1. Phylogeny  
   Tyrosine‐protein kinase Blk belongs to the Src family of non‐receptor tyrosine kinases and is classified in subfamily B, which is typified by a conserved domain architecture distinct from subfamily A members. BLK is evolutionarily conserved among vertebrates and is found exclusively in B lymphocytes, with orthologs traceable in mammalian species. Its grouping within the human kinome was originally defined in comprehensive studies of the protein kinase complement (Manning et al. 2002 Science, Manning et al. 2002 Trends Biochem Sci), and subsequent functional studies have underscored its close evolutionary relationships with other B cell–expressed Src family kinases such as Lyn and Fyn (korademirnics2000srckinasemediatedsignaling pages 2-3, barreiro2017functionalstudiesof pages 40-43).
2. Reaction Catalyzed  
   BLK catalyzes the transfer of the gamma‐phosphate group from ATP to specific tyrosine residues on its substrate proteins. In chemical notation, the general reaction is: ATP + [protein]–tyrosine → ADP + [protein]–phosphotyrosine + H⁺ (bolen1997leukocyteproteintyrosine pages 1-4, corey1999srcrelatedproteintyrosine pages 2-3).
3. Cofactor Requirements  
   As with many protein kinases, the catalytic activity of BLK depends on divalent cations, primarily Mg²⁺, which serve as essential cofactors that facilitate the binding and proper orientation of ATP for phosphoryl transfer (ingley2008srcfamilykinases pages 1-2, bolen1997leukocyteproteintyrosine pages 1-4).
4. Substrate Specificity  
   BLK has substrate specificity that targets critical immunoreceptor components. It phosphorylates CD79A at tyrosine residues 188 and 199 and CD79B at tyrosine residues 196 and 207, events central to both B-cell receptor (BCR) and pre-BCR signaling cascades (barreiro2017functionalstudiesof pages 14-23). In addition, BLK catalyzes the phosphorylation of immunoglobulin G (IgG) receptor subunits FCGR2A, FCGR2B, and FCGR2C, and it has been shown to contribute indirectly to the activation of Bruton’s tyrosine kinase (BTK) through stimulation of BTK autophosphorylation (barreiro2017functionalstudiesof pages 43-47, bolen1997leukocyteproteintyrosine pages 1-4). While detailed consensus motifs have not been definitively established, the substrates of BLK typically present with tyrosine-containing immunoreceptor activation motifs (ITAMs) embedded in an acidic context, which is characteristic of its Src family kinase relatives (corey1999srcrelatedproteintyrosine pages 3-5).
5. Structure  
   BLK displays the conserved modular organization characteristic of Src family kinases. It possesses an N-terminal SH4 domain that is post-translationally modified through N-myristoylation and palmitoylation to mediate efficient membrane localization in B cells (korademirnics2000srckinasemediatedsignaling pages 2-3, barreiro2017functionalstudiesof pages 40-43). Following this, a unique region is found that provides additional regulation and may confer subtle specificity among Src family members. BLK contains an SH3 domain that binds proline-rich sequences and plays a key role in autoregulation; notably, a naturally occurring variation such as the Ala71Thr substitution within the SH3 domain has been shown to increase ubiquitination and proteasomal degradation without affecting subcellular localization (barreiro2017functionalstudiesof pages 76-80, barreiro2017functionalstudiesof pages 92-98). The central kinase domain, which carries the ATP-binding site and catalytic machinery, is flanked by an SH2 domain which mediates binding to phosphotyrosine-containing motifs on substrate proteins. The C-terminal tail of BLK, while shorter than those found in some other Src kinases, contains regulatory tyrosine residues that are phosphorylated by upstream kinases such as Csk to maintain an inactive conformation (bolen1997leukocyteproteintyrosine pages 4-6, superti‐furga1995structure‐functionrelationshipsin pages 6-8).
6. Regulation  
   BLK activity is subject to multiple layers of regulation that are common to Src family kinases. Post-translational modifications, notably phosphorylation at specific tyrosine residues within the activation loop (which, when phosphorylated, promote full kinase activity) and at a conserved C-terminal inhibitory tyrosine (which, when phosphorylated by Csk, stabilize an inactive conformation), are critical determinants of its functional state (barreiro2017functionalstudiesof pages 98-101, bolen1997leukocyteproteintyrosine pages 6-9). In addition, the Ala71Thr variant in the SH3 domain has been documented to enhance polyubiquitination of BLK, thereby decreasing its half-life and protein levels; this modification is mediated by E3 ubiquitin ligases such as E6AP following activation (barreiro2017functionalstudiesof pages 72-76). Such regulation via phosphorylation and ubiquitination ensures that BLK-mediated signaling is tightly controlled during B cell development and activation (korademirnics2000srckinasemediatedsignaling pages 9-10, mahajan1995srcfamilyprotein pages 6-7).
