Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

BCR (Breakpoint cluster region)

Ali G Turhan

Translational Research - Cell Therapy, Laboratory, Institut Gustave Roussy, INSERM U. 362, 1 - 39, rue Camille Desmoulins, 94805 Villejuif Cedex, France (AGT)

Published in Atlas Database: April 2001

Online updated version: http://AtlasGeneticsOncology.org/Genes/BCR.html
DOI: 10.4267/2042/37746

This article is an update of: Huret JL. BCR (breakpoint cluster region). Atlas Genet Cytogenet Oncol Haematol.1997;1(2):43-45.

Identity

Other names: BCR1; PHL (Philadelphie)

HGNC (Hugo): BCR

Location: 22q11.2

Local order: Distal to IGL in 22q11.1, proximal to EWS NF2, both in 22q12.

DNA/RNA

Description

About 23 exons; 130 kb; 5' centromere - 3' telomere orientation.

Transcription

Into various mRNA, of which are 4.5 kb and 7 kb.

Protein

Description

130 kDa, 190 kDa; mainly 160 kDa (1271 amino acids); N-term ATP binding/Serine-Threonine kinase domain, SH2 binding, GTP/GDP exchange domain, and C-term domain which functions as a GTPase activating protein for p21rac.

Expression

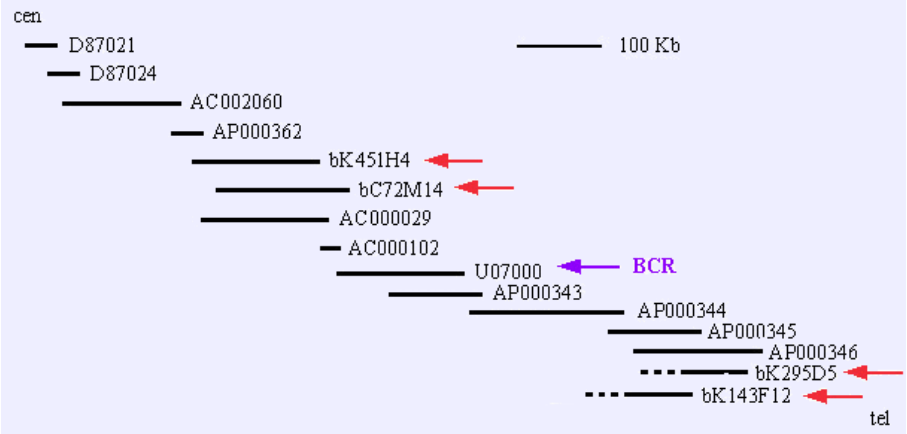
Ubiquitously expressed, with highest expression in brain and hematopoietic tissue.

Localisation

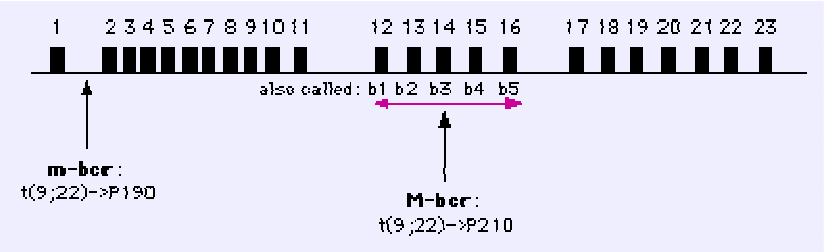
Cytoplasmic.

Function

Protein (serine/threonine) kinase; includes major signalisation domains such as:
Oligomerization domain, responsible of homotetramerization of BCR-ABL molecule and necessary for its transforming potential;



Map of the BCR region; - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are wellcome: contact M Rocchi.



DNA Diagram.

Serine threonine kinase domain, including at least three SH2 binding sites; able to interact with proteins with SH2 domains: These sites include TYR177, necessary for binding of Grb2 and activation of RAS pathway and beta-isoform of 14-3-3 proteins;
GEF domain, in which lie the binding activity to the xeroderma pigmentosum protein, involved in DNA repair;
A COOH-terminal RAC-GAP domain which does not participate to hybrid BCR-ABL proteins.

Homology

Drosophila rotund protein; other guanine-nucleotide releasing factors of the CDC24 family.

Implicated in

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) found in approximately 25% of adult ALL cases;
3- a breakpoint in the exon 19 of BCR (designed as the micr-bcr) with fusion to abl sequences (a2) has been found in neutrophilic CML, with presence of a larger protein (P230).

Abnormal protein

BCR/ABL P210 comprises the first 902 or 927 amino acids from N_term of BCR, whereas P190 BCR and P230 include 427 and 1176 amino acids respectively, from the N-term region of BCR. BCR/ABL has a cytoplasmic localization, probably by the ability of the oligomerization domain to interact with Factin. ABL is both nuclear and cytoplasmic, due to the presence of nuclear localisation and export signals (NLS and NES) within its COOH terminal region.

Oncogenesis

All three forms of BCR-ABL oncogenes have transforming potential and it is now clear that they are responsible for initiation of the leukemic process associated with BCR-ABL oncogenes: Several signalling pathways are simultaneously activated and some phenotypic correlations can be made with the molecular abnormalities.
1-Constitutive activation of RAS pathway (via TYR177 of the BCR) mimicking the growth-factor-stimulation of cells, leads to a proliferative behavior.
2-Activation of PI-3K/Akt as well as JAK/STAT pathways is most likely responsible for the anti-apoptotic potential.
3-Activation of focal adhesion molecules (FAK/paxillin) via CRK-L as well as abnormal response to SDF-1 leads to adhesive and migratory abnormalities of leukemic cells. It should be noted that specific specific signalling events leading to ALL with P190 and to CML with P210 have not been established so far.
Progression to blast crisis in CML: Multiple events could be involved, with the major phenotype being a genetic instability: 1- Mutation of P53; 2- methylation of internal ABL promoter; 3- telomere shortening; 4- Inhibition of negative regulators of BCR-ABL (such as

Abi-1); 5- More recently BCR-ABL has been found to down-regulate the major DNA-repair protein DNA-PKcs, with impairment of DNA repair which could contribute to genetic instability, especially in a context where BCR-ABL inhibits apoptosis.

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

Disease
Most often CD10+ ALL; frequent CNS involvement.

Prognosis
Is very poor (BMT is indicated); the breakpoint in M-bcr or in m-bcr (see above) 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

Heisterkamp N, Groffen J. Molecular insights into the Philadelphia translocation. Hematol Pathol. 1991;5(1):1-10

Gotoh A, Broxmeyer HE. The function of BCR/ABL and related proto-oncogenes. Curr Opin Hematol. 1997 Jan;4(1):3-11

Takeda N, Shibuya M, Maru Y. The BCR-ABL oncoprotein potentially interacts with the xeroderma pigmentosum group B protein. Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):203-7

Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. Blood. 2000 Nov 15;96(10):3343-56

Deutsch E, Dugray A, AbdulKarim B, Marangoni E, Maggiorella L, Vaganay S, M'Kacher R, Rasy SD, Eschwege F, Vainchenker W, Turhan AG, Bourhis J. BCR-ABL down-regulates the DNA repair protein DNA-PKcs. Blood. 2001 Apr 1;97(7):2084-90

Laurent E, Talpaz M, Kantarjian H, Kurzrock R. The BCR gene and philadelphia chromosome-positive leukemogenesis. Cancer Res. 2001 Mar 15;61(6):2343-55

This article should be referenced as such:

Turhan AG. BCR (Breakpoint cluster region). Atlas Genet Cytogenet Oncol Haematol. 2001; 5(3):167-169.