

Gene Section

Mini Review

ABL (*v-abl* Abelson murine leukemia viral oncogene homolog 1)

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Identity

Other names: ABL1

HGNC (Hugo): ABL1

Location: 9q34.1

Local order: CAN is more telomeric, TAN1 even more in 9q34.3.

DNA/RNA

Description

12 exons; 230 kb.

Transcription

Alternate splicing: 1a and 1b are 5' alternative exons; mRNA of 6 and 7 kb (with 1a and 1b respectively), giving rise to 2 protein of 145 kDa.

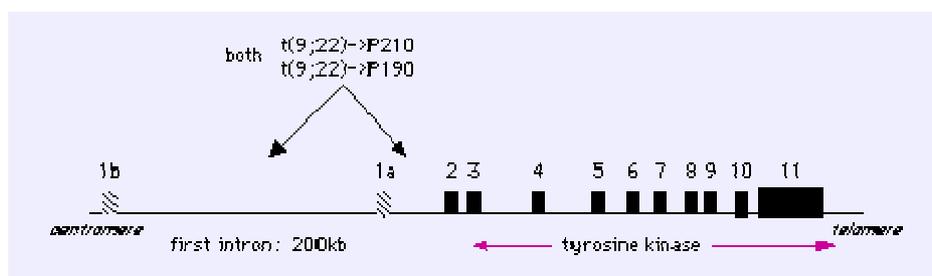
Protein

Description

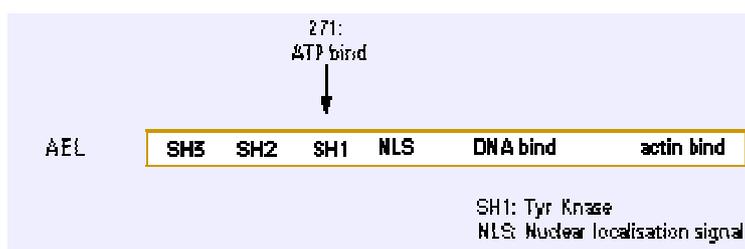
1130-1143 amino acids; 4 domains: of which are SH (SRC homology) domains; NH₂-term-- domain 1: SH3 (where can bind the binding protein BP1, to inhibit SH1 activation) and SH2 (with high affinity towards BCR first exon)-- domain 2: SH1 (with a self-phosphorylable tyrosine)—'domain' 3: nuclear localization domain (DNA binding, but not during mitosis)-- domain 4: actin binding (cytoskeleton)-- COOH-term; note: 1b (but not the 1a alternative) myristylable allowing anchorage to the membrane.

Expression

Ubiquitously expressed, *c-ABL* K/O phenotype is lethal.



DNA diagram.



Protein diagram.

Localisation

Nuclear and cytoplasmic.

Function

c-ABL exhibit a permanent nuclear and cytoplasmic shuttling activity, driven by 3 nuclear localisation signals (NLS) and a single nuclear export signal (NES) close to the C-terminal region. Recent data suggest that nuclear and cytoplasmic ABL may have different functions.

1-Nuclear c-ABL plays a major role in the regulation of cell death after DNA damage. All DNA damage inducing agents activate nuclear c-ABL kinase in a ATM-dependent manner and in the presence of the p53-homolog p73 protein. The latter is physically associated with c-ABL after DNA damage through the SH3 domain of c-ABL. DNA damage also activates simultaneously p53 pathway, leading to the activation of Rb which induces growth arrest and protects cells from apoptosis. The exact mechanisms of apoptosis induced by c-ABL are unknown. The nuclear entrapment of BCR-ABL has also been shown to induce apoptosis in leukemic cells.

2-Cytoplasmic c-ABL: possible function in adhesion signalling as an efflux of c-ABL from nucleus to the cytoplasm is found in fibroblasts after adhesion.

Homology

SRC homology; like SRC, ABL is one of the tyrosine kinases which are not membrane receptors.

Implicated in

t(9;12)(q34;p12)/ALL --> ETV6/ABL

Disease

Common ALL; yet poorly known.

Hybrid/Mutated gene

5' ETV6/TEL from 12p12 - 3' ABL from 9q34.

Abnormal protein

NH₂-term Helix Loop Helix from ETV6(TEL) fused to Tyr Kinase from ABL COOH-term; localised in the cytoskeleton.

