1. Phylogeny  
   Tyrosine‐protein kinase ETK (gene: ETK/yccC; UniProt: P38134) is a member of the bacterial tyrosine kinase (BY kinase) family. These kinases are evolutionarily distinct from eukaryotic receptor tyrosine kinases and do not share canonical Hanks‐type motifs found in most eukaryotic PTKs; instead, they harbor nucleotide‐binding motifs such as Walker A and Walker B, which are broadly conserved among P-loop proteins. In proteobacteria such as Escherichia coli K12, ETK represents the archetypal example of a proteobacterial BY kinase, exhibiting features that have been evolutionarily conserved among prokaryotic systems involved in phosphorylation‐dependent regulation of signal transduction, capsule biosynthesis and carbohydrate metabolism (engin2021bacterialproteinkinases pages 329-331, ilan1999proteintyrosinekinases pages 1-2). ETK shares significant sequence similarity with other bacterial protein tyrosine kinases, for example, its close homologues AmsA from Erwinia amylovora and Orf6 from Klebsiella pneumoniae, among others. These kinases have a narrow distribution limited to prokaryotes, and they are generally associated with virulence functions and the regulation of exopolysaccharide production through phosphorylation‐dependent molecular switches (ilan1999proteintyrosinekinases pages 5-6, ilan1999proteintyrosinekinases pages 6-7).
2. Reaction Catalyzed  
   ETK catalyzes the transfer of the γ-phosphate group from adenosine triphosphate (ATP) to specific tyrosine residues located on substrate proteins, including those on its own intracellular C-terminal tail (autophosphorylation). In this reaction, ATP serves as the phosphate donor, and the enzyme converts ATP to adenosine diphosphate (ADP) while phosphorylating the hydroxyl group of the targeted tyrosine residue. This phosphorylation reaction can be summarized by the following chemical equation:  
     ATP + [protein]-Tyr → ADP + [protein]-phosphotyrosine + H⁺  
   This catalytic reaction, which is central to the enzyme’s role in signal transduction and regulation of polysaccharide biosynthesis, is a hallmark feature of bacterial tyrosine kinases (engin2021bacterialproteinkinases pages 331-335, ilan1999proteintyrosinekinases pages 2-4, lee2008structuralandfunctional pages 25-30).
3. Cofactor Requirements  
   The kinase activity of ETK requires ATP as the phosphate donor and is dependent on divalent metal ions, most notably magnesium (Mg²⁺), which plays a crucial role in stabilizing the negative charges of the phosphate groups during catalysis. The enzyme’s catalytic mechanism, mediated by its conserved Walker motifs, is contingent upon the presence of these metal ions to correctly position the ATP and facilitate nucleophilic attack by the tyrosine hydroxyl group (engin2021bacterialproteinkinases pages 329-331, lee2008structuralandfunctional pages 25-30).
4. Substrate Specificity  
   ETK exhibits a substrate specificity that is characterized primarily by its ability to autophosphorylate on a short, tyrosine-rich sequence within its intracellular C-terminal domain. This autophosphorylation event is critical for the enzyme’s activation and subsequent downstream signaling functions. In addition, ETK demonstrates the capacity to phosphorylate external substrates such as synthetic tyrosine-rich peptides (e.g., poly(Glu:Tyr)) and regulatory proteins involved in exopolysaccharide assembly, although the precise consensus substrate motif has not been completely delineated in available reports. The substrate specificity is driven by the kinase domain’s recognition of specific tyrosine residues and is modulated by the conformational state of the enzyme; for instance, phosphorylation of a key regulatory tyrosine (Y574) in the active site modulates substrate access and catalytic efficiency (ilan1999proteintyrosinekinases pages 5-6, ilan1999proteintyrosinekinases pages 6-7, lee2008structuralandfunctional pages 138-144).
