

Chapter 2

Overview of Arrestin Mediated Signaling with Receptors and Non-receptor Binding Partners

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Abstract G protein-coupled receptors (GPCR) classically initiate G protein-dependent signaling in response to extracellular stimulation, which is followed by arrestin-mediated desensitization and receptor internalization. However, non-visual arrestins (arrestin-2 and arrestin-3) are also demonstrated to mediate G protein-independent signaling by serving as adaptors and scaffolds through the assembly of multiprotein complexes. By recruiting various protein partners including trafficking proteins and signaling molecules directly to the GPCR, non-visual arrestins can connect activated receptors to diverse signaling pathways. Particularly, both non-visual arrestins have been demonstrated to scaffold three components of mitogen activated protein kinase (MAPK) signaling modules in order to ensure the fidelity of signaling by regulating their spatial arrangement. As a large family of serine/threonine kinases that includes ERK1/2, JNK and p38 kinases, the MAPKs control many important cellular functions, including cell cycle progression, transcriptional regulation and apoptosis. Therefore, it is of great importance to explore how non-visual arrestins mediate the interaction with different GPCRs, as well as assemble different MAPKs into a signaling complex to regulate different pathways.

Keywords Arrestin • GPCRs • Cell signaling • MAPKs • Proliferation • Apoptosis

Arrestins are a small family of proteins that bind active phosphorylated G-protein coupled receptors (GPCRs) and function to stop G-protein mediated signaling. There are four arrestin subtypes in mammals and they clearly fall into two categories. One is the visual arrestins, which include arrestin-1 and arrestin-4.¹ They are

¹Various names of arrestin proteins are used: arrestin-1 is also called S-antigen, 48 kDa protein, visual or rod arrestin; arrestin-2 is also called β -arrestin or β -arrestin1; arrestin-3 is also called β -arrestin2 and hTHY-ARRX; whereas arrestin-4 is also called cone or X-arrestin (its gene is called "arrestin 3" in the HUGO database).

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exclusively expressed in rod and cone receptor cells at high levels, demonstrating specificity for their cognate receptors, rhodopsin and cone opsins. The other category is non-visual arrestins or β -arrestins, which consists of arrestin-2 (β -arrestin-1) and arrestin-3 (β -arrestin-2). The non-visual arrestins were first discovered in the late 1980s, and reported to be homologues of visual arrestin in non-retinal tissues (Benovic et al. 1987). Non-visual arrestins are expressed ubiquitously in all cell types with the highest expression levels observed in the brain and spleen (Attramadal et al. 1992; Lohse et al. 1990; Gurevich et al. 2002, 2004). The classical function of non-visual arrestins is to desensitize most GPCR signaling and initiate receptor internalization. In order to turn off the G protein-mediated signaling to prevent persistent activation, the activated receptor is first phosphorylated by a G protein coupled receptor kinase (GRK) (Gurevich et al. 2012). Receptor phosphorylation by GRK specifically prepares the activated receptor for arrestin binding (Carman and Benovic 1998). Once arrestin binds the activated and phosphorylated receptor, it physically blocks further G protein-mediated signaling and targets the receptor for internalization, whereupon the receptor can be either degraded or recycled back to the surface for another round of signaling (Gurevich and Gurevich 2004). For example, in rod photoreceptors, it is the visual arrestin-1 that specifically stops the signaling of rhodopsin. Once a photon of light is absorbed, rhodopsin undergoes a conformational change that activates the associated visual G protein transducin (Noma et al. 2007) and triggers a second messenger cascade. Upon activation of the receptor, rhodopsin kinase (systematic name GRK1) phosphorylates multiple sites on rhodopsin's C-tail, preparing the phosphorylated and activated receptor to bind visual arrestin-1 (Maeda et al. 2003). Arrestin binding prevents rhodopsin from interacting with any more transducin molecules, ending the G protein-dependent signaling (McBee et al. 2001; Gurevich et al. 2011). This arrestin-mediated desensitization mechanism is essential and universal to almost all GPCRs.

GPCRs constitute the largest, most versatile and most ubiquitous class of membrane receptors, with more than 800 members identified in the human genome (Lagerstrom and Schiöth 2008). They bind to a diverse category of ligands which include hormones, peptides, neurotransmitters, chemokines and lipids (Bockaert and Philippe Pin 1999). Upon activation, they regulate a variety of intracellular signaling pathways to produce appropriate cellular responses, such as cell growth, differentiation, metabolism and also vision and taste (Pierce et al. 2002). Since GPCR signaling critically regulates a wide range of physiological and pathophysiological processes, these receptors are among the most important drug targets, accounting for approximately one third of currently marketed drugs (Ma and Zemmel 2002).

