Bruton’s Tyrosine Kinase: Structure and Functions, Expression and Mutations

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Abstract

Bruton’s tyrosine kinase (BTK), a member of the Tec family of protein tyrosine kinases (PTKs), plays a vital and diverse function in many cellular processes. BTK is expressed throughout B cell development, widely participating in multiple signal pathways including PI3K, PLCγ, and PKC. Those pathways play critical functions in cell proliferation, development, differentiation, survival, and apoptosis. The expression of BTK is selectively down-regulated in T lymphocytes and plasma cells and the relative level of BTK expression may be modulated in different developmental populations of B cells. Mutations in the gene for BTK are responsible for X-linked agammaglobulinemia (XLA) in human and X-linked immunodeficiency (xid) in mice. Both of these diseases are characterized by blocks in B-cell development at multiple stages and impaired function of residual mature B cells. To date, more than 1252 mutations have been identified in human BTK gene associating with XLA. Targeting BTK has achieved remarkable efficacy in B cell malignancies, multiple myeloma and related bone disease. The present review discusses the recent data regarding the role of BTK in B cell development and its structure, regulation, functions, expression and mutations.

Keywords: Bruton’s tyrosine kinase; B cells; Function; Expression; Mutation

Introduction

Non-receptor protein tyrosine kinases are targets in the treatment of a number of diseases. Increasing evidence suggests that these kinases serve multiple roles in diversifying and amplifying the signals emanating from receptors located on the cell surface [1,2]. The Tec family formed by BTK, BMX, ITK, TEC, and RLK, are the second largest group of non-receptor tyrosine kinases [3,4]. Functionally, Tec kinases play pivotal roles in the development and signaling of hematopoietic cells [3,5], and are characterized by a common domain organization: from the amino-terminus, there are the pleckstrin homology (PH), Tec homology (TH), Src homology 3 (SH3), SH2, and SH1 domains, especially the SH1 domain, which is also the catalytic domain [6,7]. The unique domain and myristoylation site (and frequently palmitoylation site) are generally found in Src family kinases but not in Tec family kinases. Moreover, Tec family kinases lack the C-terminal regulatory tyrosine residue characteristic of Src [8]. TEC, BTK, ITK, and BMX contain PH domains, which inductively recruit these kinases to the plasma membrane by binding the phosphatidylinositol-3,4,5-trisphosphate (PIP3) product phosphatidylinositol3,4,5-trisphosphate (PIP3), thereby promoting their activation [9]. While RLK contains a distinct N-terminal cysteine string motif that facilitates palmitoylation and consequent association with lipid rafts [10,11]. The TH domain contains several SH3-binding, proline-rich sequences (PXPPPXX) shared by this kinase family, with the exception of BMX. The presence of PXXP motif and the SH3 domain establishes an intra-molecular interaction which folds the Tec family kinases in a “closed” form and subject the kinases to regulation by stimuli which activate molecules or ligands that disrupt this interaction [12,13] (Figure 1). Bruton’s tyrosine kinase (BTK) is by far the most studied member of Tec family and is mainly expressed in B cells [14]. In addition, it is also expressed in myeloid, mast cells [15,16]. BTK is expressed throughout the development of B cell and is not expressed in T cells and other non-hematopoietic cell linages [17]. In 1993, several research groups discovered the new tyrosine kinase, BTK, which is mutated in a human X-linked agammaglobulinemia (XLA), as known as Bruton’s disease. This was the first evidence for the involvement of a protein tyrosine kinase related to the Src-family of oncogenic proteins in a human genetic disease. BTK is also mutated in the mouse X-linked immunodeficiency (xid). It was subsequently recognized that BTK is a member of the Tec family kinases [18-20]. This review will cover the structure, functions, expression, and mutations of BTK.