Oncogenesis

Forms HLH-dependent oligomers, which may be critical for Tyr kinase activation; oncogenesis may be comparable to that induced by BCR/ABL.

t(9;22)(q34;q11)/CML --> BCR/ABL

Disease

All CML have a *t(9;22)*, at least at the molecular level (BCR/ABL); phenotype and stem cell origin: multipotent progenitor: *t(9;22)* is found in all myeloid and B- lineage progenitors.

Prognosis

Median survival => 4 years; alphaIFN therapy or BMT are indicated.

Cytogenetics

Anomalies additional to the *t(9;22)* may be found either at diagnosis or during course of the disease, or at the time of acute transformation; mainly: +der(22), +8, i(17q), +19; +21, -Y, -7, -17,+17; variant translocations: *t(9;22;V)* and apparent *t(V;22)* or *t(9;V)*, where V is a variable chromosome, karyotypes with apparently normal chromosomes 9 and 22, may be found.

Hybrid/Mutated gene

BCR/ABL the crucial event lies on der(22), id est 5' BCR - 3'. ABL hybrid gene is the crucial one, 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:

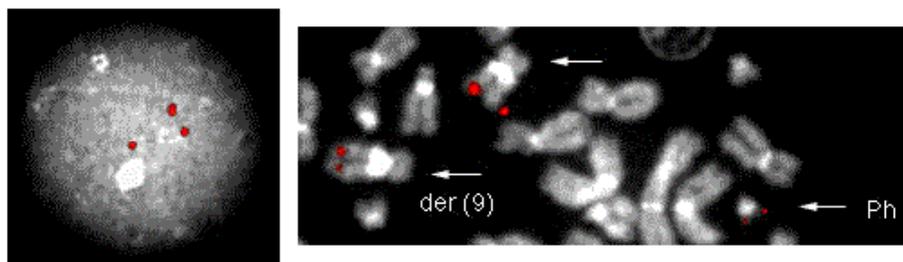
1- in a region called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210); this is found in (most cases of) CML, and in half cases of ALL or ANLL;

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); this is found in half of the cases of ALL or ANLL;

3- a breakpoint in the exon 19 of BCR (designed as micro-bcr) with fusion to abl sequences (a2) has been in neutrophilic CML, with presence of a larger protein (P230).

Abnormal protein

BCR/ABL P210 comprises the first 902 or 927 amino acids from BCR, P190 only the 427 N-term from BCR; BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear.



Probe 1132H12 on a case of CML with t(9/22). Note the splitting of the probe, evident also on interphase nuclei - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics .

Oncogenesis

BCR/ABL has a cytoplasmic localization role and all three BCR-ABL fusion proteins have been shown to exhibit oncogenic potential. All three hybrid proteins have 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:

proliferation is induced through activation by BCR/ABL of RAS signal transduction pathway, PI3-K (phosphatidyl inositol 3' kinase) pathway, and MYC;

2- BCR/ABL inhibits apoptosis;

3- BCR/ABL provokes cell adhesive abnormalities.

t(9;22)(q34;q11)/ALL --> BCR/ABL

Disease

Most often CD 10+ ALL; frequent CNS involvement.

Prognosis

Is very poor (BMT is indicated); the breakpoint in M-bcr or in m-bcr (see below) does not seem to have impact on prognosis.

Cytogenetics

The chromosome anomaly t(9;22) disappear during remission, in contrast with BC-CML cases (CML in blast crisis); additional anomalies: +der(22), -7, del(7q) most often, +8, but not an i(17q), in contrast with CML and ANLL cases; complex karyotypes, often hyperploid; variants and complex translocations may be found as in CML.

Hybrid/Mutated gene

See above.

Abnormal protein

See above.

Oncogenesis

See above.

t(9;22)(q34;q11)/ANLL --> BCR/ABL

Disease

ANLL mostly M1 or M2 ANL.

Prognosis

Is very poor.

Cytogenetics

The chromosome anomaly t(9;22) disappear during remission, in contrast with BC-CML cases (CML in blast crisis); additional anomalies: similar to what is found in CML.

Hybrid/Mutated gene

See above.

Abnormal protein

See above.

Oncogenesis

See above.

References

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