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Structural insights into the unique modes of relaxin-binding and tethered-agonist mediated activation of RXFP1 and RXFP2

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Our poor understanding of the mechanism by which the peptide-hormone H2 relaxin activates its G protein-coupled receptor, RXFP1 and the related receptor RXFP2, has hindered progress in its therapeutic development. Both receptors possess unique ectodomains that comprise of an N-terminal LDLa module joined by a linker to a Leucine Rich Repeat (LRR) domain. Truncation of the N-terminal LDLa module abolishes signalling for both receptors suggesting that the LDLa module is essential for activation and is postulated as a tethered agonist, induced to undergo a conformational change upon H2 relaxin binding.

Here, we use Small Angle X-ray Scattering (SAXS), NMR spectroscopy, cell-based receptor signalling assays to show that it is not the LDLa module, but rather a conserved motif (GDxxGWxxxF), immediately C-terminal to the LDLa, that is the essential tethered agonist. Importantly, this motif associates with the LDLa module of both RXFP1 and RXFP2, in different manners suggesting distinct mechanisms of activation. For RXFP1, the motif is flexible, weakly associates with the LDLa module, and requires H2 relaxin binding to stabilize an active-state conformation. Conversely, the motif in RXFP2 does not possess the same flexibility as it does in RXFP1, and appears to be more structured and closely associated with the LDLa module, forming an essential binding interface for H2 relaxin. H2 relaxin binding to RXFP2 needs both the LDLa module and the motif, distinct to RXFP1 and the tethered agonist activity of the motif is not driven by an induced conformational change in RXFP2, also distinct to RXFP1. These results highlight distinct differences in relaxin mediated activation mechanism of RXFP1 and RXFP2 which will aid drug development targeting these receptors.

Level of Expertise

Early Career <5 Years

Presenter Gender

Man

Pronouns

He/Him

Which facility did you use for your research

Australian Synchrotron

Students Only - Are you interested in AINSE student funding

No

Do you wish to take part in the Student Poster Slam

No

Condition of submission

Yes

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