

Gene Section

Review

BTK (Bruton agammaglobulinemia tyrosine kinase)

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Identity

Other names: AGMX1; AT; ATK; BPK; IMD1; MGC126261; MGC126262; PSCTK1; XLA

HGNC (Hugo): BTK

Location: Xq22.1

Note

BTK (Bruton's tyrosine kinase) is a cytoplasmic non-receptor protein tyrosine kinase that is essential for B cell maturation in humans and mice.

DNA/RNA

Description

The gene spans over 36 kb and is composed of 19 exons, both in human and mouse.

Transcription

The transcript is about 2,573 bps in human and about 2,477 bps mice and has UTR regions in exons 1, 2 and 19.

Protein

Description

The BTK protein is a 77 kDa protein of 659 amino acids. Translation of the BTK transcript starts at the ATG site that is located in exon 2 and ends in exon 19. The BTK protein is composed of an N-terminal Pleckstrin homology (PH) domain followed three

protein interacting domains: Tec homology (TH) region, Src homology 3 (SH3) domain and SH2 domain. A tyrosine-kinase catalytic domain is located at the C-terminal end. Two tyrosine phosphorylation sites are located at the positions Y223 and Y551, which are located in the SH3 and kinase domain, respectively. Both phosphorylation sites play a pivotal role in the activation of BTK. Y551 is transphosphorylated by Syk (or Lyn) kinases which promotes the catalytic activity of BTK, with subsequent autophosphorylation at position Y223.

Expression

BTK is expressed in all cell lineages of the hematopoietic system, except for T cells. Therefore BTK expression is found in B lymphocytes, platelets, erythroid and myeloid cells (monocytes, macrophages, granulocytes and dendritic cells). Within the B cell lineage, BTK is already expressed in the earliest detectable B cell precursors, and expression is downregulated in plasma cells.

Localisation

The protein is predominantly localized in the cytoplasm. BTK activation upon receptor signaling results in translocation of BTK protein from the cytoplasm to the membrane. The membrane association of BTK is dependent on the interaction of its PH domain with PIP3 (phosphatidylinositol (3,4,5)-trisphosphate), which is a second messenger that is synthesized from PIP2 by PI3K (phospho-inositide-3 kinase).

Signaling cascade	Cell type
(Pre-)B cell receptor	B cells
CD38	Activated B cells
TRAIL-R1	Erythroid cells
Epo Receptor	Erythroid cells
Glycoprotein (GP) Ib-IX-V complex, GPVI	Platelets
IL-5R	B cells, eosinophils, basophils
IL-6R gp130	Activated B cells, plasma cells
IL-10R	Activated T and NK cells
FcεR	Mast cells, basophils
TLR2 (MyD88 adapter-like (Mal))	Macrophage, DC
TLR4 - LPS (Mal)	Phagocytic cells, DC
CCL5	Microglia (brain)
CXCL12 (SDF1)	B cells
RANK	Osteoclasts
CD303 (BDCA2)	pDC

Table 1: BTK dependent receptor signaling cascades.

The translocation to the membrane brings the BTK protein in close proximity to the Lyn and Syk kinases that transphosphorylate BTK at tyrosine Y551. The E41K gain-of-function BTK mutant, in which the E41 residue is mutated to a lysine residue, manifests increased membrane localization in quiescent cells, independent of PI3K activity, probably resulting from increased affinity for PIP2. Transforming activity is kinase-domain dependent and is potentiated by introduction of a second mutation at position Y223.

Function

BTK is a signaling mediator downstream of a variety of receptors in several different cell types (listed in Table 1) including the B cell receptor (BCR).

Homology

BTK belongs to the TEC family of cytoplasmic tyrosine kinases. This family is composed of TEC, BTK, TXK/RLK, ITK/EMT, and BMX. Btk is highly conserved between mouse and human.

Implicated in

Pre-B cell tumors

Note

Truncated BTK forms in human BCR-ABL1 + leukemia.

BTK is constitutively phosphorylated by the oncogenic BCR- ABL1 fusion product. Inhibition of BTK activity specifically induces apoptosis in BCR-ABL1+ leukemia cells to a similar extent as inhibition of BCR-ABL1 kinase activity itself. BCR-ABL1 cannot directly bind to full-length BTK, but induces the expression of a truncated BTK splice variant that acts as a linker between the two kinases. Thus, truncated BTK enables BCR-ABL1-dependent activation of full-length BTK, which initiates downstream survival signals and mimics pre-B cell receptor signaling.

Defective expression of BTK in acute lympho-blastic leukemia (ALL)

In an analysis of BTK protein and mRNA expression in infant B-lineage leukemia cells variable but often reduced levels of BTK expression was found. RT-PCR revealed the presence of aberrant transcripts which would encode BTK proteins with either a deleted or a truncated kinase domain. In infant pre-B MLL-AF4+ leukemia cells full-length BTK was detectable in only half of the cases, whereas in ALL cells harboring other fusion genes (including BCR-ABL1, E2A- PBX1 and TEL- AML1) full-length BTK was typically co-expressed with kinase-deficient variants. Thus, lack of BTK or expression of dominant-negative BTK splice variants in B cell precursor leukemia cells can inhibit differentiation beyond the pre-B cell stage and protect from radiation-induced apoptosis.

