## Phylogeny

Tyrosine-protein kinase Etk (gene name yccC) is a member of the bacterial tyrosine kinase (BY-kinase) family that is broadly distributed in proteobacteria. Etk clusters with single-polypeptide BY-kinases such as Wzc and SopA, which harbour transmembrane sensory segments fused to an intracellular catalytic domain and share the conserved Walker A, Walker A′ and Walker B motifs that define their ATPase fold (Hansen et al., 2013, pp. 1–3; Engin, 2021, pp. 329–331).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate + H⁺ (Hansen et al., 2013, pp. 2–3).

## Cofactor Requirements

Mg²⁺ is required; the ion coordinates the ATP phosphates and stabilises the transition state during phosphoryl transfer (Engin, 2021, pp. 329–331).

## Substrate Specificity

Etk phosphorylates tyrosine residues. Phosphoproteomic surveys in Escherichia coli detected >500 phosphotyrosine sites that are direct or indirect Etk/BY-kinase targets (Hansen et al., 2013, pp. 3–4). Preferred sequence features include:  
• Lysine or other basic residues at +3 to +5,  
• Glycine at −1,  
• Aspartate at +1 relative to the modified tyrosine (Hansen et al., 2013, pp. 3–8).  
Substrates are typically located in flexible, solvent-exposed regions and include virulence factors (e.g., Type III secretion proteins) and metabolic enzymes (Hansen et al., 2013, pp. 5–9).

## Structure

Etk is a single polypeptide comprising N-terminal transmembrane helices and a cytosolic kinase domain built around an eight-stranded parallel β-sheet flanked by α-helices (Lee et al., 2008, pp. 1–2). Key structural elements:  
• Walker A/A′/B motifs form the nucleotide-binding pocket.  
• Tyr574, positioned at the start of an α-helix near the active site, acts as a molecular switch; its phosphorylation triggers a conformational change that removes steric blockage of the substrate channel via interaction with Arg614 (Lee et al., 2008, pp. 6–7; Lee, 2008, pp. 94–100).  
• A C-terminal tyrosine-rich cluster undergoes autophosphorylation and, together with a neighbouring basic “RK-cluster,” modulates oligomerisation and engagement with the polysaccharide export machinery (Lee et al., 2008, pp. 5–6; Lee, 2008, pp. 156–162).

## Regulation

Activity is controlled by reversible phosphorylation:  
• Autophosphorylation of the C-terminal tyrosine cluster and of Tyr574 enhances catalytic competence and favours lower-order oligomeric states (Lee et al., 2008, pp. 6–7; Hansen et al., 2013, pp. 10–11).  
• A cognate phosphotyrosine phosphatase removes these phosphates, resetting Etk activity (Hansen et al., 2013, pp. 12–13).  
These cycles tune Etk-dependent control of capsule formation and virulence factor production (Hansen et al., 2013, pp. 9–10).

## Function

Etk orchestrates extracellular polysaccharide (capsule) biosynthesis and export, thereby contributing to biofilm formation and protection from host immunity. It also phosphorylates T3SS components and metabolic enzymes, linking signal transduction to virulence and central metabolism. Etk-mediated phosphorylation aids bacterial adaptation to stress and can influence antibiotic resistance (Hansen et al., 2013, pp. 2–10; Engin, 2021, pp. 331–335).

## Inhibitors

ATP-competitive small molecules and neutralising antibodies that target BY-kinases, including Etk, are under investigation as anti-virulence agents; however, functional redundancy within the BY-kinase family complicates efficacy (Hansen et al., 2013, pp. 13–14; Engin, 2021, pp. 331–335).

## Other Comments

Dynamic interplay between the phosphorylated C-terminal tyrosine cluster and the adjacent basic RK-region governs Etk oligomerisation and activity, directly impacting capsule export machinery function (Lee, 2008, pp. 156–162; Hansen et al., 2013, pp. 2–3).

## 9. References

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