t(9;22)(q34;q11) in ANLL
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Identity

Note: Although the same hybrid genes issued from ABL and BCR are the hallmark of the t(9;22) translocation, this translocation may be seen in the following diseases: CML, ANLL, and ALL, and will therefore be described in the 3 different situations: t(9;22)(q34;q11) in CML, t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL. t(9;22)(q34;q11) in ANLL is herein described.
**Clinics and pathology**

**Disease**
ANLL

**Phenotype / cell stem origin**
Mostly M1 or M2 ANLL.

**Epidemiology**
3% of ANLL; 1% in childhood ANLL.

**Prognosis**
Is very poor.

**Cytogenetics**

**Cytogenetics, morphological**
The chromosomal anomaly disappears during remission, in contrast with BC-CML cases when treated with conventional therapies.

**Genes involved and Proteins**

**ABL**

**Location:** 9q34

**DNA / RNA**
Alternate splicing (1a and 1b) in 5'.

**Protein**
Giving rise to 2 proteins of 145 kDa; contains SH (SRC homology) domains; N-term SH3 and SH2 - SH1 (tyrosine kinase) - DNA binding motif - actin binding domain C-term; widely expressed; localisation is mainly nuclear; inhibits cell growth.

**BCR**

**Location:** 22q11

**DNA / RNA**
Various splicings.

**Protein**
Main form: 160 kDa; N-term Serine-Treonine kinase domain, SH2 binding, and C-term domain which functions as a GTPase activating protein for p21rac; widely expressed; cytoplasmic localisation; Protein kinase; probable role in signal transduction.

**Results of the chromosomal anomaly**

**Hybrid gene**

**Description**
The crucial event lies on der(22), id est 5' BCR/3' ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed;

Breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5' of 1b, or 3' of 1a, but always 5' of exon 2;

Breakpoint in BCR is either (as in ALL cases):
1- in the same region as in CML, called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210), with the first 902 or 927 amino acids from BCR;
2- in a 35 kb region between exons 1 and 2, called m-bcr (minor breakpoint cluster region), → 7 kb mRNA, resulting in a 190 kDa protein (P190), with the 427 N-terminal amino acids from BCR.

**Transcript**
7 or 8.5 kb
**Fusion protein**

**Description**

190 or 210 kDa (see diagram); BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear; this may have a carcinogenic role. The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hiding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated.

**Oncogenesis**

1-Proliferation is induced: there is activation by BCR/ABL of Ras signal transduction pathway via it’s linkage to son-of-sevenless (SOS), a Ras activator; PI3-K (phosphatidyl inositol 3’ kinase) pathway is also activated; MYC as well;
2-BCR/ABL inhibits apoptosis;
3-BCR/ABL provokes cell adhesive abnormalities: impaired adherence to bone marrow stroma cells, which allows unregulated proliferation of leukaemic progenitors.

**To be noted**

Blast crisis is sometimes at the first onset of CML, and those cases may be indistinguishable from true ANLL with t(9;22) and P210 BCR/ABL hybrid.

**References**


*This article should be referenced as such:*