Relaxin Receptor (RXFP1) in Focus: Structural Insights into Activation

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Crucial in modulating cardiovascular function during pregnancy, the peptide hormone relaxin, an endogenous agonist of the G protein-coupled receptor RXFP1, holds therapeutic potential for cardiovascular and fibrotic diseases. Relaxin and its analogues are in clinical trials for heart failure treatment, Relaxin and its analogues are in clinical trials for heart failure treatment, but a deeper understanding of their mechanism of action is essential for successful clinical translation. Despite its importance, the unique activation mechanism of RXFP1 remains poorly understood, largely due to the limited structural information available for the receptor.

Employing state-of-the-art technology in protein engineering and structural biology, the work presented herein is dedicated to garnering comprehensive insights into the activation mechanism of the RXFP1 receptor by determining its structure using cryo-electron microscopy (cryo-EM). With an evolved signalling-competent and expression-enhanced receptor, we determined the first ligand-free RXFP1 structure at a resolution of 3.5 Å and achieved relaxin-RXFP1-G protein complexes at low resolution. Here, we uncovered previously unreported structural features of RXFP1 in its inactive state, highlighting interactions involved in the regulatory mechanisms governing its activation. These findings offer additional insights into its signal transduction and help explain the challenges faced by past drug discovery efforts in identifying novel drug leads for RXFP1.