

Chronic myelogenous leukaemia (CML) (updated: old version not available)

Clinics and Pathology

Disease	CML is a malignant chronic myeloproliferative disorder (MPD) of the hematopoietic stem cell.
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) in ALL , t(9;22)(q34;q11) in ANLL)
Treatment	a IFN 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	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: this translocation may also be seen in ALL, and in ANLL (see: t(9;22)(q34;q11) in ALL , t(9;22)(q34;q11) in ANLL), and the same genes are involved in the three diseases; in CML, the chromosomal anomaly persists during remission, in contrast with 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 and apparent t(V;22) or t(9;V), where V is a variable

Variants

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

Gene Name

[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

Gene Name

[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

Result of the chromosomal anomaly

Hybrid gene

Description

1. 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;
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 maior breakpoint cluster reacion). 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 (PI63K/Akt/STAT5) .
2. BCR/ABL induces cell adhesive and migratory abnormalities in vitro in the presence of fibronectin 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.
4. Molecular events associated with blast crisis: P53 mutation, methylation of ABL promoter, telomere shortening, Abi-1 inactivation.

To be noted

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. JCML (juvenile chronic myelogenous leukaemia) is not the juvenile form of chronic myelogenous leukaemia: there is no t(9;22) nor BCR/ABL hybrid in JCML, 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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