## Phylogeny

FAM20C is an extracellular serine/threonine protein kinase belonging to the secretory FAM20 family (Fam20A, Fam20B, Fam20C). Orthologues are found from Hydra magnipapillata and Caenorhabditis elegans to Danio rerio and vertebrates, indicating deep conservation of the kinase core (Zhang et al., 2018, pp. 1-3; Cui et al., 2017, pp. 1-2). Phylogenetic analyses place the family in a distinct clade outside the canonical human kinome. Diversification yielded (i) Fam20B, a xylosyl-kinase, (ii) the pseudokinase Fam20A and (iii) the catalytically active Fam20C (Filatova, 2015, pp. 17-20; Zhang et al., 2018, pp. 2-3). Appearance of Fam20C correlates with vertebrate biomineralisation, consistent with its predominant roles in bone and tooth development (Palma-Lara et al., 2023, pp. 1-2).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[secreted protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[secreted protein] (Xu et al., 2021, pp. 1-2; Da et al., 2019, pp. 1-2).

## Cofactor Requirements

Activity depends on divalent cations, with a marked preference for Mn²⁺ over Mg²⁺ in the Golgi milieu (Zhang et al., 2018, EMBO J., pp. 1-2; Xiao et al., 2013, p. 1).

## Substrate Specificity

FAM20C phosphorylates secretory-pathway proteins bearing the Ser-x-Glu/pSer consensus; variants such as Ser-x-Sp are also accepted (Messana et al., 2023, pp. 12-13; Cui et al., 2015, pp. 1-2). This breadth underlies regulation of proteins involved in biomineralisation, extracellular matrix remodelling and other extracellular processes (Palma-Lara et al., 2023, pp. 9-10).

## Structure

The enzyme is synthesised with an N-terminal signal peptide directing it to the Golgi. The mature protein contains a two-lobed protein-kinase-like fold featuring a glycine-rich loop, catalytic loop with a conserved Asp, and an αC helix (Filatova, 2015, pp. 20-24; Xiao et al., 2013, pp. 1-3). Crystal studies of ceFam20 show an N-terminal arm wrapping the C-lobe and an insertion domain capping the N-lobe (Xiao et al., 2013, pp. 4-5). Absence of a classical activation loop contributes to constitutive activity, and unique substitutions within the glycine-rich loop adjust ATP and peptide orientation (Xiao et al., 2013, pp. 5-6). AlphaFold models support the preserved kinase fold and predict Golgi-compatible stabilising disulphides and glycosylation sites (Xu et al., 2021, pp. 1-2; Cui et al., 2017, pp. 2-5).

## Regulation

• Allosteric activation by hetero- or homodimerisation with the pseudokinase Fam20A enhances catalytic output and stabilises mutant forms (Cui et al., 2015, pp. 11-13; Cui et al., 2017, pp. 15-16).  
• Autophosphorylation has been reported and may fine-tune activity (Ishikawa et al., 2012, pp. 1-2).  
• Under ER stress FAM20C phosphorylates P4HB/PDIA1, converting it from an oxidoreductase to a chaperone, and phosphorylates ERO1A to reinforce oxidative folding capacity, thereby maintaining ER redox homeostasis (Liu et al., 2023, pp. 19-20; Zhang et al., 2018, EMBO J., pp. 1-2; Fulcher & Sapkota, 2020, pp. 14-15).

## Function

Principal kinase of the secreted phosphoproteome, influencing:  
• Biomineralisation – phosphorylates casein, AMELX, AMTN, ENAM, SPP1/OPN and related proteins essential for bone and enamel formation (Filatova, 2015, pp. 20-24; Xiao et al., 2013, pp. 5-6).  
• ER proteostasis – modulates ERO1A and P4HB activities to mitigate ER stress (Xu et al., 2021, pp. 1-2; Liu et al., 2023, pp. 19-20).  
• Additional roles in lipid balance, wound repair, cell adhesion / migration and general extracellular matrix dynamics (Palma-Lara et al., 2023, pp. 1-2; Brutsch, 2022, pp. 37-41).  
Loss-of-function mutations cause Raine syndrome, characterised by osteosclerotic dysplasia and hypophosphataemia (Ishikawa et al., 2012, pp. 1-2; Palma-Lara et al., 2023, pp. 10-13).

## Inhibitors

No dedicated inhibitors are yet characterised; FAM20C shows resistance to broad-spectrum kinase inhibitors such as staurosporine, indicating a distinctive inhibitor profile (Zhang et al., 2018, EMBO J., pp. 1-2).

## Other Comments

Alternative names include Dentin Matrix Protein 4 (DMP4), Golgi casein kinase and Golgi-enriched fraction casein kinase. Dysregulation of its wide substrate repertoire links FAM20C to disorders involving extracellular matrix and represents a potential therapeutic target (Du et al., 2023, pp. 4-5).

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