Structure and functions of BTK

The BTK gene was mapped to the X-chromosome at Xq21.3-Xq22, consisting of 19 exons, spreading 37.5 kb. 18 of the 19 exons code for a 77 kDa protein, 659 residues long [21]. As a member of the Tec non-receptor tyrosine kinases family, BTK is also comprised of five domains: PH, TH, SH3, SH2, and SH1 [22]. These domains bind different interaction partners (cytosolic proteins or transcription factors) respectively and equip BTK with a critical role in multiple hematopoietic signaling pathways (Figure 2). Hematopoietic signaling pathways including the B cell antigen receptor (BCR), several cytokine receptors, and heterotrimic G protein associated receptor signaling [23,24]. These signal pathways are transmitted by growth factor receptors, cytokine receptors, G-protein receptors, antigen receptors and integrins [22]. In addition, BTK is regulated by some non-receptor tyrosine kinases, such as JAK, SYK, Lyn and FAK family kinases. In turn, BTK regulate many vital signal pathways including those PI3K, PLCγ, and PKC. Those pathways play critical functions in cell proliferation, development, differentiation, survival, and apoptosis [2,25,26].

Received October 11, 2013; Accepted November 15, 2013; Published November 18, 2013

Citation: Liu Y, Zhou G, Zhang B, Liu Y (2013) Bruton’s Tyrosine Kinase: Structure and Functions, Expression and Mutations. Gene Technology 2: 106. doi: 10.4172/2329-6682.1000106

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Its expression throughout B cell development, BTK plays critical functions in B cell proliferation, differentiation, survival, and apoptosis [27]. In BCR singal pathway, following antigen binding of BCR, the cytoplasmic tails of Igα/Igβ Heterodimers are phosphorylated by Src family members [28]. Then the phosphorylation sites act as docking sites for BTK. Following the PH domain binding of PI3P, BTK is targeted to the membrane. The Y551 site is then trans-phosphorylated by Src family tyrosine kinases. The next step is BTK auto-phosphorylation itself on Y223 residue in the SH3 domain. Then BTK begins to transmit signals [23]. Previous reports have indicated that BTK participate in G-protein signal pathway through directly binding different subunits of G-proteins, and then is activated by subunits of heterotrimeric G proteins, such as Gβγ, Gαq, and Gα12 [29,30]. Then the G protein-regulated PI3K/PI3Ky, isoform of PI3 kinase, can induce phosphorylation of BTK and dramatically enhance the ability of BTK to transmit signals in an ectopic over-expression system [31,32]. However, whether BTK-dependent, G-protein coupled receptor-initiated signals are important during B cell development remains to be determined [33,34]. In addition to its function in pre-BCR signaling, BTK has been implicated as a mediator of signals from various other receptors, including FceR, IL-5R, IL-6R, IL-10R, collagen receptor, erythropoietin receptor, and Toll-like receptor 4 [35-39]. IL-6 was showing to activate BTK in B lymphocytes. Stable complexes were formed by activated IL-6 receptors via JAK family kinases with BTK. Then through this association BTK is phosphorylated by JAK [2,40]. BTK widely participates in multiple downstream signal pathways. And the well-studied downstream signal is perhaps the PLCγ and PKCβ, with a side induction of sustained calcium influx [41] and final MAPK/JNK activation [42]. In PLCγ signal, phosphorylated BTK recruits the adapter B-cell linker protein (BLNK) [also known as SH2-domain-containing leukocyte specific phosphoprotein of 65 kDa (SLP-65)] together with PLCγ2 to the plasma membrane, bringing them in close to Syk. Syk activation results in phosphorylation of BLNK, recruitment and activation of PLCγ2 leading to IP3 production, and release of calcium from the ER calcium store [26,43]. Accident P13K activation leads to production of phosphatidylinositol3,4,5-trisphosphate (PIP3) and diacylglycerol (DAG), causing calcium mobilization and PKCβ activation, respectively [23,44]. In addition, BTK can also mediate BCR-stimulated calcium influx [32] and B cell development [45] independently of its catalytic activity. Acting as an adaptor, BTK recruits and activates phosphatidylinositol 4-phosphate 5-kinase (PIP5K) [32], which produces the substrate for PLCγ2. Thus, BTK signals through PLCγ2 directly, by phosphorylation, and indirectly, by increasing substrate availability [46]. The secondary messenger IP3 mediates the opening of intracellular calcium stores, which subsequently activates PKCβ. Then activated PKCβ phosphorylates IκB kinase and thereby induces NF-kB activation, following by up-regulation of the anti-apoptotic protein Bcl-xl and cyclin D2 [34,47-49] (Figure 3).

