Cryo-EM structures and HDX-MS data of PAC1R splice isoforms in different states of activation

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The pituitary adenylate cyclase-activating polypeptide 1 receptor (PAC1R) is a class B1 G protein-coupled receptor (GPCR) implicated in the pathophysiology of migraine. PAC1R is activated through peptide hormones, e.g. PACAP38 (P38), and can instigate signaling events through G proteins from the cell membrane; it does so primarily through the Gs signal transducer subtype, though also through the Gq subtype. Furthermore, there are endogenous splice variants of PAC1R, e.g. PAC1Rn and PAC1Rhop, that display different G protein signaling profiles. As Gs and Gq signaling pathways are involved in PAC1R-mediated disease structural and dynamic information about PAC1R activation and interactions with these transducers is important for drug discovery. Here, cryo-electron microscopy (cryo-EM) structures reveal PAC1R features important for Gq selectivity, and hydrogen deuterium exchange-mass spectrometry (HDX-MS) studies show the dynamics associated with the conformational changes that occur during PAC1R activation.