Btk as a tumor suppressor in pre-B cell leukemia in mice

Expression of the pre-B cell receptor (pre-BCR) leads to activation of the adaptor molecule Slp65 (also termed Bash or Blnk) and Btk. Spontaneous pre-B cell leukemia development in Slp65-deficient mice demonstrate that Slp65 acts as a tumor suppressor. Slp65 and Btk have a synergistic role in the developmental progression of large cycling into small resting pre-B cells. Btk/Slp65 double mutant mice have a dramatically increased pre-B cell tumor incidence (approximately 75%, 16 wk of age), as compared with Slp65 single deficient mice (<10%). Therefore, Btk cooperates with Slp65 as a tumor suppressor in pre-B cells. Moreover, transgenic expression of a constitutive active form of Btk, the E41K-Y223F mutant, prevented tumor formation in Btk/Slp65 double mutant mice, indicating that constitutive active Btk can substitute for Slp65 as a tumor suppressor. Using a kinase-inactive K430R-Btk mutant, it was shown that Btk exerts its tumor suppressor function in pre-B cells as an adaptor protein, independent of its catalytic activity.

Furthermore, loss of Btk and Tec increases the tumor frequency in Eμ-myc transgenic mice, expressing the c-myc oncogenic transcription factor that promotes both proliferation and differentiation.

X-linked agammaglobulinemia (XLA).

Note

In 1993 BTK was identified as the gene defective in the human immunodeficiency disease X-linked agammaglobulinemia (XLA). The XLA disease, which was first described by Dr. O.C. Bruton in 1952, is characterized by protracted and recurrent bacterial infections.

Clinical manifestations of XLA

XLA Patients have less than 1% of the normal number of peripheral B cells. Serum levels of all Ig classes are very low due to the lack of plasma cells in the secondary lymphoid organs. In XLA patients, B cell development is almost completely arrested at the pre-B cell stage: the pre-B cell fraction mainly consists of small cells, suggesting that Btk is necessary for their proliferative expansion. Heterozygous female XLA carriers do not have clinical or immunological symptoms, but manifest a unilateral X chromosome inactivation in the peripheral blood B lymphocyte population, because of a selective disadvantage of cells that have the defective Btk gene on the active X chromosome. In contrast to XLA, Btk-deficiency in the mouse, termed X-linked immunodeficiency (xid), is associated with a very mild early B cell developmental block, but with impaired maturation and poor survival of peripheral B cells. XLA is a hetero-geneous disease, even within single families and no correlation has been observed between the position of the mutation and phenotypic variables, such as age at time of diagnosis or severity of the clinical or immunological symptoms. Therefore, this hetero-geneity might be related to other genetic or environmental factors.

Mutations in BTK gene that cause XLA

The BTK mutations that have been identified in XLA patients compromise BTK function either through gross structural changes (such as deletions or altered protein folding) or through specific loss of functionally relevant residues. Strikingly, none of the found unique missense mutations found in XLA patients is located in the SH3 domain of BTK, which harbors the Y223 tyrosine residue. An international registry for XLA (<http://bioinf.uta.fi/BTKbase/>) shows that mutations in all domains of the BTK gene cause the disease.

Approximately 80-90% of the patients that have agammaglobulinemia patients have a deficiency of the BTK protein. The other about 15% of the agammaglobulinemia cases are caused by defects in autosomal genes such as the constant region of immunoglobulin (Ig) heavy chain, $\lambda 5$, (IGLL), I α (CD79a), I β (CD79b), or SLP65 (BLNK) resemble the clinical manifestation of XLA.

References

Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, Klisak I, Sparkes RS, Kubagawa H, Mohandas T, Quan S. Deficient expression of a B cell cytoplasmic tyrosine kinase in

human X-linked agammaglobulinemia. *Cell*. 1993 Jan 29;72(2):279-90

Vetrie D, Vorechovský I, Sideras P, Holland J, Davies A, Flinter F, Hammarström L, Kinnon C, Levinsky R, Bobrow M. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. *Nature*. 1993 Jan 21;361(6409):226-33

Khan WN, Alt FW, Gerstein RM, Malynn BA, Larsson I, Rathbun G, Davidson L, Müller S, Kantor AB, Herzenberg LA. Defective B cell development and function in Btk-deficient mice. *Immunity*. 1995 Sep;3(3):283-99

Li T, Tsukada S, Satterthwaite A, Havlik MH, Park H, Takatsu K, Witte ON. Activation of Bruton's tyrosine kinase (BTK) by a point mutation in its pleckstrin homology (PH) domain. *Immunity*. 1995 May;2(5):451-60

Hendriks RW, de Bruijn MF, Maas A, Dingjan GM, Karis A, Grosveld F. Inactivation of Btk by insertion of lacZ reveals defects in B cell development only past the pre-B cell stage. *EMBO J*. 1996 Sep 16;15(18):4862-72