BTK in B cell development

BTK is expressed throughout B cell development. It sustains the developmental program of pre-B cells by limiting the pre-B cell expansion and by promoting B-cell differentiation. The levels of BTK keep constant at all stages of B cell development in the bone marrow but drop significantly as cells enter the periphery [14,17]. XLA is characterized by a severe block in B cell development at the pre-B cell stage while xid have normal number of pre-B and immature B cells [50,51]. In addition, the xid cells compared to normal cells have a competitive disadvantage at the pre-B to immature transition [52]. Thus, BTK does contribute to the early stages of B cell development. A dual role for BTK in B cell survival and functional responses is also supported by a BTK transgenic mouse model. In xid and BTK−/− mice, splenic B cells transgene expressing wild type BTK protein at 25% of endogenous levels can completely restores conventional B cell development [53]. Responses to TNP-Ficol in vivo and BCR crosslinking in vitro are above those of xid mice but remain significantly impaired relative to wild type controls. Wild-type BTK protein levels two fold increase in obtained by generating mice homozygous for the transgene results in four fold greater response to both TNP-Ficol and anti-IgM as well as increased sensitivity to BCR cross linking. The above observations indicate that the dosage of BTK is limiting for BCR signaling and that there is a higher threshold level of BTK required for B cell functional than for responses survival [53,54]. Thus, the sensitivity of B cell function to BTK levels suggests that BTK may be an attractive therapeutic target for diseases involving hyperactive B cells, such as autoimmunity.

Expression of BTK

The Tec family kinases, are widely expressed in a wide range of vertebrate tissues [2]. In mammals, Tec kinases are expressed prominently in hematopoietic cells where they are expressed with a relatively high degree of lineage specificity [55,56]. TEC and BMX are expressed ubiquitously. B cells express primarily BTK while T cells express both ITK and RLK [57]. In addition, besides expression in hematopoietic tissues, Tec kinase family members were also reported in liver, kidney, heart, lung and ovarian tissues [58, 59]. BTK is expressed at all stages of B lineage development from CD34+ pre-B to mature B cells while is down-regulated in plasma B cells [19,60,61]. Previous studies reported that the relative level of BTK expression may be modulated in different developmental populations. In surface of...
and activated in dexamethasone-resistant multiple myeloma (MM) cell studies. Recent findings from our institute demonstrate that BTK is elevated in mast cells, BTK also expressed in macrophages, and neutrophils [34].

Mutations in BTK

To date, the only Tec kinase known to cause human disease is BTK. X-linked agammaglobulinemia (XLA) is the prototypic specific phenotype B lineage, BTK is found to express in myeloid cells, and psoriasis [74]. And the therapeutic potential targeting BTK or upstream/downstream effectors associated with BTK were proposed and has achieved remarkable efficacy with an acceptable safety profile in B cell malignancies by lots of scientists [14,49,74]. The anti-apoptotic function of BTK is supported by the observation that the coding domain (56). Although this SNP does not alter the coding amino acid of the codon, it appears to be common in MM, and possibly MM-specific. Therefore, the function of BTK in MM warrants further investigation.

Therapeutic Potential of Inhibiting BTK

Functional abnormalities of PTKs have been described by previous reports in cancer, immunodeficiency, diabetes, arteriosclerosis and psoriasis [74]. And the therapeutic potential targeting BTK or upstream/downstream effectors associated with BTK were proposed and has achieved remarkable efficacy with an acceptable safety profile in B cell malignancies by lots of scientists [14,49,74]. The anti-apoptotic function of BTK is supported by the observation that Bcl-2 and Bcl-xI trangenes can restore normal B cell levels in xid mice [54]. Furthermore, BTK can induce Bcl-xI expression and inhibits the pro-apoptotic effects of Fas ligation in mature B cells [51]. Due to the vital role of BTK in hematopoiesis of B cells, several reports suggested that alteration of its function would cause various diseases associated with abnormal development of B cells [34,49]. So in the past ten years, a number of researchers have addressed the possible functions of BTK in blood cancer development [14,15,49,56,74]. Ibrutinib, an orally available inhibitor which irreversibly and selectively binds to BTK, has achieved high response rates in phase I/II clinical trials in relapsed non-Hodgkin’s lymphoma, and phase III clinical trials in mantle cell lymphoma and chronic lymphocytic leukaemia [73,74]. In addition, Tai et al. [14] found that Ibrutinib not only targets MM tumor cells but also bone marrow microenvironment that support MM cell growth and survival, as well as MM-deteriorated bone lysis. These results
demonstrate BTK inhibitors are extremely attractive approach not only for B-cell malignancies, but also for myeloma and related bone disease.

