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CELL SIGNALLING

Crystallizing active arrestins

> two groups report the first X-ray crystal structures of active arrestins

PHOTODISC

Arrestins bind phosphorylated G protein-coupled receptors (GPCRs) to terminate their signalling by G proteins and trigger G protein-independent signalling. Although structures of inactive arrestins are available, it has proved challenging to crystallize these proteins in their active form. Now, two groups report the first X-ray crystal structures of active arrestins.

Arrestins interact with phosphates on GPCRs. This displaces the carboxy-terminal tail of arrestin, priming it for a conformational change that favours high affinity arrestin–GPCR binding. To gain further insight into this mechanism of activation, Kim *et al.* solved the crystal structure of the bovine arrestin 1 splice variant p44 at 3.0 Å. This active variant of visual arrestin 1, which is naturally occurring, was prepared by replacing its last 35 amino acids with a single Ala residue. Shukla *et al.* crystallized non-visual β-arrestin 1 (also known as arrestin 2) in complex with a phosphopeptide derived from a GPCR (to activate it) and the antigen binding fragment Fab30 (to stabilize it) at 2.6 Å.

So, what differences between the inactive and active forms of arrestins did these studies reveal? Of particular note, Kim *et al.* observed a ~21° rotation of the amino- and C-terminal domains of p44, relative to each other, as compared with inactive arrestin 1, and Shukla *et al.* observed a ~20° rotation of the N- and C-terminal domains of β-arrestin 1 following activation. Both groups also observed conformational changes that occur upon arrestin activation, including in the 'finger loop', 'middle loop' (also known as 'loop 139') and the 'lariat loop', all of which have previously been implicated in the activation of arrestins and their interaction with GPCRs. Together, these studies suggest that arrestins are activated by a common mechanism and pave the way for further structural studies on this topic.

Finally, in a commentary on these papers, Borshchevskiy and Büldt superimposed the structure of active p44 with that of active β-arrestin 1, and found that these structures are very similar. Thus, they suggest that it is highly probable that fully active arrestins were crystallized in these studies.

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ORIGINAL RESEARCH PAPERS Kim, Y. J. *et al.* Crystal structure of pre-activated arrestin p44. *Nature* **497**, 142–146 (2013) | Shukla, A. K. *et al.* Structure of active β-arrestin-1 bound to a G-protein-coupled receptor phosphopeptide. *Nature* **497**, 137–141 (2013)
FURTHER READING Borshchevskiy, V. & Büldt, G. Structural biology: active arrestin proteins crystallized. *Nature* **497**, 45–46 (2013)