Park H, Wahl MI, Afar DE, Turck CW, Rawlings DJ, Tam C, Scharenberg AM, Kinet JP, Witte ON. Regulation of Btk function by a major autophosphorylation site within the SH3 domain. *Immunity*. 1996 May;4(5):515-25

Uckun FM, Waddick KG, Mahajan S, Jun X, Takata M, Bolen J, Kurosaki T. BTK as a mediator of radiation-induced apoptosis in DT-40 lymphoma B cells. *Science*. 1996 Aug 23;273(5278):1096-100

Mahajan S, Ghosh S, Sudbeck EA, Zheng Y, Downs S, Hupke M, Uckun FM. Rational design and synthesis of a novel anti-leukemic agent targeting Bruton's tyrosine kinase (BTK), LFM-A13 [α -cyano- β -hydroxy- β -methyl-N-(2, 5-dibromophenyl)propenamide]. *J Biol Chem*. 1999 Apr 2;274(14):9587-99

Nomura K, Kanegane H, Karasuyama H, Tsukada S, Agematsu K, Murakami G, Sakazume S, Sako M, Tanaka R, Kuniya Y, Komeno T, Ishihara S, Hayashi K, Kishimoto T, Miyawaki T. Genetic defect in human X-linked agammaglobulinemia impedes a maturational evolution of pre-B cells into a later stage of pre-B cells in the B-cell differentiation pathway. *Blood*. 2000 Jul 15;96(2):610-7

Middendorp S, Dingjan GM, Hendriks RW. Impaired precursor B cell differentiation in Bruton's tyrosine kinase-deficient mice. *J Immunol*. 2002 Mar 15;168(6):2695-703

Goodman PA, Wood CM, Vassilev AO, Mao C, Uckun FM. Defective expression of Bruton's tyrosine kinase in acute lymphoblastic leukemia. *Leuk Lymphoma*. 2003 Jun;44(6):1011-8

Kersseboom R, Middendorp S, Dingjan GM, Dahlenborg K, Reth M, Jumaa H, Hendriks RW. Bruton's tyrosine kinase cooperates with the B cell linker protein SLP-65 as a tumor suppressor in Pre-B cells. *J Exp Med*. 2003 Jul 7;198(1):91-8

Hendriks RW, Middendorp S. The pre-BCR checkpoint as a cell-autonomous proliferation switch. *Trends Immunol*. 2004 May;25(5):249-56

Feldhahn N, Klein F, Mooster JL, Hadweh P, Sprangers M, Wartenberg M, Bekhite MM, Hofmann WK, Herzog S, Jumaa H, Rowley JD, Müschen M. Mimicry of a constitutively active pre-B cell receptor in acute lymphoblastic leukemia cells. *J Exp Med*. 2005 Jun 6;201(11):1837-52

Feldhahn N, Río P, Soh BN, Liedtke S, Sprangers M, Klein F, Wernet P, Jumaa H, Hofmann WK, Hanenberg H, Rowley JD, Müschen M. Deficiency of Bruton's tyrosine kinase in B cell precursor leukemia cells. *Proc Natl Acad Sci U S A*. 2005 Sep 13;102(37):13266-71

Jumaa H, Hendriks RW, Reth M. B cell signaling and tumorigenesis. *Annu Rev Immunol.* 2005;23:415-45

Middendorp S, Zijlstra AJ, Kersseboom R, Dingjan GM, Jumaa H, Hendriks RW. Tumor suppressor function of Bruton tyrosine kinase is independent of its catalytic activity. *Blood.* 2005 Jan 1;105(1):259-65

Hendriks RW, Kersseboom R. Involvement of SLP-65 and Btk in tumor suppression and malignant transformation of pre-B cells. *Semin Immunol.* 2006 Feb;18(1):67-76

Väliaho J, Smith CI, Vihinen M. BTKbase: the mutation database for X-linked agammaglobulinemia. *Hum Mutat.* 2006 Dec;27(12):1209-17

Habib T, Park H, Tsang M, de Alborán IM, Nicks A, Wilson L, Knoepfler PS, Andrews S, Rawlings DJ, Eisenman RN, Iritani BM. Myc stimulates B lymphocyte differentiation and amplifies calcium signaling. *J Cell Biol.* 2007 Nov 19;179(4):717-31

Hantschel O, Rix U, Schmidt U, Bürckstümmer T, Kneidinger M, Schütze G, Colinge J, Bennett KL, Ellmeier W, Valent P, Superti-Furga G. The Btk tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib. *Proc Natl Acad Sci U S A.* 2007 Aug 14;104(33):13283-8

Uckun F, Ozer Z, Vassilev A. Bruton's tyrosine kinase prevents activation of the anti-apoptotic transcription factor STAT3 and promotes apoptosis in neoplastic B-cells and B-cell precursors exposed to oxidative stress. *Br J Haematol.* 2007 Feb;136(4):574-89

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