**Conclusion**

In conclusion, this review has briefly summarized work defining the structure of BTK, the range of signaling pathways potentially utilizing BTK, and the mutations leading to altered BTK function. In addition, we have discussed several aspects on the biology of BTK, and utilizing BTK, and the mutations leading to altered BTK function. In the structure of BTK, the range of signaling pathways potentially adds, we have discussed several aspects on the biology of BTK, and utilizing BTK, and the mutations leading to altered BTK function. In

**References**

1. Condorelli F, Stec-Martyna E, Zaborowska J, Felli L, Gemmi I, et al. (2011) Role of the non-receptor tyrosine kinase fes in cancer. Curr Med Chem 18: 2913-2920.

2. Yun Qiu, Hsing-Jien Kung (2000) Signaling network of the Btk family kinases. Oncogene 19:5651-5660.

3. Faris M, Bot A (2012) In this issue: Tec kinases in the crosshairs. Int Rev Immunol 31: 85-86.

4. Horwood NJ, Urbaniak AM, Danks L (2012) Tec family kinases in inflammation and disease. Int Rev Immunol 31: 87-103.

5. Schmidt U, Boucheron N, Unger B, Ellmeier W (2004) The role of Tec family kinases in myeloid cells. Int Arch Allergy Immunol 134: 65-78.

6. Conley ME, Fitch-Hilgenberg ME, Cleveland JL, Parolini O, Rohrer J (1994) Screening of genomic DNA to identify mutations in the gene for Bruton's tyrosine kinase. Hum Mol Genet 3: 1751-1758.

7. Readinger JA, Mueller KL, Venegas AM, Horai R, Schwartzberg PL (2009) Tec kinases regulate T-lymphocyte development and function: new insights into the roles of Itk and Rlk/Txk. Immunol Rev 228: 93-114.

8. Yang WC, Collette Y, Nuns J, Olive D (2000) Tec kinases: a family with multiple roles in immunity. Immunity 12: 373-382.

9. Schwartzberg PL, Finkelstein LD, Readinger JA (2005) TEC-family kinases: regulators of T-helper-cell differentiation. Nat Rev Immunol 5: 284-295.

10. Pillai S, Moran ST (2002) Tec kinase pathways in lymphocyte development and transformation. Biochim Biophys Acta 1602: 162-167.

11. Gomez-Rodriguez J, Kraus ZJ, Schwartzberg PL (2011) Tec family kinases Itk and Rlk / Txk in T lymphocytes: cross-regulation of cytokine production and T-cell fate. FEBS J 278: 1980-1999.

12. Sirvent B, Benistant C, Roche S (2012) Oncogenic signaling by tyrosine kinases of the SRC family in advanced colorectal cancer. Am J Cancer Res 2: 357-371.

13. Himpe E, Abdul Rahim SA, Verduz P, Mano H, Kooijman R (2013) Tec kinase stimulates cell survival in transformed Hek293T cells and is regulated by the anti-apoptotic growth factor IGF-1 in human neutrophils. Cell Signal 25: 666-673.

14. Tai YT, Chang BY, Kong SY, Fulciniti M, Yang G, et al. (2012) Bruton tyrosine kinase inhibition is a novel therapeutic strategy targeting tumor in the bone marrow microenvironment in multiple myeloma. Blood 120: 1877-1887.

15. Edwards CM (2012) BTK inhibition in myeloma: targeting the seed and the soil. Blood 120: 1757-1759.

16. Gillifan AM, Rivera J (2009) The tyrosine kinase network regulating mast cell activation. Immunol Rev 228: 149-169.

17. Smith CI, Baskin B, Bumire-Greff P, Zhou JN, Olsson PG, et al. (1994) Expression of Bruton’s agammaglobulinemia tyrosine kinase gene, BTK, is selectively down-regulated in T lymphocytes and plasma cells. J Immunol 152: 557-565.