7. Function  
   BLK plays a crucial role in B lymphocyte development, differentiation, and signaling. It is predominantly expressed in B cells and is essential for transmitting signals initiated by the B-cell receptor (BCR). Binding of antigen to the BCR triggers signaling pathways in which BLK phosphorylates the CD79A and CD79B components, facilitating downstream pathways that include NF-kappa-B activation and contributing to the transition from pro-B to pre-B cells (barreiro2017functionalstudiesof pages 14-23, barreiro2017functionalstudiesof pages 50-60). In addition to its classical role in B-cell signaling, BLK has been implicated in modulating beta-cell function in pancreatic islets via the up-regulation of key transcription factors PDX1 and NKX6-1, thereby influencing insulin secretion in response to glucose (Information section, PubMed:19667185). BLK also phosphorylates CGAS, promoting its retention in the cytosol, which may affect innate immune signaling pathways (Information section, PubMed:30356214). Through its interactions, including with adaptor molecules such as BANK1, BLK coordinates signaling events that determine B-cell activation thresholds and long-term cellular responses (barreiro2017functionalstudiesof pages 43-47, bolen1997leukocyteproteintyrosine pages 1-4).
8. Other Comments  
   Several Src family kinase inhibitors that target the ATP-binding pocket or allosteric sites have been shown to inhibit kinases such as BLK. For instance, FDA-approved inhibitors including Dasatinib, Ponatinib, and Saracatinib have activity against Src family members and therefore are relevant to BLK inhibition (sumera2023pharmacophorebasedhigh pages 1-2, sumera2023pharmacophorebasedhigh pages 9-9). BLK has been genetically associated with autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis; risk-associated variants frequently result in diminished BLK expression and dysregulation of B-cell signaling (barreiro2017functionalstudiesof pages 14-23, barreiro2017functionalstudiesof pages 50-60). In addition, its expression profile and role in B cell signaling suggest potential implications in B-cell malignancies, although knockout studies have demonstrated functional redundancy among Src family kinases in B lymphocytes (bolen1997leukocyteproteintyrosine pages 1-4, korademirnics2000srckinasemediatedsignaling pages 4-5).
9. References

* bolen1997leukocyteproteintyrosine pages 1-4
* bolen1997leukocyteproteintyrosine pages 4-6
* corey1999srcrelatedproteintyrosine pages 2-3
* corey1999srcrelatedproteintyrosine pages 3-5
* ingley2008srcfamilykinases pages 1-2
* korademirnics2000srckinasemediatedsignaling pages 2-3
* korademirnics2000srckinasemediatedsignaling pages 9-10
* barreiro2017functionalstudiesof pages 14-23
* barreiro2017functionalstudiesof pages 40-43
* barreiro2017functionalstudiesof pages 43-47
* barreiro2017functionalstudiesof pages 50-60
* barreiro2017functionalstudiesof pages 72-76
* barreiro2017functionalstudiesof pages 76-80
* barreiro2017functionalstudiesof pages 92-98
* barreiro2017functionalstudiesof pages 98-101
* sumera2023pharmacophorebasedhigh pages 1-2
* sumera2023pharmacophorebasedhigh pages 9-9

References

1. (barreiro2017functionalstudiesof pages 40-43): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
2. (barreiro2017functionalstudiesof pages 43-47): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
3. (barreiro2017functionalstudiesof pages 76-80): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
4. (bolen1997leukocyteproteintyrosine pages 1-4): Joseph B. Bolen and Joan S. Brugge. Leukocyte protein tyrosine kinases:potential targets for drug discovery. Annual Review of Immunology, 15:371-404, Apr 1997. URL: https://doi.org/10.1146/annurev.immunol.15.1.371, doi:10.1146/annurev.immunol.15.1.371. This article has 242 citations and is from a highest quality peer-reviewed journal.
5. (sumera2023pharmacophorebasedhigh pages 1-2): Sana Sumera, Sanjai Srinivasan, Harshitha BV, Sharanagoud Biradar, and Shankarrao Patil. Pharmacophore based high throughput virtual screening towards the discovery of novel blk (b-lymphocyte kinase)- tyrosine kinase inhibitors. Indian Journal of Pharmaceutical Education and Research, 57:s174-s182, Mar 2023. URL: https://doi.org/10.5530/ijper.57.1s.21, doi:10.5530/ijper.57.1s.21. This article has 0 citations and is from a poor quality or predatory journal.
6. (barreiro2017functionalstudiesof pages 14-23): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
7. (barreiro2017functionalstudiesof pages 50-60): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
8. (barreiro2017functionalstudiesof pages 72-76): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
9. (barreiro2017functionalstudiesof pages 92-98): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
10. (barreiro2017functionalstudiesof pages 98-101): A Díaz Barreiro. Functional studies of the sle-risk genes bank1 and blk in b-cell pathways. Unknown journal, 2017.
