

Gene Section

Review

ABL1 (v-abl Abelson murine leukemia viral oncogene homolog 1)

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Identity

Other names: ABL

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.

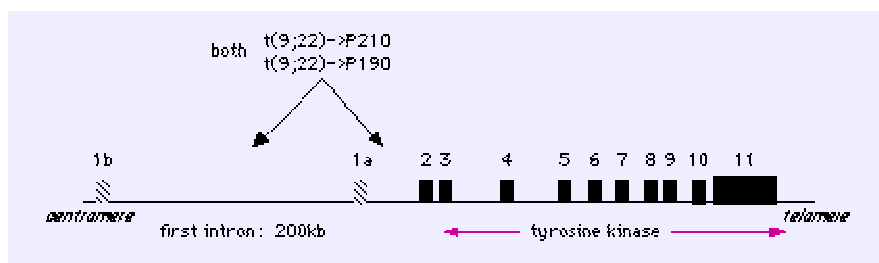
Transcription

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.

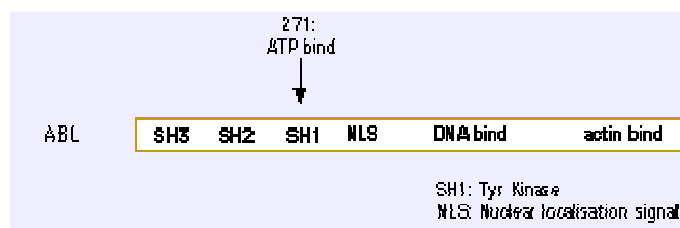
Protein

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-phosphorylatable 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. Normal ABL has a tri-dimensional structure which is tightly preserved in a closed, inactive conformation order to prevent oncogenic activation. The maintenance of this inactive conformation is possible by:



DNA diagram



Protein diagram

1- the "latching" of the myristylated NH₂-terminal sequence which is directly linked to a myristylation recognition sequence on the c-lobe of the SH1 kinase domain;

2- the close contact between SH3 and SH2 domain;

3- the interactions between SH3 domain and the C-lobe of the kinase domain. These interactions clamp the structure and prevent the kinase to switch to an active conformation, a process which requires the phosphorylation of Tyr 412 residue and the "unlatching" of the myristoyl group from the C-lobe of the kinase domain. The attachment of proline-rich SH2 and SH3 ligands leads to the complete switch of the protein to an open, active conformation of the kinase. The NH₂-terminal myristylation (autoregulatory role) is deleted during the t(9;22) translocation.

Expression

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

Localisation

c-abl is localized to the nucleus, plasma membrane and actin cytoskeleton.

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 translocation of cytoplasmic c-ABL to the nucleus has been shown to be due to its release from 14-3-3 proteins to which c-ABL is associated in the cytoplasm. JNK-dependent phosphorylation of 14-3-3 upon an oxidative stress, allows this release process and translocation of c-ABL to the nucleus. The oncoprotein MUC has also been shown to block nuclear translocation of c-ABL after

apoptotic stimuli. 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.

Regulation: Experiments using purified c-abl in vitro allowed to elucidate the mechanism of c-abl regulation which is mediated by an intrinsic property of the molecule. This is the 80 amino-acid N terminal "cap" of the protein is able and sufficient its tyrosine kinase activity and the loss of this cap portion activates the oncogenic potential of c-abl. From the structural point of view, this inhibition is generated by the docking of the myristylated N-terminal of c-abl into the kinase domain. The current view is the fact that c-abl localized in the nucleus, plasma membrane and the actin cytoskeleton undergo different types of regulation. In the membrane-associated c-abl, the myristylated N-terminal end of membrane form can not interact with the kinase c-lobe and it has been suggested that phosphatidylinositol 4-5 bi-phosphate could play an inhibitory role. The autoregulatory mechanism remains functional in the cytoplasmic and nuclear form of c-abl. The latter is also negatively regulated by Rb in the G-phase of the cell cycle. Beside the structural auto-inhibition, several cellular proteins have been shown to inhibit c-ABL: Pag (or Peroxiredoxin-I), Rb and F(actin). Regulation of ABL could therefore be due to a dual mechanism, involving an autoinhibition in the presence of co-inhibitors, which can be active on normal ABL-kinase activity but inactive against increased TK activity of BCR-ABL proteins.

Recent data suggest that pharmacological inhibition of endogenous ABL could lead to a genetic instability, potentially by inhibition of mismatch repair mechanisms. Long-term inhibition of c-ABL by TKI therapies could therefore be responsible of the occurrence of mutator phenotypes.

Activation of ABL can also be detected in solid malignant tumors (lung and breast). Similarly, it has been shown that tumor suppression induced by Ephrin receptor EphB4 requires the presence of an active ABL and phosphorylation of the downstream target CRK by ABL.