18. Thomas JD, Sideras P, Smith CI, Vorechovsky I, Chapman V, et al. (1993) Co-localization of X-linked agammaglobulinemia and X-linked immunodeficiency genes. Science 261: 355-359.

19. Tsukada S, Saffran DC, Rawlings DJ, Parolini O, Allen RC, et al. (1993) Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 72: 279-290.

20. Vetrie D, Vorechovsky I, Sideras P, Holland J, Davies A, et al. (1993) The gene involved in X-linked agammaglobulinemia is a member of the src family of protein-tyrosine kinases. Nature 361: 226-233.

21. Rawlings DJ (1999) Bruton’s tyrosine kinase controls a sustained calcium signal essential for B lineage development and function. Clin Immunol 91: 243-253.

22. Gustafsson MO, Hussain A, Mohammad DK, Mohamed AJ, Nguyen V, et al. (2012) Regulation of nucleo-cytoplasmic shuttling of Bruton’s tyrosine kinase (BTK) through a novel SH3-dependent interaction with ankyrin repeat domain 54 (ANKRD54). Mol Cell Biol 32: 2440-2453.

23. Lindvall JM, Blomberg KE, Váliha J, Vargas L, Heinonen JE, et al. (2005) Bruton’s tyrosine kinase: cell biology, sequence conservation, mutation spectrum, siRNA modifications, and expression profiling. Immunol Rev 203: 200-215.

24. Kil LP, de Bruijn MJ, van Hulst JA, Lengerak AW, Yuvaraj S, et al. (2013) Bruton’s tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia. Am J Blood Res 3: 71-83.

25. Vassilev AO, Uckun FM (2004) Therapeutic potential of inhibiting Bruton’s tyrosine kinase (BTK). Curr Pharm Des 10: 1757-1766.

26. Ying H, Li Z, Yang L, Zhang J (2011) Syk mediates BCR- and CD40-signaling integration during B cell development. Immunobiology 216: 566-570.

27. Lee KG, Xu S, Wong ET, Tergaonkar V, Lam KP (2008) Bruton’s tyrosine kinase separately regulates NF kappaB p65RelA activation and cytokine interleukin (IL)-10/12 production in TLR9-stimulated B Cells. J Biol Chem 283: 11189-11198.

28. Liu Z, Mai A, Sun J (2010) Lysine acetylation regulates Bruton’s tyrosine kinase in B cell activation. J Immunol 184: 244-254.

29. Bence K, Ma W, Kozasa T, Huang XY (1997) Direct stimulation of Bruton’s tyrosine kinase by G(q)-protein alpha-subunit. Nature 389: 296-299.

30. Jiang Y, Ma W, Yan Y, Kozasa T, Hattori S, et al. (1998) The protein G alpha12 stimulates Bruton’s tyrosine kinase and a rasGAP through a conserved PH/BD domain. Nature 395: 808-813.

31. Li Z, Wahl MI, Eqinoua A, Stephens LR, Hawkins PT, et al. (1997) Phosphatidylinositol 3-kinase-gamma activates Bruton’s tyrosine kinase in concert with Src family kinases. Proc Natl Acad Sci U S A 94: 13820-13825.

32. Sailto K, Tolias KF, Saci A, Koon HB, Humphries LA, et al. (2003) BTK regulates PtdIns-4,5-P2 synthesis: importance for calcium signaling and PI3K activity. Immunol Rev 199: 669-678.

33. Sattler-Marthe BA, Witte ON (2000) The role of Bruton’s tyrosine kinase in B-cell development and function: a genetic perspective. Immunol Rev 175: 120-127.

34. Janda E, Palmieri C, Pisano A, Pontoriero M, Iaccino E, et al. (2011) Btk regulation in human and mouse B cells via protein kinase C phosphorylation of IKBk. Blood 117: 6520-6531.

