1. Phylogeny  
   Tyrosine‐protein kinase Tec is a non‐receptor tyrosine kinase that belongs to the Tec family, a subgroup within the wider tyrosine kinase branch of the human kinome. Tec and its close relatives—including Bruton’s tyrosine kinase (BTK) and interleukin‐2–inducible T-cell kinase (ITK)—are evolutionarily related and share a common ancestry with other cytoplasmic tyrosine kinases that emerged early in the evolution of metazoans (kwon2019tracingtheevolution pages 32-37). Orthologs of Tec have been identified in all mammalian species, indicating its conservation across vertebrates, and the enzyme shares significant sequence homology and domain organization with other members of the Tec family. In phylogenetic analyses based on sequence motifs and domain composition, Tec is placed within the Src module subgroup, which is characterized by the presence of SH3–SH2–kinase domain arrangements as well as additional regulatory regions that enable fine-tuning of its catalytic function (marcotte2010structuresofhuman pages 1-3, kwon2019tracingtheevolution pages 32-37).
2. Reaction Catalyzed  
   Tec catalyzes the transfer of the γ-phosphate group from ATP to specific tyrosine residues on protein substrates. The overall chemical reaction can be summarized as follows:  
    ATP + protein–tyrosine → ADP + protein–phosphotyrosine + H⁺  
   This reaction is fundamental to tyrosine phosphorylation and is central to signal transduction processes mediated by Tec (banerjee2013phosphorylationubiquitylationand pages 20-26).
3. Cofactor Requirements  
   The catalytic activity of Tec, like that of most protein kinases, depends on the presence of divalent metal ions. In particular, Mg²⁺ is required to coordinate ATP binding at the active site and to facilitate the phosphate transfer reaction. This cofactor is essential for proper alignment of ATP and the substrate, stabilizing transition states during catalysis (banerjee2013phosphorylationubiquitylationand pages 20-26).
4. Substrate Specificity  
   The substrate specificity of Tec is determined by its ability to recognize tyrosine residues within specific sequence contexts and by its associated phosphotyrosine-binding domains. Tec phosphorylates substrates that display particular amino acid motifs surrounding the target tyrosine residue. For example, Tec has been shown to phosphorylate proteins such as DOK1 and STAP1, where recognition typically involves a phosphorylated tyrosine residue flanked by hydrophobic or other selectively favored amino acids at positions immediately following the phosphorylation site (for instance, positions +1 to +3) (diop2022sh2domainsfolding pages 6-8, cesareni2005modularproteindomains pages 31-33). Although detailed consensus motifs specific to Tec have not been explicitly delineated in the available literature, its substrate specificity is in line with general features observed for tyrosine kinases that utilize their SH2 domains to mediate selective interactions with phosphopeptides.
5. Structure  
   Tec is composed of multiple domains arranged in a modular format that is characteristic of the Tec family kinases. At its N-terminus, Tec contains a pleckstrin homology (PH) domain, which is pivotal for binding phosphoinositides such as PIP3 and thereby mediating membrane localization. Adjacent to the PH domain is the Tec homology (TH) region, which includes motifs such as a Btk homology domain and proline-rich regions that participate in protein–protein interactions. This is followed by an SH3 domain that binds proline-rich sequences, an SH2 domain that engages phosphotyrosine-containing motifs, and finally the C-terminal kinase catalytic domain (also known as the SH1 domain) which carries out the phosphorylation reaction (marcotte2010structuresofhuman pages 1-3, kwon2019tracingtheevolution pages 32-37).

Within the kinase catalytic domain, Tec displays a bilobal structure composed of a smaller N-terminal lobe enriched with β-sheets and a larger C-terminal lobe predominantly formed by α-helices. Key structural features include a glycine-rich loop involved in ATP binding, a conserved lysine in the β3 strand that interacts with ATP, an activation loop whose conformation regulates access to the active site, and a C-helix that plays a crucial role in aligning catalytic residues. Moreover, Tec’s catalytic domain encompasses a hydrophobic regulatory spine (R-spine), the assembly of which is critical for its transition from inactive to active conformations (kwon2019tracingtheevolution pages 32-37, mcclendon2020structurefunctionand pages 1-3). Experimental models and predicted three-dimensional structures suggest that Tec shares this canonical kinase fold with minor family-specific insertions that may contribute to its unique regulatory properties.

