Chapter 1
Arrestins: Discovery of the Family and Functional Role of Conformational Flexibility

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Abstract Arrestins were first discovered as negative regulators of G protein-mediated signaling by GPCRs: they bind GRK-phosphorylated active receptors and preclude their further coupling to cognate G proteins. Vertebrates have only four arrestin subtypes, two of which are specifically expressed in photoreceptors in the retina, whereas the two non-visual arrestins are ubiquitously expressed and apparently regulate hundreds of different GPCRs. Later studies showed that, in addition to receptors, non-visual arrestins interact with dozens of other signaling proteins. Current view is that arrestins are versatile regulators organizing multi-protein signaling complexes and localizing them to particular subcellular compartments. Arrestins can exist in several distinct conformations, the best-studied being basal and receptor-bound (often termed "active"), which differentially engage various partners. Identification of the arrestin elements engaged by each partner and construction of signaling-biased arrestins where individual functions are selectively disrupted or enhanced, helps us to elucidate their biological roles in the cell.

Keywords Arrestin · GPCR · Desensitization · Signaling proteins · Scaffolding · Protein conformation

Brief History of Arrestins

All key players in G protein-coupled receptor (GPCR) signalling were first discovered in photoreceptors, and arrestin is no exception. Unlike others, this protein was discovered before its biological function was established: it was first described

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as soluble antigen (S-antigen for short) targeted by auto-antibodies in uveitis (Wacker et al. 1977; Wacker and Lipton 1965). Its gene is still called *Sag* in the HUGO database. Meanwhile, pioneering studies by Kuhn identified a 48 kDa protein (that was the name he gave it) that specifically binds light-activated rhodopsin (Kuhn 1978). He then showed that the binding of 48 kDa protein increases upon rhodopsin phosphorylation (Kuhn et al. 1984) and that it blocks light-induced activation of photoreceptor phosphodiesterase by rhodopsin (Wilden et al. 1986). Next, it was established that S-antigen and 48 kDa protein were the same protein (Pfister et al. 1984, 1985). As S-antigen/48 kDa protein stopped ("arrested") rhodopsin signaling, it received a new name, arrestin (Zuckerman and Cheasty 1986). Arrestin was reported to bind ATP (Zuckerman and Cheasty 1988) and Ca^{2+} (Huppertz et al. 1990), but subsequent experiments debunked these claims (Palczewski and Hargrave 1991). Within a few years, arrestin was cloned (Yamaki et al. 1987; Shinohara et al. 1987). Its primary sequence suggested possible structural homology with the α-subunit of transducin (Yamaki et al. 1987; Tsuda et al. 1988), but the crystal structures of these proteins disproved this hypothesis (Noel et al. 1993; Sondek et al. 1994; Hirsch et al. 1999; Granzin et al. 1998).

Seminal discovery that β2-adrenergic receptor (β2AR) (Dixon et al. 1986) structurally resembles rhodopsin (Ovchinnikov 1982) revealed the existence of a family of rhodopsin-like GPCRs (now called class A). Ever since the idea that key signaling and desensitization mechanisms are shared by all GPCRs is widely accepted in the field. The kinase that preferentially phosphorylates agonist-activated β2AR, similar to activation-dependent phosphorylation of rhodopsin by rhodopsin kinase (Shichi and Somers 1978), was cloned in 1989 (Benovic et al. 1989). By analogy with the rhodopsin kinase [which was cloned later (Lorenz et al. 1991); modern systematic name GRK1], this new kinase was named βARK (β2AR kinase) (Benovic et al. 1989) (modern systematic name GRK2). βARK was purified and found not to reduce β2AR-mediated activation of cognate G protein much, which suggested that there must be an equivalent of arrestin that binds phosphorylated β2AR (Benovic et al. 1987). Then the first non-visual arrestin was cloned by homology (Lohse et al. 1990). It showed clear preference for β2AR over rhodopsin, and therefore was termed β-arrestin, while the original arrestin was renamed visual or rod arrestin (Lohse et al. 1990, 1992). All three names turned out to be not quite correct. The cloning of cone-specific arrestin [termed cone (Craft et al. 1994) or X-arrestin (Murakami et al. 1993)] made the term "visual" equivocal. Subsequent finding that the expression of this specific subtype in cone photoreceptors was relatively low (Chan et al. 2007), whereas cones contain ~50-fold higher level of "rod" subtype (Nikonov et al. 2008) showed that the terms "cone" and "rod" arrestin are inaccurate. After cloning of another non-visual subtype, which was called β-arrestin2 (Attramadal et al. 1992) [independently discovered under the name hTHY-ARRX (Rapoport et al. 1992)], the original non-visual arrestin was renamed β-arrestin1. Finally, the demonstration that β-arrestin1 binds not only β2AR, but numerous GPCRs (Barak et al. 1997; Gurevich et al. 1993, 1995), showed that the term "β-arrestin" is also inaccurate. Arrestin nomenclature remains confusing to this day. Here we use systematic names of arrestin proteins, numbered

