT45A1 gene, was deleted (Cerveira et al., 2010).

**Transcript**

5’-MLL/CT45A2-3’ chimeric transcript. The MLL exon 9 is fused in-frame with nucleotide 240 of the CT45A2 transcript. This fusion transcript contains 6 bp from the 5-UTR of CT45A2 exon 2 coding for two additional amino acids (Cerveira et al., 2010). This type of fusion is known as a spliced fusion since the chimeric MLL-CT45A2 is only generated at the RNA level and can occur either by transcriptional read-through followed by a subsequent splice event or by trans-splicing. Regardless of the underlying mechanism, the chimeric MLL-CT45A2 fusion is only produced at the RNA level (Cerveira et al., 2010).

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Schematic representation of MLL-CT45A2 genomic breakpoints, as a result of a cryptic insertion of 11q23 in Xq26.3, leading to the fusion of MLL exon 9 to the entire open reading frame of the CT45A2.

Schematic representation of MLL-CT45A2 fusion protein.
**Fusion protein**

**Description**
The in-frame fusion is predicted to give rise to a chimeric protein where the N-terminus of MLL is fused to the entire open reading frame of CT45A2 (Cerveira et al., 2010). The putative MLL-CT45A2 fusion protein of 1514 amino acids contains 1325 amino acids from the N-terminal portion of MLL and 189 amino acids deriving from the CT45A2 protein (Cerveira et al., 2010).

**Expression / Localisation**
MLL fusion genes codes for chimeric proteins that reside in the nucleus (Marschalek, 2011).

**Oncogenesis**
Deregulation of MLL protein activity result in abnormal patterns of target genes expression, including genes from the HOX family (Cerveira et al., 2011; Marschalek, 2011). HOX genes are normally expressed in lineage- and stage-specific combinations during hematopoiesis; however, cell commitment to myeloid or erythroid lineages is accompanied by global downregulation of HOX gene expression (Cerveira et al., 2011; Marschalek, 2011). A failure to downregulate HOX expression can inhibit hematopoietic maturation and lead to leukemia. However, it seems that the leukemia phenotype also depends on the fusion partner, indicating that, at least for some fusion partners, the gene involved is critical for leukemogenesis. A consequence of this fusion is that the expression of the CT45A2 protein, usually restricted to testicular tissue, is activated. The phenotypic consequences of CT45A2 expression in the leukemia cells of leukemia patients are currently unknown (Cerveira et al., 2010).

**References**


