1. Phylogeny  
   Extracellular serine/threonine protein kinase FAM20C (UniProt Q8IXL6) is a member of the Fam20 family of secretory kinases that includes FAM20A, FAM20B, and FAM20C itself. FAM20C is evolutionarily conserved across vertebrates, with validated orthologs present in species ranging from mouse to human and even lower metazoans, which underscores its fundamental roles in extracellular protein phosphorylation. Within the human kinome, FAM20C occupies a unique branch distinct from conventional intracellular kinases, aligning with findings that group it with the kinases dedicated to the secretory pathway (palmalara2021fam20coverviewclassic pages 1-2, cozza2015“genuine”caseinkinase pages 9-12). Evolutionary analyses have placed the Fam20 proteins within a core set of kinases present since the emergence of eukaryotes (as supported by the broader perspective outlined in Manning et al. 2002 and Manning et al. 2002, not shown here but required for context), with FAM20C representing one outcome of gene duplication events in the secretory branch. This conservation and grouping support a phylogenetic assignment of FAM20C into a distinct secretory kinase family that is separate from the standard AGC or tyrosine kinase families.
2. Reaction Catalyzed  
   FAM20C catalyzes an ATP-dependent phosphorylation reaction in which a phosphate group is transferred from ATP to the hydroxyl group of target serine and, in some cases, threonine residues on secretory proteins. In its canonical reaction, the enzyme converts ATP and a protein substrate containing a serine (–OH) group to ADP, a phosphorylated protein containing a –PO₄ group on the serine residue, and a proton (H⁺). This reaction is analogous to that described for other protein kinases but is specialized for secreted substrates within the extracellular pathway (tagliabracci2013phosphorylationofsubstrates pages 1-2, chen2021proteolyticprocessingof pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of FAM20C depends on divalent metal ion cofactors in addition to ATP. FAM20C preferentially utilizes manganese (Mn²⁺) as its cofactor, although magnesium (Mg²⁺) may also support low-level activity under certain conditions. This requirement for Mn²⁺, rather than the more common Mg²⁺ used by most intracellular kinases, is a distinguishing feature of FAM20C’s enzymatic mechanism (cozza2015anewrole pages 1-2, xiao2013crystalstructureof pages 5-6).
4. Substrate Specificity  
   FAM20C exhibits substrate specificity primarily for secreted proteins, modifying serine residues within a consensus motif that is generally described as Ser–x–Glu (or phosphoSer) (S-x-E/pS). Although this motif is the principal target, FAM20C also displays broader substrate recognition capabilities that accommodate additional sequences, such as S-x-Q-x-x-D-E in some substrates. Such specificity has been mapped through extensive phosphoproteomic studies and in vitro kinase assays, with recent atlas studies of the human serine/threonine kinome further supporting that serine/threonine kinases like FAM20C preferentially target motifs that include acidic residues in the +1 (and sometimes further) positions (cui2015asecretorykinase pages 1-2, Johnson2023Nature pages 759-766). The atlas of substrate specificities for serine/threonine kinases provides a context in which FAM20C’s selective phosphorylation contributes to the generation of the majority of the extracellular phosphoproteome. For completeness in comparing substrate preferences, note that studies of tyrosine kinase specificity have shown distinct recognition patterns (Yaron-Barir2024Nature pages 1174-1181); however, FAM20C is categorized as a serine/threonine kinase.
5. Structure  
   FAM20C features an atypical protein kinase domain that is embedded in a unique structural context. It is a type II transmembrane protein possessing an N-terminal hydrophobic transmembrane domain that functions as a Golgi retention signal, ensuring its localization in the Golgi apparatus (chen2021proteolyticprocessingof pages 1-2, ohyama2016fam20abindsto pages 1-2). The soluble portion, oriented towards the lumen of the secretory pathway, is composed of a central catalytic domain with a protein kinase-like fold. Structural studies, including the crystal structure of the Caenorhabditis elegans Fam20 ortholog, have revealed that this domain is organized into two lobes—an N-lobe and a C-lobe—with an insertion domain that forms a cap-like or shell-like structure over the active site (xiao2013crystalstructureof pages 1-3, xiao2013crystalstructureof pages 4-5). Key catalytic features include a conserved lysine critical for ATP binding, a variant DFG motif in which unique residues contribute to the catalytic and regulatory spine, and a lack of a typical activation loop, suggesting that FAM20C is constitutively competent for catalysis (cui2015asecretorykinase pages 4-6, tagliabracci2013phosphorylationofsubstrates pages 1-2). In addition, numerous disulfide bonds and N-linked glycosylation sites have been identified that support proper folding and stability of the secreted kinase (palmalara2021fam20coverviewclassic pages 2-4).
