Structure and evolution of the Fam20 kinases

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The family with sequence similarity 20 (Fam20) kinases function in the secretory pathway to phosphorylate proteins and proteoglycans. The human genome encodes three Fam20 paralogues: Fam20A, Fam20B, and Fam20C. Fam20C is the physiological casein kinase and phosphorylates hundreds of proteins involved in biomineralization, phosphate metabolism, cell adhesion and migration, and cardiac function. Diminished activity of Fam20C causes Raine syndrome, an incurable malady associated with severe calcification disorders. Fam20A functions as a pseudokinase to enhance Fam20C activity and mutations in *FAM20A* lead to dental and renal abnormalities. However, the molecular mechanisms by which Fam20A regulates Fam20C activity are not well understood. In contrast, Fam20B regulates the biosynthesis of proteoglycans by phosphorylating a xylose residue within the tetrasaccharide linker region of heparin and chondroitin sulfate proteoglycans. Despite having high sequence similarity, the mechanisms by which Fam20B and Fam20C achieve select substrate specificity are unknown. Here we systematically investigate the structure and function of the Fam20 kinases. We show that Fam20C activation results from the formation of an evolutionarily conserved homodimer or heterodimer with Fam20A. Compared to Fam20C itself, Fam20A has an optimized Fam20C-binding surface and is therefore a specialized Fam20C-allosteric activator. We further show that the monomeric Fam20B xylosylkinase activity preceded the appearance of the dimeric Fam20C protein kinase in animals. The crystal structure of a Fam20B orthologue in complex with the Galβ1-4Xylβ1 disaccharide reveals the substrate recognition mechanism of Fam20B. Further structural analyses suggest that the dimerization trait of Fam20C has emerged concomitantly with a change in substrate specificity. These results provide comprehensive insights into the function of this unique and biomedically important family of kinases and shed light on their evolutionary history.