Homology

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

Implicated in

t(9;12)(q34;p12)/acute lymphoblastic leukemia (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)/chronic myelogenous leukemia (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

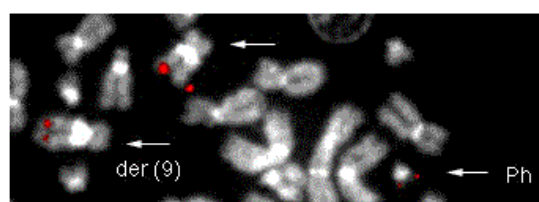
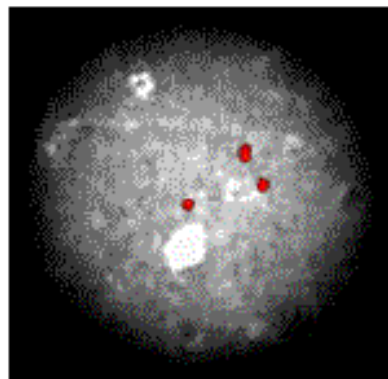
The prognosis of CML has changed radically over the last 10 years, due to the development of novel drugs able to target the enhanced tyrosine kinase activity of BCR-ABL. The first of these therapies is Imatinib Mesylate (Gleevec) which has become the first line therapy for all patients with CML (See CML). In the first cohort trial of patients treated with Imatinib mesylate, the rates of complete cytogenetics responses (CCR) were exceptionally high (82%) as compared to standard IFN-alpha - ARA-C therapy. At the most recent 6-year update, the overall survival is 90% and most interestingly, the rates of progression towards more aggressive phases have been found to be progressively decreasing in all patients with major molecular responses (MMR). (For definition of MMR see CML). In IM-resistant or relapsing Ph1+ CML patients, second generation tyrosine kinase inhibitor (TKI) therapies such as Dasatinib (a dual SRC and ABL inhibitor) and Nilotinib have also recently become available.

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

See below.



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

Abnormal protein

See below.

Oncogenesis

See below.

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

Disease

Most often CD 10+ B-ALL; frequent CNS involvement.

Prognosis

The prognosis of Ph1+ ALL has changed since the introduction of tyrosine-kinase inhibitor therapies, especially imatinib mesylate which is currently used as a first line therapy associated with either high dose chemotherapy or classical ALL-type induction (steroids+ vincristine) and maintenance. Allogeneic stem cell transplantation is indicated in Ph1+ ALL patients relapsing after Imatinib-based regimens. In IM-resistant or relapsing Ph1+ ALL patients, second generation tyrosine kinase inhibitor (TKI) therapies such as Dasatinib (a dual SRC and ABL inhibitor) and Nilotinib have also recently become available.

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 AML cases; complex karyotypes, often hyperploid; variants and complex translocations may be found as in CML.

Hybrid/Mutated gene

See below. In Both CML and Ph1+ ALL, detection and quantification of p210 BCR-ABL and p190 BCR-ABL have become the cornerstones of monitoring targeted therapies.

Abnormal protein

See below.

Oncogenesis

See below.

t(9;22)(q34;q11)/acute myeloid leukemia (AML) --> BCR/ABL**Disease**

AML mostly M1 or M2 AML.

Prognosis

High rates of hematologic, cytogenetic and molecular responses have been reported in de novo PH1+ AML, which is a rare entity.

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 below.

Abnormal protein

See below.

Oncogenesis

See below.

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 AML.

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 AML.

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.

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

1- 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 (via activation of STAT5 and BclXL)

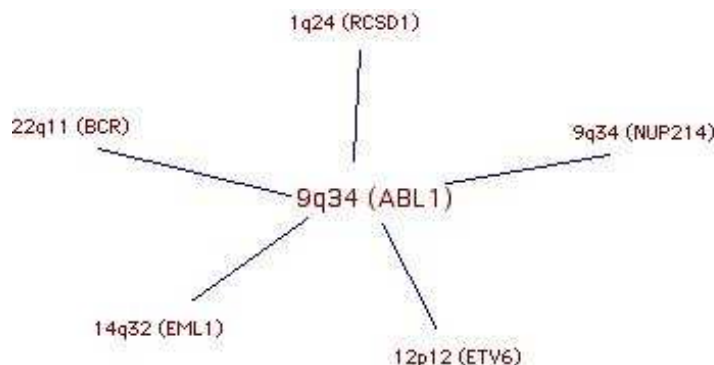
3- BCR/ABL provokes cell adhesive abnormalities (via CRK-L, FAK) as well as abnormalities of cell migration (via CXCR-4 whose expression is downregulated in CML cells expressing high levels of BCR-ABL).

In experimental settings CD44 has been shown to play a major role in homing of BCR-ABL expressing cells.

4- BCR-ABL induces a major genetic instability: Molecular pathways involved in this phenomenon have recently been elucidated (See BCR-ABL).

5-BCR-ABL and endogenous ABL have been shown to be the target of miR 203 which is heavily methylated in CML cell lines expressing BCR-ABL. Restoration of miR 203 expression leads to reduction of BCR-ABL levels, suggesting a potential use of this strategy for therapeutic purposes.

Breakpoints



ABL1 and partners. Editor 07/2005; last update 05/2008

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