## 1. Phylogeny

Tyrosine‐protein kinase BTK, commonly known as Bruton tyrosine kinase, belongs to the Tec family of non‐receptor tyrosine kinases and is evolutionarily conserved across vertebrates (alu2022btkinhibitorsin pages 1-3). Within the kinome, BTK groups with other Tec kinases—including ITK, TEC, BMX, and TXK—which share a common domain architecture, suggesting that BTK evolved from an ancestral Tec family kinase present in early metazoans (zain2021structurefunctionrelationshipsof pages 1-2, duarte2020btksh2kinaseinterface pages 1-5). Orthologs of BTK have been identified in various mammalian species, indicating its essential and conserved role in immune function, and its evolutionary conservation is underscored by the persistence of key catalytic and regulatory residues such as the active‐site cysteine (alu2022btkinhibitorsin pages 1-3, zain2021structurefunctionrelationshipsof pages 1-2).

## 2. Reaction Catalyzed

BTK catalyzes the transfer of the gamma phosphate group from ATP to specific tyrosine residues on substrate proteins, a classic phosphorylation reaction that produces ADP and a phosphotyrosine-modified substrate (joseph2020differentialimpactof pages 1-2). In the context of B-cell receptor signaling, one of its best-characterized reactions is the phosphorylation of phospholipase C gamma 2 (PLCG2) at multiple tyrosine sites, which subsequently drives calcium mobilization and downstream activation of protein kinase C family members (alu2022btkinhibitorsin pages 3-5). This phosphorylation reaction, typical of tyrosine kinases, is central to the propagation of signals initiated by antigen binding and is vital for B lymphocyte activation and subsequent cellular responses (mcdonald2021theroleof pages 1-2).

## 3. Cofactor Requirements

The catalytic activity of BTK is dependent on ATP as the phosphate donor, and this enzymatic process requires a divalent metal ion—commonly Mg²⁺—to coordinate the binding of ATP and facilitate the phosphoryl transfer (lin2023structureofbtk pages 2-4). In addition to Mg²⁺, structural studies imply that appropriate membrane lipids such as phosphatidylinositol 3,4,5-trisphosphate (PIP3) are critical for the recruitment of BTK to the plasma membrane via its pleckstrin homology (PH) domain, thereby indirectly influencing its catalytic efficiency (alu2022btkinhibitorsin pages 3-5, messex2021targetingbtksignaling pages 6-7).

## 4. Substrate Specificity

BTK exhibits a high degree of substrate specificity by phosphorylating key substrates that include PLCγ2, which is essential for mediating calcium flux in B cells following B-cell receptor (BCR) engagement (alu2022btkinhibitorsin pages 3-5, joseph2020differentialimpactof pages 25-26). The enzyme does not recognize a broad amino acid motif in the same way that serine/threonine kinases might; rather, its specificity is determined by both the spatial conformation of the substrate and the formation of docking complexes with adaptor proteins such as BLNK, which facilitates correct substrate presentation (joseph2020differentialimpactof pages 2-4, mcdonald2021theroleof pages 25-28). In addition to PLCγ2, BTK substrates extend to proteins involved in Toll-like receptor (TLR) signaling, such as TIRAP, and even to molecules that participate in the assembly of the NLRP3 inflammasome, further emphasizing its role in both adaptive and innate immune responses (OpenTargets Search: -BTK).

## 5. Structure

BTK comprises a modular domain architecture that underpins its multifunctional role in immune signaling. The protein contains an N-terminal Pleckstrin Homology (PH) domain that mediates binding to phosphoinositide lipids at the plasma membrane and is essential for proper subcellular localization (alu2022btkinhibitorsin pages 3-5, messex2021targetingbtksignaling pages 4-6). Immediately following the PH domain is a Tec Homology (TH) region that contains a proline-rich segment and zinc finger motif, contributing to the protein’s stability and potential intermolecular interactions (alu2022btkinhibitorsin pages 3-5). BTK also harbors an SH3 domain that facilitates interactions with proline-rich regions in binding partners and an SH2 domain that binds phosphotyrosine motifs, offering a means for assembling multi-protein complexes and mediating autoinhibitory contacts (zain2021structurefunctionrelationshipsof pages 1-2, alu2022btkinhibitorsin pages 3-5). The C-terminal kinase (SH1) domain is responsible for the catalytic activity of BTK, with key residues such as Y551, whose phosphorylation leads to activation, and C481, which serves as the covalent binding site for clinically approved BTK inhibitors (alu2022btkinhibitorsin pages 3-5, lin2023structureofbtk pages 11-12, joseph2020differentialimpactof pages 27-27). High-resolution crystal structures and AlphaFold models have provided significant insights into these domains, confirming the overall fold typical for tyrosine kinases and revealing subtle conformational changes that regulate kinase activity and inhibitor binding (lin2023structureofbtk pages 2-4, joseph2020differentialimpactof pages 25-26).