5. Structure  
   ETK is a multi-domain protein that is typically anchored to the plasma membrane via two transmembrane segments, a characteristic feature of bacterial BY kinases. The overall domain organization comprises a short extracellular sensory domain, two transmembrane helices, and a sizable intracellular catalytic domain. The intracellular region harbors conserved motifs critical for nucleotide binding and catalysis, including the Walker A, Walker A′, and Walker B motifs. Structural studies, particularly those using X-ray crystallography of the kinase domain, have revealed a semispherical structure with a central β-sheet core that is flanked by α-helices. A key regulatory feature of the kinase domain is the presence of the tyrosine residue Y574, which when unphosphorylated can sterically block the active site, thereby preventing substrate and cofactor binding; phosphorylation of Y574 induces a conformational shift that repositions its side chain—facilitated by critical interaction with residue R614—to permit substrate access (lee2008structuralandfunctional pages 100-109, lee2008structuralandfunctional pages 109-115). In addition, the intracellular domain contains a C-terminal tyrosine-rich cluster that undergoes multiple autophosphorylation events that are essential for regulating the oligomerization state of the enzyme and its function in polysaccharide export. Studies employing analytical ultracentrifugation and chemical cross-linking have demonstrated that ETK’s N-terminal domain contributes to its oligomerization, forming structures ranging from monomers to tetramers and higher molecular weight aggregates (lee2008structuralandfunctional pages 123-131, lee2008structuralandfunctional pages 144-149).
6. Regulation  
   The regulatory mechanisms controlling ETK activity are tightly linked to its phosphorylation state. Autophosphorylation of tyrosine residues – notably within the critical C-terminal cluster and the key regulatory residue Y574 – governs the enzyme’s catalytic activity and its oligomeric conformation. In its inactive state, the unphosphorylated Y574 side chain occupies a position within the active site, impeding substrate binding; however, upon autophosphorylation at Y574, a conformational change occurs that relieves this steric blockade and enables catalytic activity (lee2008structuralandfunctional pages 100-109, lee2008structuralandfunctional pages 138-144). Oligomerization is also influenced by the phosphorylation status: fully dephosphorylated ETK tends to form high molecular weight aggregates due to strong intermolecular interactions mediated by non-phosphorylated tyrosine residues in the C-terminal cluster, whereas an intermediate phosphorylation level facilitates the formation of the tetrameric species that are functionally active in the export of capsular polysaccharides (lee2008structuralandfunctional pages 149-156, lee2008structuralandfunctional pages 156-162). In addition, ETK is subject to dephosphorylation by specific tyrosine phosphatases, such as YopH, which serve to inactivate the kinase by removing the phosphate groups and thereby restoring the autoinhibited conformation (ilan1999proteintyrosinekinases pages 7-8, lee2008structuralandfunctional pages 162-167).
7. Function  
   ETK plays a central role in bacterial physiology by regulating the synthesis and export of extracellular or capsular polysaccharides (EPS/CPS), which are critical determinants of biofilm formation, virulence, and antibiotic resistance in pathogenic strains of Escherichia coli. Its autophosphorylation and subsequent phosphorylation of downstream regulatory proteins facilitate the assembly and export of high-molecular-weight polysaccharides that form the bacterial capsule, an essential structure for evading host immune responses. In addition to its role in capsule biogenesis, ETK has been implicated in the regulation of carbohydrate transport systems, and functional studies have identified substrate proteins such as UDP-glucose dehydrogenase (Ugd) and other associated components of the polysaccharide export machinery that undergo tyrosine phosphorylation mediated by ETK. Expression of ETK appears to be restricted to pathogenic strains, such as enteropathogenic E. coli (EPEC), and alterations in its phosphorylation state correlate with changes in virulence phenotypes, including sensitivity to antibiotics like polymyxin B. Consequently, ETK is regarded as a critical regulatory node in bacterial signaling networks that integrate environmental cues to modulate cell envelope composition and, thereby, bacterial fitness during host infection (engin2021bacterialproteinkinases pages 331-335, ilan1999proteintyrosinekinases pages 4-5, lee2008structuralandfunctional pages 25-30, lee2008structuralandfunctional pages 47-52).
8. Other Comments  
   Despite the extensive biochemical and structural characterization of ETK, specific inhibitors for this bacterial tyrosine kinase have not been thoroughly developed or described in the literature provided. However, given its pivotal role in regulating exopolysaccharide synthesis and bacterial virulence, ETK represents a potential target for the development of antimicrobial agents aimed at disrupting capsule formation and biofilm integrity. In this context, ETK’s restricted expression in pathogenic strains further emphasizes its utility as a therapeutic target. No direct information regarding disease associations beyond its contribution to bacterial pathogenicity is available from the sources cited, although its involvement in virulence mechanisms implies that targeting ETK may attenuate bacterial infections (ilan1999proteintyrosinekinases pages 4-5, engin2021bacterialproteinkinases pages 358-360, lee2008structuralandfunctional pages 167-172).
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