in the order of cloning: arrestin-1 (historic names S-antigen, 48 kDa protein, visual or rod arrestin), arrestin-2 (β-arrestin or β-arrestin1), arrestin-3 (β-arrestin2 or hTHY-ARRX), and arrestin-4 (cone or X-arrestin).

The first function of arrestins discovered was selective binding to active phosphorylated GPCRs, which blocked receptor interactions with G proteins by simple competition (Wilden 1995; Krupnick et al. 1997a). This aspect was recently confirmed by crystallography: Gs in the complex with β2AR (Rasmussen et al. 2007) and arrestin-1 in complex with rhodopsin (Kang et al. 2015) engage the same cavity that opens on the cytoplasmic side between the helices upon GPCR activation (Farrens et al. 1996). The binding of non-visual arrestins to non-receptor partners was only discovered in 1996, when clathrin, the key component of the internalization machinery of coated pits, was shown to bind both non-visual arrestins directly (Goodman et al. 1996). Many additional non-GPCR partners of arrestin proteins were described since: clathrin adaptor AP2 (Laporte et al. 1999), protein kinases c-Src (Luttrell et al. 1999; DeFea et al. 2000a), JNK3 (McDonald et al. 2000), and ERK1/2 (DeFea et al. 2000b; Luttrell et al. 2001) and their upstream activators were shown to bind non-visual arrestins. The number of arrestin binding partners now exceeds 100 (Xiao et al. 2007), and new ones keep being discovered, including ubiquitin ligases AIP4 (Bhandari et al. 2007) and parkin (Ahmed et al. 2011), protein deubiquitinase USP33 (Shenoy et al. 2009), etc.

The Functional Cycle of Arrestins

Arrestins bind many non-receptor signaling proteins, but the concept of arrestin functional cycle is still dominated by receptor binding: the first recognized functional (and likely structural) states of arrestins were “free” and GPCR-bound (Gurevich and Gurevich 2003, 2004, 2006a). A very convincing early study demonstrated that receptor binding involves a global conformational change in arrestin-1 (Schleicher et al. 1989), which was subsequently shown to include the release of the arrestin C-terminus (Palczewski et al. 1991a, b). Thus, the finding that both clathrin and AP2 binding sites are localized in the C-termini of non-visual arrestins (Goodman et al. 1996; Laporte et al. 1999; Kim and Benovic 2002) made perfect sense: only receptor-bound arrestin needs to help recruit its partner to the coated pit (Gurevich and Gurevich 2003). Indeed, the expression of separated C-terminus of arrestin-2 inhibited GPCR internalization, apparently via successful competition with the arrestin-receptor complexes for clathrin and AP2 (Krupnick et al. 1997b). The first studies of arrestin-mediated activation of protein kinases c-Src, JNK3, and ERK1/2 showed that the signaling in these pathways was triggered by GPCR activation, i.e., was mediated by receptor-bound arrestins (Luttrell et al. 1999, 2001; McDonald et al. 2000; DeFea et al. 2000a, b). These findings established a new paradigm of the G protein-independent arrestin-mediated GPCR signalling (DeWire et al. 2007), while also implying that free arrestin molecules do not do anything of importance. Based on this assumption, the basal conformation of