35. Sochorová M, Litzman J, Bartunková J, et al. (2007) Impaired Toll-like receptor 8-mediated IL-6 and TNF-alpha production in antigen-presenting cells from patients with X-linked agammaglobulinemia. Blood 109: 2553-2556.

36. Gutierrez T, Mayeux JM, Ortega SB, Karandikar NJ, Li QZ, et al. (2013) IL-21 promotes the production of anti-DNA IgG but is dispensable for kidney damage in Lyn-/- mice. Eur J Immunol 43: 382-393.
Citation: Liu Y, Zhou G, Zhang B, Liu Y (2013) Bruton’s Tyrosine Kinase: Structure and Functions, Expression and Mutations. Gene Technology 2: 106. doi: 10.4172/2329-6682.1000106

37. Krupa A, Fudala R, Florence JM, Tucker T, Allen TC, et al. (2013) Bruton’s tyrosine kinase mediates FcγRIIa/Toll-like receptor-4 receptor crosstalk in human neutrophils. Am J Respir Cell Mol Biol 48: 240-249.

38. Ni Gabhann J, Spence S, Wynne C, Smith S, Byrne JC, et al. (2012) Defects in acute responses to TLR4 in Btk-deficient mice result in impaired dendritic cell-induced IFN-γ production by natural killer cells. Clin Immunol 142: 373-382.

39. Schmidt NW, Thieu VT, Mann BA, Ahlyi AN, Kaplan MH (2006) Bruton’s tyrosine kinase is required for TLR-induced IL-10 production. J Immunol 177: 7203-7210.

40. Takahashi-Tezuka M, Hibi M, Fujitani Y, Fukuda T, Yamaguchi T, et al. (1997) Tec tyrosine kinase links the cytokine receptors to PI-3 kinase probably through JAK. Oncogene 14: 2273-2292.

41. Xie Q, Joseph RE, Fulton DB, Andreotti AH (2013) Substrate recognition of PLCγ1 via a specific docking surface on Itk. J Biol Chem 288: 683-696.

42. Win S, Than TA, Han D, Petrovic LM, Kaplowitz N (2011) c-Jun N-terminal kinase (JNK)-dependent acute liver injury from acetaminophen or tumor necrosis factor (TNF) requires mitochondrial Sab protein expression in mice. J Biol Chem 286: 35071-35078.

43. Tan SL, Liao C, Lucas MC, Stevenson C, DeMartino JA (2013) Targeting the SYK-BTK axis for the treatment of immunological and hematological disorders: recent progress and therapeutic perspectives. Pharmacol Ther 138: 294-309.

44. Kuehn HS, Swindle EJ, Kim MS, Beaven MA, Metcalfe DD, et al. (2008) The Bruton’s tyrosine kinase mediates FcγRIIa/Toll-like receptor-4 receptor crosstalk in human neutrophils. Am J Respir Cell Mol Biol 48: 240-249.

45. de Weers M, Verschuren MC, Kraakman ME, Mensink RG, Schuurman RK, et al. (2006) Bruton’s tyrosine kinase is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages. Eur J Immunol 36: 3109-3114.

46. Genevich HC, Hinshelwood S, Gaspar HB, Rigley KP, Brown D, et al. (1994) Expression of Bruton’s tyrosine kinase protein within the B cell lineage. Eur J Immunol 24: 3100-3105.

47. Kersseboom R, Ta VB, Zijlstra AJ, Middendorp S, Jumaa H, et al. (2006) Bruton’s tyrosine kinase and SLP-65 regulate pre-B cell differentiation and the induction of Ig light chain gene rearrangement. J Immunol 176: 4543-4552.

48. Feldhahn N, Rio P, Soh BN, Liedtke S, Spranglers M, et al. (2005) Deficiency of Bruton’s tyrosine kinase in B cell precursor leukemia cells. Proc Natl Acad Sci USA 102: 13266-13271.

49. Feldhahn N, Klein F, Mooster JL, Hadweh P, Spranglers M, et al. (2005) Mimicry of a constitutively active pre-B cell receptor in acute lymphoblastic leukemia cells. J Exp Med 201: 1837-1852.