## 6. Regulation

BTK is regulated through multiple, interdependent mechanisms that include phosphorylation, protein–protein interactions, and subcellular localization changes. Upon B-cell antigen receptor (BCR) engagement, upstream kinases such as SYK or Src family kinases phosphorylate BTK at Y551 within the kinase domain, which then triggers autophosphorylation at Y223 in the SH3 domain, a modification necessary for full catalytic activation (alu2022btkinhibitorsin pages 3-5, joseph2020differentialimpactof pages 1-2). Additionally, the binding of PIP3 to the PH domain is critical for membrane localization and subsequent activation of BTK, linking lipid signaling to kinase regulation (messex2021targetingbtksignaling pages 6-7, lin2023structureofbtk pages 2-4). BTK also acts as a platform for assembling signaling complexes, and its interactions with adaptor proteins like BLNK facilitate substrate recognition and feedback regulation (joseph2020differentialimpactof pages 2-4, mcdonald2021theroleof pages 15-17). In terms of negative regulation, BTK can be modulated by phosphatases and by post-translational modifications such as ubiquitination that lead to its degradation, although detailed mechanisms in these contexts remain an area of active research (alu2022btkinhibitorsin pages 25-26, eisen2025conditionalrequirementfor pages 26-28).

## 7. Function

BTK is indispensable for the development, differentiation, and signaling of B lymphocytes. Its activation following antigen binding to the B-cell receptor initiates a cascade that results in the phosphorylation of PLCγ2, subsequent calcium mobilization, and the activation of downstream effectors including protein kinase C, ultimately leading to B-cell activation, proliferation, and survival (OpenTargets Search: -BTK, mcdonald2021theroleof pages 1-2). Beyond its canonical role in adaptive immunity, BTK is implicated in the regulation of innate immune responses; it participates in Toll-like receptor (TLR) signaling pathways where it phosphorylates TIRAP leading to its degradation, thereby modulating the inflammatory response and pathogen surveillance (mcdonald2021theroleof pages 22-25, OpenTargets Search: -BTK). Moreover, BTK has been shown to play a part in transcriptional regulation by stimulating NF-κB activity and by transiently phosphorylating transcription factors such as GTF2I, which then translocate to the nucleus to influence gene expression (mcdonald2021theroleof pages 1-2, OpenTargets Search: -BTK). BTK is furthermore involved in the activation of the NLRP3 inflammasome via phosphorylation of NLRP3, highlighting its dual role in immune signaling and inflammatory responses (OpenTargets Search: -BTK). Expressed primarily in B cells and to a lesser extent in myeloid cells, its proper function is critical for normal immune development, whereas mutations or dysregulation of BTK can lead to immunodeficiency disorders such as X-linked agammaglobulinemia (XLA) and contribute to the pathology of B-cell malignancies (alu2022btkinhibitorsin pages 1-3, zain2021structurefunctionrelationshipsof pages 7-9).

## 8. Other Comments

Clinically, BTK is a validated and highly pursued therapeutic target; several inhibitors have been developed that target its kinase domain by covalently binding to the C481 residue, with ibrutinib being the prototypical example (estupinan2021btkgatekeeperresidue pages 12-13, tasso2021thedevelopmentof pages 26-28). Second-generation inhibitors such as acalabrutinib, zanubrutinib, tirabrutinib, and the reversible BTK inhibitor pirtobrutinib have been developed to improve selectivity and overcome resistance often conferred by mutations such as C481S (naeem2023pirtobrutinibtargetsbtk pages 14-15, joseph2024impactofthe pages 26-27). BTK inhibitors have not only revolutionized the treatment of B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström macroglobulinemia, but there is also increasing interest in their utility for autoimmune disorders and inflammatory diseases owing to BTK’s role in TLR signaling and innate immunity (mcdonald2021theroleof pages 17-22, ringheim2021bruton’styrosinekinase pages 1-2). Notably, resistance mutations—both within the kinase domain (e.g., at residues C481, T474) and in downstream effectors—pose significant clinical challenges and continue to drive research into next-generation BTK inhibitors and combination therapies (estupinan2021btkgatekeeperresidue pages 12-13, joseph2020differentialimpactof pages 27-27). Furthermore, BTK’s emerging roles in transcriptional regulation, such as its influence on NF-κB and its indirect effects on apoptosis and interferon response via STING1-mediated pathways, highlight additional dimensions of its biological impact that are under active investigation (OpenTargets Search: -BTK, mcdonald2021theroleof pages 1-2). Consequently, BTK remains a focal point in translational research aimed at improving therapies for immunodeficiency, leukemia, lymphoma, and inflammatory diseases (alu2022btkinhibitorsin pages 27-28, messex2021targetingbtksignaling pages 6-7).

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