arrestins was termed "inactive". The findings that at least two binding partners, ubiquitin ligases Mdm2 (Song et al. 2006) and parkin (Ahmed et al. 2011), preferentially bind arrestins in their basal conformation, and that "pre-activated" arrestin-3 mutant with enhanced receptor-binding ability fails to facilitate the activation of JNK3 (Breitman et al. 2012), suggest that this notion is unlikely to be correct. In addition, most reviews of the subject also implied that only non-visual arrestins do anything interesting, whereas visual arrestin-1 and -4 only bind active phosphorylated photopigments, terminating their signaling via cognate G proteins. However, recent findings that arrestin-1 and arrestin-4 bind Mdm2 and JNK3 (Song et al. 2006, 2007), arrestin-1 binds NSF and regulates its activity in rods (Huang et al. 2010), and that arrestin-1 binds AP2 in photoreceptors with high enough affinity to deplete it and cause cell death (Moaven et al. 2013) suggest otherwise. Finally, arrestins bind microtubules (Hanson et al. 2006a, 2007), and this interaction also induces a conformational change, distinct from that induced by receptor binding (Hanson et al. 2006a), which suggests that arrestins can assume yet another conformation, microtubule-bound. Since phenomenology of arrestin-mediated signalling has been extensively reviewed (DeWire et al. 2007; Gurevich and Gurevich 2006b, 2014), here we focus on conformational selectivity of arrestin-binding proteins. Existing evidence suggests that arrestin binding partners have different preferences: some interact with receptor-bound arrestins with the highest affinity, some with free (basal) forms, some with microtubule-associated, whereas there are partners that do not show a clear preference, apparently engaging arrestin elements that are exposed in all these states and do not change much.

The Structural Evidence for Distinct Arrestin Conformations

The first structures of the four vertebrate subtypes, arrestin-1 (Hirsch et al. 1999; Granzin et al. 1998), arrestin-2 (Han et al. 2001; Milano et al. 2002), arrestin-3 (Zhan et al. 2011a), and arrestin-4 (Sutton et al. 2005), represented the basal state. They turned out to be very similar overall, with a few subtle differences (Fig. 1.1). All arrestins are elongated two-domain molecules with relatively few contacts between the domains, perfectly suited for a large conformational change suggested by earlier biophysical (Schleicher et al. 1989) and mutagenesis (Gurevich and Benovic 1993) studies. Three main inter-domain interactions were identified (Hirsch et al. 1999): (1) the "polar core", an arrangement of five charged residues from both N- and C-domains and the C-tail, which are largely solvent-excluded; (2) three-element interaction of the C-tail with β-strand I and α-helix I, which anchors the C-tail to the N-domain (corresponding to predicted on the basis of mutagenesis data (Gurevich and Benovic 1993; Gurevich et al. 1994) interaction of the N- and C-termini of arrestin); and a number of hydrophobic interactions between the residues in both domains at their interface. Interestingly, the polar core