6. Regulation  
   Regulation of FAM20C occurs at multiple levels. One key regulatory mechanism is the proteolytic processing by Site-1 Protease (S1P), a Golgi-resident subtilisin-like proprotein convertase that cleaves FAM20C’s propeptide, resulting in enhanced secretion and increased kinase activity. The uncleaved full-length protein displays lower basal activity and partially resides in the endoplasmic reticulum, thereby phosphorylating select substrates under stress conditions, whereas the mature, cleaved form is fully active in the secretory pathway (chen2021proteolyticprocessingof pages 8-10). Furthermore, FAM20C activity is subject to allosteric modulation via heterodimerization with its catalytically inactive paralog FAM20A. This interaction enhances FAM20C activity and directs its localization and secretion from the Golgi into the extracellular space (cui2015asecretorykinase pages 11-13, ohyama2016fam20abindsto pages 3-5). Additionally, sphingolipid signaling has been shown to modulate FAM20C’s catalytic efficiency, with sphingosine and related compounds acting as activators that increase the kinase’s activity in vitro (cozza2017fam20cisunder pages 12-15). These regulatory mechanisms ensure that FAM20C-mediated phosphorylation is tightly controlled to meet the demands of biomineralization, endoplasmic reticulum proteostasis, and extracellular matrix modification.
7. Function  
   FAM20C plays a critical role as the primary kinase for extracellular proteins, thereby generating the majority of the secreted phosphoproteome. It phosphorylates key proteins involved in biomineralization, including milk proteins such as casein and secretory calcium-binding proteins such as amelogenin (AMELX), enamelin (ENAM), ameloblastin (AMBN), and osteopontin (SPP1/OPN). These phosphorylation events are essential for proper mineral deposition during bone and tooth formation and are critical for the differentiation of osteoblasts (chen2021proteolyticprocessingof pages 1-2, ishikawa2012therainesyndrome pages 1-2). Beyond its role in biomineralization, FAM20C phosphorylates endoplasmic reticulum proteins such as ERO1A; phosphorylation of ERO1A enhances its activity, supporting oxidative protein folding and redox homeostasis, whereas phosphorylation of P4HB/PDIA1 alters its functional state from an oxidoreductase to a chaperone during ER stress (cui2015asecretorykinase pages 4-6, palmalara2021fam20coverviewclassic pages 35-36). These modifications are critical under conditions of ER stress, ensuring proteostasis and cell survival. In addition, FAM20C activity influences lipid homeostasis, wound healing, and cell migration and adhesion, extending its functional impact beyond mineralized tissues (cui2015asecretorykinase pages 2-4, filatova2015theroleof pages 20-24). Expression patterns indicate that FAM20C is highly expressed in mineralizing tissues such as bones and teeth, as well as in the lactating mammary gland, which further supports its role in extracellular protein regulation and phosphoproteome generation (ishikawa2012therainesyndrome pages 9-10, zuo2021fam20cregulatesbone pages 1-1).
8. Other Comments  
   FAM20C has been linked to several human diseases through loss-of-function mutations. Notably, pathogenic variants in FAM20C underlie Raine syndrome, a rare autosomal recessive osteosclerotic bone dysplasia characterized by severe mineralization defects, dental anomalies, and hypophosphatemia (ishikawa2012therainesyndrome pages 1-2, palmalara2021fam20coverviewclassic pages 35-36). In addition, deficiencies in FAM20C activity have been associated with non-lethal mineralization defects, including forms of hypophosphatemic rickets and amelogenesis imperfecta, which arise from defective phosphorylation of enamel matrix proteins (ravindran2015dentinmatrixproteins pages 14-19, vogel2012amelogenesisimperfectaand pages 1-2). Although specific small-molecule inhibitors for FAM20C have not been successfully developed, research into its regulation by sphingolipids (cozza2017fam20cisunder pages 12-15) and proteolytic processing by S1P (chen2021proteolyticprocessingof pages 8-10) provides potential therapeutic avenues. Its unique structure and regulation make it a promising target for interventions aimed at controlling extracellular phosphorylation in biomineralization and ER proteostasis.
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   Additionally, for substrate specificity data of serine/threonine kinases, refer to Johnson2023Nature pages 759-766, and for comparative studies with tyrosine kinases, see Yaron-Barir2024Nature pages 1174-1181; for phylogenetic context, consult Manning et al. (2002) as outlined in the original template.

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