11. (bolen1997leukocyteproteintyrosine pages 6-9): Joseph B. Bolen and Joan S. Brugge. Leukocyte protein tyrosine kinases:potential targets for drug discovery. Annual Review of Immunology, 15:371-404, Apr 1997. URL: https://doi.org/10.1146/annurev.immunol.15.1.371, doi:10.1146/annurev.immunol.15.1.371. This article has 242 citations and is from a highest quality peer-reviewed journal.
12. (corey1999srcrelatedproteintyrosine pages 2-3): Seth J. Corey and Steven M. Anderson. Src-related protein tyrosine kinases in hematopoiesis. Blood, 93:1-14, Jan 1999. URL: https://doi.org/10.1182/blood.v93.1.1.401a45\_1\_14, doi:10.1182/blood.v93.1.1.401a45\_1\_14. This article has 185 citations and is from a highest quality peer-reviewed journal.
13. (corey1999srcrelatedproteintyrosine pages 3-5): Seth J. Corey and Steven M. Anderson. Src-related protein tyrosine kinases in hematopoiesis. Blood, 93:1-14, Jan 1999. URL: https://doi.org/10.1182/blood.v93.1.1.401a45\_1\_14, doi:10.1182/blood.v93.1.1.401a45\_1\_14. This article has 185 citations and is from a highest quality peer-reviewed journal.
14. (ingley2008srcfamilykinases pages 1-2): Evan Ingley. Src family kinases: regulation of their activities, levels and identification of new pathways. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1784:56-65, Jan 2008. URL: https://doi.org/10.1016/j.bbapap.2007.08.012, doi:10.1016/j.bbapap.2007.08.012. This article has 435 citations.
15. (korademirnics2000srckinasemediatedsignaling pages 2-3): Željka Korade-Mirnics and Seth J Corey. Src kinase-mediated signaling in leukocytes. Journal of Leukocyte Biology, 68:603-613, Nov 2000. URL: https://doi.org/10.1189/jlb.68.5.603, doi:10.1189/jlb.68.5.603. This article has 160 citations and is from a peer-reviewed journal.
16. (korademirnics2000srckinasemediatedsignaling pages 9-10): Željka Korade-Mirnics and Seth J Corey. Src kinase-mediated signaling in leukocytes. Journal of Leukocyte Biology, 68:603-613, Nov 2000. URL: https://doi.org/10.1189/jlb.68.5.603, doi:10.1189/jlb.68.5.603. This article has 160 citations and is from a peer-reviewed journal.
17. (mahajan1995srcfamilyprotein pages 6-7): Sandeep Mahajan, Joseph Fargnoli, Anne L. Burkhardt, Stephanie A. Kut, Sandra J. Saouaf, and Joseph B. Bolen. Src family protein tyrosine kinases induce autoactivation of bruton’s tyrosine kinase. Molecular and Cellular Biology, 15:5304-5311, Oct 1995. URL: https://doi.org/10.1128/mcb.15.10.5304, doi:10.1128/mcb.15.10.5304. This article has 188 citations and is from a domain leading peer-reviewed journal.
18. (sumera2023pharmacophorebasedhigh pages 9-9): Sana Sumera, Sanjai Srinivasan, Harshitha BV, Sharanagoud Biradar, and Shankarrao Patil. Pharmacophore based high throughput virtual screening towards the discovery of novel blk (b-lymphocyte kinase)- tyrosine kinase inhibitors. Indian Journal of Pharmaceutical Education and Research, 57:s174-s182, Mar 2023. URL: https://doi.org/10.5530/ijper.57.1s.21, doi:10.5530/ijper.57.1s.21. This article has 0 citations and is from a poor quality or predatory journal.
19. (superti‐furga1995structure‐functionrelationshipsin pages 6-8): Giulio Superti‐Furga and Sara A. Courtneidge. Structure‐function relationships in src family and related protein tyrosine kinases. BioEssays, 17:321-330, Apr 1995. URL: https://doi.org/10.1002/bies.950170408, doi:10.1002/bies.950170408. This article has 277 citations and is from a peer-reviewed journal.
20. (bolen1997leukocyteproteintyrosine pages 4-6): Joseph B. Bolen and Joan S. Brugge. Leukocyte protein tyrosine kinases:potential targets for drug discovery. Annual Review of Immunology, 15:371-404, Apr 1997. URL: https://doi.org/10.1146/annurev.immunol.15.1.371, doi:10.1146/annurev.immunol.15.1.371. This article has 242 citations and is from a highest quality peer-reviewed journal.
21. (korademirnics2000srckinasemediatedsignaling pages 4-5): Željka Korade-Mirnics and Seth J Corey. Src kinase-mediated signaling in leukocytes. Journal of Leukocyte Biology, 68:603-613, Nov 2000. URL: https://doi.org/10.1189/jlb.68.5.603, doi:10.1189/jlb.68.5.603. This article has 160 citations and is from a peer-reviewed journal.