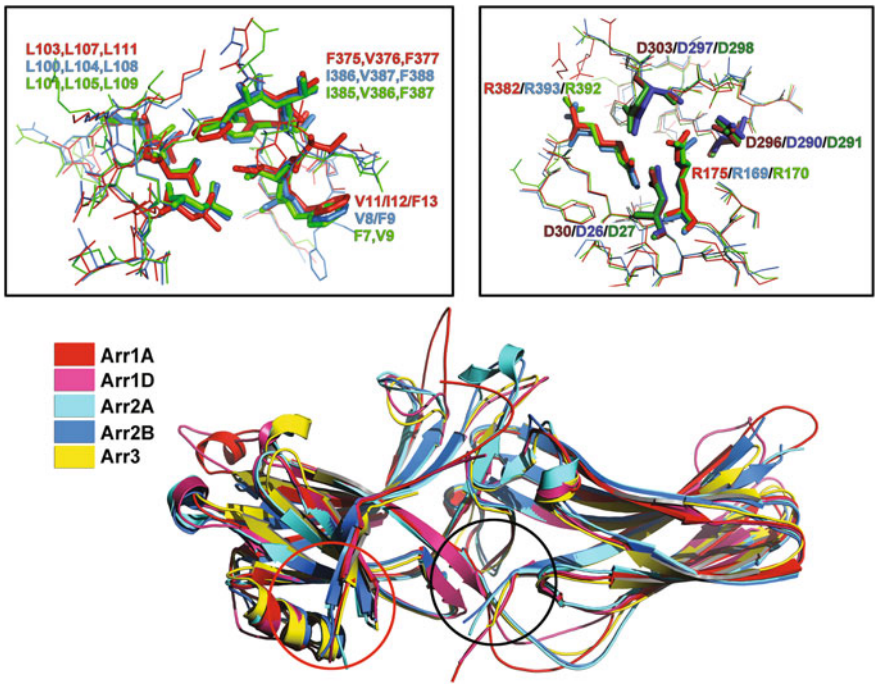

Fig. 1.1 Basal conformation of different arrestin subtypes. Superimposition of the crystal structures of the two monomers in arrestin-1 tetramer [*Arr1A red*, and *Arr1D pink*; PDB ID 1CF1 (Hirsch et al. 1999)], two monomers of arrestin-2 dimer [*Arr2A light blue*, and *Arr2B dark blue*; PDB ID 1G4M (Han et al. 2001)], and arrestin-3 [*Arr3 yellow*; PDB ID 3P2D (Zhan et al. 2011a)] shows remarkably similar cores of both domains and variable structure of the loops. Importantly, the variability of each loop in different monomers of the same arrestin (compare *Arr1A* and *Arr1D*, as well as *Arr2A* and *Arr2B*) is essentially as great as between arrestin subtypes, suggesting that it reflects the flexibility of these loops, rather than their subtype-specific conformations. *Black* and *red circles* show the location of the two key intra-molecular interactions that hold arrestins in their basal state, the polar core and the three-element interaction between β-strand I, α-helix I, and the β-strand XX in the C-tail, respectively. The panels above show detailed structure of these elements. *Right* the polar core, main phosphate sensor; *left* the three-element interaction. In both panels residue numbers are indicated, as follows: arrestin-1 *red*, arrestin-2 *blue*, arrestin-3 *green*

of arrestin-1 included Arg175, earlier predicted to be the key part of the phosphate sensor ensuring preferential binding to phosphorylated receptors (Gurevich and Benovic 1995, 1997). Indeed, the disruption by receptor-attached phosphates of the salt bridge between Arg175 and Asp296 in the polar core was shown to be the mechanism of arrestin "activation" by the receptor-attached phosphates (Hirsch et al. 1999; Vishnivetskiy et al. 1999). Importantly, the disruption of this salt bridge by charge reversal mutations of either residue yields "pre-activated" arrestins that do not require phosphates, binding both phosphorylated and unphosphorylated active GPCRs with high affinity (Gurevich and Benovic 1995, 1997). This phosphorylation-independent interaction was shown to be strong enough to block G

protein activation in vitro (Gray-Keller et al. 1997), in cells (Celver et al. 2001, 2002; Kovoor et al. 1999), and even in living animals (Song et al. 2009a).

Parts of the C-terminus that are not attached to the N-domain via three-element interaction (Fig. 1.1) were not visible in any of these structures, strongly suggesting that these elements are "disordered", i.e., flexible. The conclusion that receptor binding induces a global conformational change in arrestin was first made based on high Arrhenius activation energy of arrestin-1 binding to rhodopsin (Schleicher et al. 1989) before any structural information became available. The evidence that this conformational change involves the release of the arrestin C-terminus was also reported long before structures (Palczewski et al. 1991a). Interestingly, both phosphorhodopsin and polyanion heparin were found to induce this release (Palczewski et al. 1991a), suggesting that any molecule with multiple negative charges can do it. The receptor binding-induced C-terminus release was later confirmed by EPR, as evidenced by an increase in distance between spin label in the C-tail and both β-strand I (Hanson et al. 2006b) and α-helix (Vishnivetskiy et al. 2010) involved in three-element interaction with it (Hirsch et al. 1999), and by NMR, demonstrating an increased mobility of the distal C-tail upon receptor binding (Zhuang et al. 2013). This agrees with the prediction of a previous mutagenesis study that not only the polar core, but also the three-element interaction must be disrupted by the receptor to ensure high-affinity arrestin binding (Vishnivetskiy et al. 2000). An extensive study using pulse EPR method DEER to measure intra-molecular distances in free and rhodopsin-bound arrestin-1 (Kim et al. 2012) revealed several additional receptor binding-induced conformational changes: the outward movement of the "finger loop" in the central crest of the receptor-binding surface, large movement of the adjacent "139-loop" to the side and towards the N-domain, as well as the movements of distal tips of both domains. Small deletions in the 139-loop facilitated both the release of the C-tail (Kim et al. 2012) and arrestin-1 binding to rhodopsin (Vishnivetskiy et al. 2013). Importantly, very similar (although not identical) changes were detected in receptor-bound arrestin-2 and -3 by DEER-based measurements of intra-molecular distances (Zhuo et al. 2014), supporting the idea that the molecular mechanism of receptor binding-induced activation is shared by all members of the arrestin family (Gurevich and Gurevich 2004).