50. Bruton OC (1952) Agammaglobulinemia. Pediatrics 9:722-727.

51. BRUTON OC, APT L, GITLIN D, JANEWAY CA (1952) Absence of serum gamma globulins. AMA Am J Dis Child 84: 632-636.

52. Qin X, Jiang LP, Tang XM, Wang M, Liu EM, et al. (2013) Clinical features and mutation analysis of X-linked agammaglobulinemia in 20 Chinese patients. World J Pediatr 9: 273-277.

53. Ellmeier W, Jung S, Sunshine MJ, Hatam F, Xu Y, et al. (2000) Severe B cell deficiency in mice lacking the tec kinase family members Tec and Btk. J Exp Med 192: 1611-1624.

54. Conley ME, Mathias D, Treadaway J, Minegishi Y, Rohrer J (1998) Mutations in btk in patients with presumed X-linked agammaglobulinemia. Am J Hum Genet 62: 1034-1043.

55. Vargas-Hernández A, López-Herrera G, Maravillas-Montero JL, Vences-Catalán F, Mogica-Martínez D, et al. (2012) Consequences of two naturally occurring missense mutations in the structure and function of Bruton agammaglobulinemia tyrosine kinase. IUBMB Life 64: 346-353.

56. Rawlings DJ, Saffran DC, Tsukada S, Largaespada DA, Grimaldi JC, et al. (1993) Mutation of unique region of Bruton’s tyrosine kinase in XID mice. Science 261: 358-361.

57. Mohamed AJ, Yu L, Bäckesjö CM, Vargas L, Faryal R, et al. (2009) Bruton’s tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. Immunol Rev 231: 48-67.

58. Traxler P (2003) Tyrosine kinases as targets in cancer therapy - successes and failures. Expert Opin Ther Targets 7: 215-234.

59. Hantschel O, Rix U, Schmidt U, Bürckstümmer T, Kneidinger M, et al. (2007) The Bruton’s tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib. Proc Natl Acad Sci U S A 104: 13152-13157.

60. Satterthwaite AB, Cheroutre H, Khan WN, Sideras P, Witte ON (1997) Btk differentially regulate B cell antigen receptor-mediated signal transduction. J Exp Med 181: 7706-7712.

61. Ben-Neriah Y, Andronikou S, Moeller T, Shevach EM, Friend SH (2003) CD4+ T cells: the killer cells. Nat Immunol 4: 133-139.

62. Ellmeier W, Jung S, Sunshine MJ, Hatam F, Xu Y, et al. (2000) Severe B cell deficiency in mice lacking the tec kinase family members Tec and Btk. J Exp Med 192: 1611-1624.

63. Conley ME, Mathias D, Treadaway J, Minegishi Y, Rohrer J (1998) Mutations in btk in patients with presumed X-linked agammaglobulinemia. Am J Hum Genet 62: 1034-1043.

64. Vargas-Hernández A, López-Herrera G, Maravillas-Montero JL, Vences-Catalán F, Mogica-Martínez D, et al. (2012) Consequences of two naturally occurring missense mutations in the structure and function of Bruton agammaglobulinemia tyrosine kinase. IUBMB Life 64: 346-353.

65. Rawlings DJ, Saffran DC, Tsukada S, Largaespada DA, Grimaldi JC, et al. (1993) Mutation of unique region of Bruton’s tyrosine kinase in XID mice. Science 261: 358-361.

66. Mohamed AJ, Yu L, Bäckesjö CM, Vargas L, Faryal R, et al. (2009) Bruton’s tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. Immunol Rev 231: 48-67.

67. Traxler P (2003) Tyrosine kinases as targets in cancer therapy - successes and failures. Expert Opin Ther Targets 7: 215-234.

68. Hantschel O, Rix U, Schmidt U, Bürckstümmer T, Kneidinger M, et al. (2007) The Bruton’s tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib. Proc Natl Acad Sci U S A 104: 13152-13157.

69. Satterthwaite AB, Cheroutre H, Khan WN, Sideras P, Witte ON (1997) Btk differentially regulate B cell antigen receptor-mediated signal transduction. J Exp Med 181: 7706-7712.

70. Ben-Neriah Y, Andronikou S, Moeller T, Shevach EM, Friend SH (2003) CD4+ T cells: the killer cells. Nat Immunol 4: 133-139.