

The Structural Basis of Arrestin Functions

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Editor

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Preface

Arrestin, like all key players in the G protein-coupled receptor (GPCR) signaling, was first discovered in the visual system, where it was shown to specifically bind active phosphorylated rhodopsin, “arresting” its coupling to a cognate G protein. Subsequently, three homologues of visual arrestin were cloned and functionally characterized. All members of the arrestin family bind active phosphorylated forms of their cognate receptors and stop G protein-mediated signaling of most GPCRs. Structurally ~45 kDa arrestin proteins are elongated two-domain molecules with the overall fold shared with (likely inherited from) arrestin domain-containing proteins (ARRDCs) involved in trafficking of membrane vesicles and proteins. Vertebrates (except bony fish that underwent an additional whole-genome duplication event) express only four arrestin subtypes, whereas other animals have even fewer arrestins. Recently, the focus has shifted to the non-visual arrestins, two subtypes of which are expressed in every vertebrate species. These two arrestins bind hundreds of different GPCRs and interact with numerous non-receptor partners, including various trafficking and signaling proteins. Interactions with some partners do not depend on receptor binding, whereas others are facilitated or suppressed by GPCR interactions. Thus, arrestins are at a crossroads of signaling pathways, participating in the integration of external and internal stimuli into coherent behavior of the cell. High biological importance stimulated structure-function studies of arrestins. This book summarizes the structural insights into arrestin functions gained in the last few years, focusing on the mechanisms of arrestin-mediated regulation of GPCRs and other signaling proteins in healthy cells, as well as in disease. The chapters, written by the people who made those discoveries, describe the molecular mechanisms of arrestin binding to GPCRs and other partners, emphasizing the therapeutic potential of modifying individual arrestin functions. By binding GPCRs and other partners, arrestins organize

multi-protein signaling complexes and localize them to specific compartments in the cell. Importantly, arrestins act via protein–protein interactions, which underlie most vital cellular functions. On the basis of structure-function information, modified arrestins or their mono-functional elements can serve as prototypical next-generation tools for research and therapy that channel cell signaling to desired outcomes.

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