Several crystal structures of arrestins in "active" receptor-bound-like conformation were solved recently (Fig. 1.2): "pre-activated" form of arrestin-1, short splice variant p44 (Kim et al. 2013), C-terminally truncated arrestin-2 in complex with multi-phosphorylated peptide corresponding to the C-terminus of vasopressin V2 receptor (Shukla et al. 2013), and more recently pre-activated arrestin-1 mutant in complex with constitutively active unphosphorylated rhodopsin (Kang et al. 2015). Several features that are evident in all three structures are likely the hallmarks of arrestin "activation" by a GPCR. The most prominent one is the rotation of the two domains relative to each other by $\sim 17°–20°$, which was predicted to become possible upon the disruption of the polar core and three-element interaction based on "slippery" nature of purely hydrophobic interactions between the domains (Gurevich and Gurevich 2006a). Domain rotation of this magnitude in

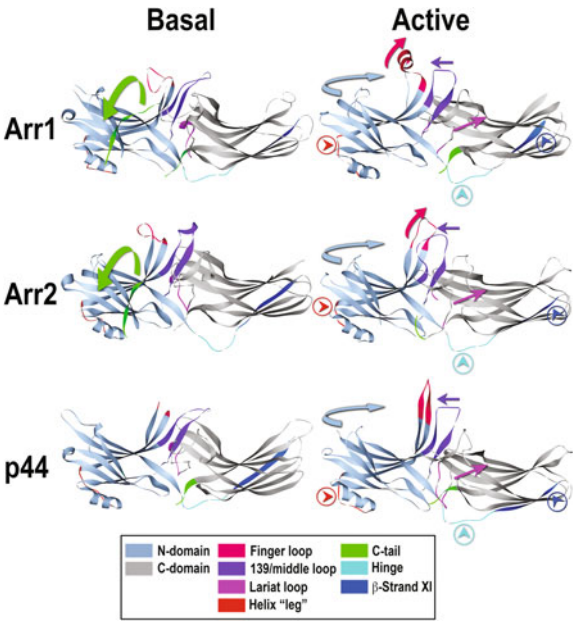

Fig. 1.2 Comparison of the basal and "active" conformations of arrestin proteins. Crystal structures of arrestin-1 (Arr1) [PDB ID 1CF1 (*left*) (Hirsch et al. 1999) and 4ZWJ (*right*) (Kang et al. 2015)], arrestin-2 (Arr2) [PDB ID 1G4M (*left*) (Han et al. 2001) and 4JQI (*right*) (Shukla et al. 2013)], and short splice variant of arrestin-1, p44 [PDB ID 3UGU (*left*) (Granzin et al. 2012) and 4J2Q (*right*) (Kim et al. 2013)] in their basal (*left*) and presumed active (*right*) conformations are shown. The elements undergoing conformational changes upon activation are shown, as follows: the C-tail *green* (it is pushed out of its basal position by receptor binding; absent in p44); inter-domain hinge *light blue* (assumes the same conformation in all activated arrestins, in contrast to a variety of conformations in the basal state); β-strand XI *dark blue* (undergoes register shift by one residue in arrestin-2, which "flips" it by 180°, and by two residues in arrestin-1 and p44); finger loop *red* (moves towards the receptor and assumes helical conformation); 139/middle loop *violet* (moves towards the N-domain and changes shape); lariat loop *magenta* (moves out of its basal position, removing two out of three negative charges from the polar core); the "leg" of the α-helix *pink* (changes conformation). The twist of the two domains (N-domain *teal*; C-domain *gray*) relative to each other by 17°–20° is shown by an *arrow*

