t(9;22)(q34;q11) in CML

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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: chronic myelogenous leukemia (CML), acute non lymphocytic leukemia (ANLL), and acute lymphocytic leukemia (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 CML is herein described.

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9 t(9;22)(q34;q11) G- banding (left) - Courtesy Jean-Luc Lai and Alain Vanderhaegen (3 top) and Diane H. Norback, Eric B. Johnson, and Sara Morrison-Delap, UW Cytogenetic Services (2 bottom); R-banding (right) top: Editor; 2 others Courtesy Jean-Luc Lai and Alain Vanderhaegen); diagram and breakpoints (Editor).
Clinics and pathology

Disease
CML: all CML have a t(9;22), at least at the molecular level (see below); but not all t(9;22) are found in CML, as already noted.

Phenotype/cell stem origin
Evidence exists for the involvement of the most primitive and quiescent hematopoietic stem cell compartment (CD34+/CD38-, Thy1+): t(9;22) is found in myeloid progenitor and in B-lymphocytes progenitors, but, involvement of the T-cell lineage is extremely rare.

Epidemiology
Annual incidence: 10/10^6 (from 1/10^6 in childhood to 30/10^6 after 60 yrs); median age: 30-60 yrs; sex ratio: 1.2M/1F.

Clinics
Splenomegaly; chronic phase (lasts about 3 yrs) with maintained cell's normal activities, followed by accelerated phase(s) (blasts still < 15%), and blast crisis (BC-CML) with blast cells > 30%; blood data: WBC: 100 X 10^9/l and more during chronic phase, with basophilia; a few blasts; thrombocytosis may be present; low leucocyte alkaline phosphatases; typical acute leukaemia (AL) blood data at the time of myeloid or lymphoid -type blast crisis.

Cytology
Hyperplastic bone marrow; granulocytes proliferation, with maturation; followed by typical AL cytology (see t(9;22)(q34;q11)/ANLL, and t(9;22)(q34;q11)/ALL).

Treatment
aIFN therapy or allogeneic bone marrow transplantation (BMT), donor leukocytes infusions.

Prognosis
Median survival: 4 yrs with conventional therapy (hydroxyurea, busulfan), 6 yrs with aIFN therapy; allogeneic bone marrow transplantation may cure the patient; otherwise, the best treatment to date associates interferon a, hydroxyurea and cytarabine.

Cytogenetics

Cytogenetics morphological
The chromosomal anomaly persists during remission, in contrast with acute leukemia (AL) cases.

Cytogenetics molecular
Is a useful tool for diagnostic ascertainment in the case of a 'masked Philadelphia' chromosome, where chromosomes 9 and 22 all appear to be normal, but where cryptic insertion of 3' ABL within a chromosome 22 can be demonstrated.

Additional anomalies
1. May be present at diagnosis (in 10%, possibly with unfavourable significance), or may appear during course of the disease, they do not indicate the imminence of a blast crisis, although these additional anomalies also emerge frequently at the time of acute transformation;
2. These are: +der(22), +8, i(17q), +19, most often, but also: +21, -Y, -7, -17, +17; acute transformation can also be accompanied with t(3;21) (q26;q22) (1% of cases); near haploidy can occur; of note, although rare, is the occurrence of chromosome anomalies which are typical of a given BC phenotype (e.g. t(15;17) in a promyelocytic transformation, dic(9;12) in a CD10+ lymphoblastic BC ...); +8, +19, +21, and i(17q) occur more often in myeloid -rather than lymphoid- blast crises.

Variants
t(9;22;V) and apparent t(V;22) or t(9;V), where V is a variable chromosome, are found in 5-10% of cases; however, 9q34-3'ABL always joins 22q11-5'BCR in true CML; the third chromosome and breakpoint is, at times, not random. In a way, masked Philadelphia chromosomes (see above) are also variants.

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 splicing.

**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.

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**
1. The crucial event lies on der(22), i.e. est 5' BCR/3' ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed;
2. 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;
3. Breakpoint in BCR is in a narrow region, therefore 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**
8.5 kb mRNA, resulting in a 210 KDa chimeric protein.

**Detection**
RT-PCR for minimal residual disease detection.

**Fusion protein**

**Description**
P210 with the first 902 or 927 amino acids from BCR; BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear. It is now clearly established that BCR-ABL is the oncogene responsible for the occurrence of CML. 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**
A- Major molecular pathways activated by BCR-ABL.
1. BCR/ABL activates RAS signaling through the GRB2 adaptor molecule which interacts specifically with the Y177 of BCR.
2. PI3-K (phosphatidyl inositol 3' kinase) pathway is also activated with secondary activation of the AKT/PKB pathway.
3. Integrity of transcription machinery induced by MYC is necessary for the transforming action of BCR-ABL.
4. More recently, activation of STAT (Signal transducers and activators of transcription) molecules has been described as a major molecular signaling event induced by BCR-ABL, with activation of essentially STAT5, 1, and 6.
5. Activation of the molecules of the focal adhesion complex (PAXILLIN, FAK) by BCR-ABL requires the role of the adaptor molecule CRK-L.
6. BCR-ABL activates negative regulatory molecules such as PTP1B and Abi-1 and their inactivation could be associated with progression into blast crisis.

B- Correlations between molecular pathways and leukemic phenotype observed in primary CML cells or in BCR-ABL-transduced cells are currently limited.
1. BCR-ABL has anti-apoptotic activity (Pf63K/Akt/STAT5).
2. BCR/ABL induces cell adhesive and migratory abnormalities in vitro in the presence of fibronecton or in transwell assays (Abnormal integrin signaling/FAK/CRK-L/Abnormal response to chemokine SDF-1).
3. BCR-ABL induces a dose-effect relationship in CML cells with increased BCR-ABL mRNA during progression into blast crisis, with induction of genetic instability.

**To be noted**

**Note**
1. Blast crisis is sometimes at the first onset of CML, and those cases may be undistinguishable from true ALL or ANLL with t(9;22) and P210 BCR/ABL hybrid;
2. JCMC (juvenile chronic myelogenous leukaemia) is not the juvenile form of chronic myelogenous leukaemia: there is no t(9;22) nor BCR/ABL hybrid in JCMC, and clinical features (including a worse prognosis) are not similar to those found in CML;
3. so called BCR/ABL negative CML should not be called so!
4. P53 is altered in 1/3 of BC-CML cases
5. Most recent developments: Evidence of telomere shortening in CML cells during progression into blast crisis.
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