1. Regulation  
   Tec kinase activity is tightly controlled by several regulatory mechanisms that include post-translational modifications as well as intramolecular and intermolecular protein interactions. One pivotal mode of regulation is through phosphorylation at key tyrosine residues in the activation loop of the kinase domain. Phosphorylation events serve to disrupt autoinhibitory conformations and promote alignment of the catalytic machinery for effective ATP binding and substrate phosphorylation. In addition, reciprocal phosphorylation with kinases such as JAK2 is known to modulate downstream transcriptional pathways—for instance, the activation of FOS transcription—thereby integrating Tec activity within broader cytokine-driven signaling cascades (naylor2021brutonstyrosinekinase pages 173-176, zarrin2021kinaseinhibitionin pages 12-13).

Besides autophosphorylation, Tec is regulated by its membrane recruitment via the PH domain. Upon binding to specific phospholipids at the plasma membrane, Tec is brought into close proximity with substrates and other signaling partners, which facilitates its activation in response to receptor engagement. Interactions mediated by the SH3 and SH2 domains further modulate Tec activity by promoting substrate association and stabilizing distinct conformational states. These domain interactions may also participate in negative regulation by maintaining Tec in a closed, autoinhibited conformation until cellular signals trigger a conformational shift that exposes the catalytic domain (kwon2019tracingtheevolution pages 41-45, ji2015widescalequantitativephosphoproteomic pages 10-11).

1. Function  
   Tec plays a multifaceted role in signal transduction pathways across various cell types, with a particularly prominent role in the adaptive immune response. In T lymphocytes, Tec is required for T cell receptor (TCR)–dependent interleukin-2 (IL2) gene induction and thus contributes to conventional T cell development, differentiation, and function. Tec’s activity in T cells also extends to the regulation of nonconventional natural killer T (NKT) cells (Information section). In B cells, Tec functions redundantly with BTK to mediate B cell receptor (BCR) signaling that is critical for B cell development and activation, including the phosphorylation of substrates such as STAP1 (Information section, naylor2021brutonstyrosinekinase pages 49-52).

In mast cells, Tec is required for efficient cytokine production following activation, further demonstrating its role in immune cell function. Beyond lymphocytes and mast cells, Tec participates in signaling downstream of receptors in myeloid cells; for example, it is activated by granulocyte colony-stimulating factor (CSF3) and contributes to myeloid cell growth, differentiation, and functional activation. Additionally, Tec is involved in platelet signaling downstream of integrin activation, where it modulates pathways essential for platelet aggregation and secretion. In hepatocytes, Tec plays a part in hepatocyte proliferation and liver regeneration by engaging in the hepatocyte growth factor (HGF)–induced extracellular signal-regulated kinase (ERK) signaling pathway and is also implicated in the regulation of fibroblast growth factor 2 (FGF2) secretion through a noncanonical mechanism that bypasses the classical endoplasmic reticulum/Golgi route (Information section, castelosoccio2023proteinkinasesdrug pages 1-2).

Tec further mediates cross-talk between distinct signaling cascades by phosphorylating substrates involved in both growth and differentiation. For instance, Tec phosphorylates DOK1 and the adaptor protein GRB10, which are implicated in CD28 and cytokine receptor signaling pathways, respectively. This interconnected role positions Tec as an important signal transducer whose activity influences cell proliferation, immune cell activation, and even osteoclast differentiation in bone biology (Information section, zarrin2021kinaseinhibitionin pages 12-13).

1. Other Comments  
   Several small-molecule inhibitors developed primarily for other Tec family kinases, such as BTK inhibitors ibrutinib and acalabrutinib, also inhibit Tec due to overlapping active site features and sequence homology within the Tec family. These inhibitors have been reported to impact platelet activation as well as immune cell function, highlighting the clinical relevance of targeting Tec in diseases where its activity is dysregulated (naylor2021brutonstyrosinekinase pages 173-176, zarrin2021kinaseinhibitionin pages 12-13).

In terms of disease association, aberrant Tec signaling has been implicated in various immune disorders including immunodeficiencies, given its redundant role with ITK in regulating adaptive immunity, and in hematologic malignancies where dysregulation of BCR or TCR signaling may contribute to oncogenesis. Moreover, Tec’s involvement in integrin-mediated platelet activation and hepatocyte proliferation also suggests potential roles in conditions such as thrombosis and liver regeneration. Notable disease mutations have not been exhaustively characterized in the available literature; however, alterations that affect Tec’s kinase activity or regulatory interactions could conceivably result in impaired immune function or aberrant cellular growth.

Additional studies employing kinome array profiling have identified Tec activity alterations in pancreatic ductal adenocarcinoma, where differential kinase activity profiles suggest its involvement in the complex signaling networks that underlie oncogenesis and desmoplastic stromal development (creeden2020kinomearrayprofiling pages 16-18, creeden2020kinomearrayprofiling pages 28-30).

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