receptor-bound arrestin was also predicted by molecular modeling (Modzelewska et al. 2006), based on the requirement of a long inter-domain "hinge" in arrestin for receptor binding (Vishnivetskiy et al. 2002). The other was a disruption of the three-element interaction and consequent release of the arrestin C-tail, which became totally invisible in these structures. The movement of the 139-loop [termed middle loop in the arrestin-2 (Shukla et al. 2013)] was also invariably observed. The tip of the finger loop in the arrestin-1-rhodopsin complex assumed α-helical conformation (Kang et al. 2015) earlier predicted based on arrestin peptide co-structure with rhodopsin (Szczepek et al. 2014).

Preferential Interaction of Signalling Proteins with Arrestins in Particular Conformations

Whereas arrestin-mediated activation of protein kinases c-Src (Luttrell et al. 1999), JNK3 (McDonald et al. 2000), ERK1/2 (Luttrell et al. 2001), and p38 (Bruchas et al. 2006) was originally reported to depend on GPCR activation, suggesting that this must be a function of receptor-bound arrestins, subsequent studies showed that this is not always the case. So far every study supports the notion that ERK1/2 bind with reasonably high affinity only to receptor-associated arrestins, even though their upstream activators MEK1 and c-Raf1 do not show this clear preference (Coffa et al. 2011). In contrast, the ability of arrestin-3 [but not other isoforms, even highly homologous arrestin-2 (Attramadal et al. 1992; Sterne-Marr et al. 1993)] to facilitate the activation of JNK family kinases does not depend on GPCRs (Miller et al. 2001; Song et al. 2009b; Seo et al. 2011; Zhan et al. 2011b, 2013; Kook et al. 2014). When the activity of both ERK and JNK is analyzed in the same cell, the former is strictly dependent on the receptor activation, whereas the latter is not (Breitman et al. 2012). There is no general rule for arrestin non-receptor partners: some prefer "active" receptor bound conformation, like ERK1/2 (Coffa et al. 2011), clathrin and AP2 (Kim and Benovic 2002), some prefer basal state, like Mdm2 (Song et al. 2006, 2007) or parkin (Ahmed et al. 2011), whereas others appear to bind both, like JNK3, MEK1, c-Raf1, etc. (Song et al. 2006, 2007, 2009b; Coffa et al. 2011).

These distinct conformational preferences of arrestin binding partners likely have functional significance, which is obvious in some cases, and remains to be elucidated in others (Gurevich and Gurevich 2003). Biologically, preferential binding of key components of the internalization machinery clathrin and AP2 to the active arrestins ensure that receptor-bound arrestins promote GPCR endocytosis, whereas free arrestins in the cytoplasm do not get in the way (Gurevich and Gurevich 2003). Structurally, this is ensured by the anchoring of the C-terminus to the body of the arrestin molecule (Fig. 1.1) and its release upon receptor binding (Palczewski et al. 1991a; Hanson et al. 2006b; Vishnivetskiy et al. 2010; Zhuang et al. 2013; Kim et al. 2012). Indeed, separated arrestin C-terminus expressed in cells binds clathrin and AP2, outcompeting the arrestin-receptor complexes, thereby suppressing arrestin-dependent GPCR internalization via coated pits (Orsini and Benovic 1998). Apparently, preferential interaction of ERK1/2 with receptor-bound arrestins (Coffa et al. 2011) ensures GPCR control of ERK activity, although the biological importance of this phenomenon remains unclear. Mdm2 preference for free arrestins (Song et al. 2006), along with the finding that Mdm2 recruited via arrestins ubiquitinates GPCRs (Ahmed et al. 2011; Shenoy et al. 2001, 2009), ensures only limited ubiquitination of active receptor due to release of bound Mdm2 from receptor-associated arrestins. This is consistent with the role of receptor ubiquitination in its trafficking, rather than in degradation (Shenoy et al. 2009).

Functional role of comparable binding of signaling proteins, such as JNK3 (Song et al. 2006), MEK1, c-Raf1, MKK4, and MKK7 (Coffa et al. 2011;

Song et al. 2009b; Zhan et al. 2011b, 2013) to free and receptor-bound arrestins is unclear. In fact, JNK3 and upstream kinases MKK4, MKK7, and ASK1 bind a small 25-residue peptide of arrestin-3 (Zhan et al. 2016), which is unlikely to have a preferred conformation as a separate entity. In general, an enormous number of proteins were reported to bind arrestins (Xiao et al. 2007). We are only beginning to elucidate conformational preferences of arrestin non-receptor partners, let alone the biological significance of these preferences. It appears that quite a few proteins readily bind microtubule-associated arrestins (Hanson et al. 2007; Coffa et al. 2011), and the role of these interactions also remains obscure.

Thus, while in recent years a lot of novel information about arrestin conformations appeared and the ability of arrestins to change shape is now widely recognized (Gurevich and Gurevich 2014), comprehensive elucidation of the biological role of the conformational changes in arrestins requires further investigation. Accumulating data suggesting that distinct arrestin conformations promote different branches of the arrestin-mediated signaling (Nuber et al. 2016; Lee et al. 2016) are intriguing, but are not comprehensive enough to draw general conclusions. While it is tempting to speculate that different patterns of GPCR phosphorylation by distinct GRKs are decoded by arrestins that assume different conformation upon binding [barcode hypothesis (Tobin et al. 2008; Nobles et al. 2011; Lau et al. 2011)], and there is some structural evidence supporting this notion (Yang et al. 2015), the jury is still out. Possible biological role of distinct conformations of the receptor-bound arrestins is discussed in Chaps. 11, 13 and 18.

To obtain unambiguous answers we need co-structures of arrestins with differentially phosphorylated GPCRs and downstream signaling proteins. However, the complexes of three or more proteins including GPCRs are unlikely to be crystallized any time soon. Considering that the first arrestin-receptor structure has been solved (Kang et al. 2015), it would be helpful to co-crystallize the same non-visual arrestin with the same GPCR phosphorylated at different positions. Hopefully, these structures would reveal conformational differences in bound arrestin induced by distinct patterns of receptor phosphorylation. In addition, we need structures of arrestin complexes with non-receptor signaling proteins, which might reveal subtle conformational preferences of different binding partners. Collectively these structures have a chance to prove the barcode hypothesis, which appears very attractive because it makes perfect sense biologically.

Another aspect that requires further investigation is the biological role of different arrestin-mediated signaling pathways in the cell. Virtually every signaling protein reported to be activated via arrestins, can be activated via other arrestin-independent mechanisms. This is true for Src, ERK1/2, JNK1/2/3, p38, Akt, PI3K, etc. In most cases arrestin-mediated activity constitutes a relatively small proportion of the total. Thus, to be biologically meaningful, arrestin-mediated activation of these signaling proteins must have some unique characteristics. One possibility is the subcellular localization of kinases activated with the help of arrestin, as opposed to other activators or scaffolds. There is evidence that this might be the case for MAP kinases: arrestin-activated ERK1/2 (Luttrell et al. 1999, 2001) and JNK3 (McDonald et al. 2000; Breitman et al. 2012) were reported to

remain in the cytoplasm, where these kinases likely phosphorylate different targets than in the nucleus. Arrestins often organize multi-protein signaling complexes after binding to GPCRs, which localizes signaling proteins activated with the help of arrestins to the plasma membrane and/or endosomes, directing their activity to the targets co-localized in the same compartment. In the same vein, Mdm2 was reported to be recruited to the microtubules via arrestins, and that appears to direct its activity towards microtubule-associated proteins (Hanson et al. 2007). In general, arrestins likely play a role in compartment-specific signaling, but in most cases this needs to be demonstrated, and the biological role of this compartmentalization needs to be elucidated.

To summarize, unexpected discoveries of the multi-faceted role of arrestins as ubiquitous signaling regulators yielded many new questions that need to be answered experimentally.

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