Although different GPCRs have various primary structures, they do share a conserved seven-transmembrane domain architecture, which consists of a single polypeptide chain that spans the lipid membrane seven times (Baldwin et al. 1997). At the transmembrane region, there is a seven α -helical bundle with hydrophobic helices linked by three extracellular and three intracellular loops. Several crystal structures have confirmed that the GPCRs have a tertiary structure resembling a

barrel, with the seven transmembrane helices forming a cavity within the plasma membrane that serves as a ligand-binding domain that is often covered by extracellular loop-2 (Cherezov et al. 2007; Palczewski et al. 2000; Jaakola et al. 2008; Wu et al. 2010; Huang et al. 2015; Hua et al. 2016; Yin et al. 2015; Dore et al. 2014). GPCRs in vertebrates are commonly divided into five families based on their sequence and structural similarity: rhodopsin (family A), secretin (family B), glutamate (family C), adhesion and Frizzled/Taste2 (Fredriksson et al. 2003). The rhodopsin family is by far the largest and most diverse class and is characterized by several conserved sequence motifs (Fredriksson et al. 2003). The rhodopsin-like receptors include many important drug targets, including chemokine receptors, adrenergic receptors, angiotensin receptors, dopamine receptors, serotonin receptors, histamine receptors, neuropeptide Y receptors and glycoprotein receptors. The crystal structure of dark-state bovine rhodopsin reported in 2000 was considered an important milestone for understanding the structure and function of GPCRs (Palczewski et al. 2000).

The interaction of arrestins with GPCRs generally requires two consecutive structural changes in the receptor: the ligand-induced conformational changes associated with the activation and phosphorylation by GRK at intracellular loops and/or the C-terminal tail of the receptor. Once bound to arrestin, the receptor is linked to the clathrin-dependent endocytic machinery and the complex persists on a time scale of minutes to hours (Charest et al. 2005). The traditional GPCR function is that these receptors catalyze the activation of heterotrimeric G proteins, whose dissociated subunits interact with second messenger-generating or -degrading enzymes to amplify the signal (Hepler and Gilman 1992). Interestingly, recently it has also been demonstrated that the binding of arrestins to GPCRs initiates diverse signaling pathways that are independent of G proteins (Reiter et al. 2012). Preferential activation of one of a number of possible downstream pathways of a receptor by a particular ligand is referred to as biased agonism, which means a certain ligand can activate either G protein-dependent or arrestin-dependent signaling pathways (DeWire et al. 2007). The molecular mechanism of GPCR biased agonism suggested the ability of the receptor to adopt distinct conformations. A large number of studies using different full and partial agonist ligands, site-directed mutagenesis and probes placed in different places on the receptors (Hoffmann et al. 2008; Lohse et al. 2008; Seifert and Dove 2009) have confirmed the existence of distinct active conformations of GPCRs in response to various ligands. Moreover, accumulated evidence has also revealed that GPCRs are dynamic proteins and their conformational plasticity contributes to their interactions with multiple signaling partners including G proteins, GRKs and arrestins (Mahoney and Sunahara 2016; Kenakin 2013).

In recent years, the investigation of arrestin-dependent signaling via GPCRs has identified that both non-visual arrestins not only mediate receptor desensitization and internalization, but also regulate GPCR signal transduction in a G protein-independent manner (Lefkowitz and Shenoy 2005; Shenoy et al. 2001; Shenoy and Lefkowitz 2003; DeFea 2007; Abraham et al. 2016; Mancini et al. 2015; Yang et al. 2016). There is an ever increasing list of kinases and regulatory

proteins that bind specifically to one or both non-visual arrestin isoforms (Lefkowitz and Shenoy 2005). For example, non-visual arrestin scaffolding of intracellular signaling molecules was first demonstrated for the non-receptor tyrosine kinase c-Src (Miller et al. 2000; DeFea et al. 2000a; Luttrell et al. 1999). In these studies, Src was shown to assemble on the agonist-stimulated β_2 -adrenergic receptor (β_2 AR) in a non-visual arrestin-dependent manner. This arrestin-dependent c-Src recruitment to the receptors results in the activation of extracellular signal-regulated kinases (ERK1/2) (Miller et al. 2000; DeFea et al. 2000a; Luttrell et al. 1999). A mutational analysis indicated that some mutant receptors do not couple to their cognate G proteins but still recruit non-visual arrestins in response to agonist stimulation (Gáborik et al. 2003; Wei et al. 2003a). Another group, using the angiotensin II type 1a receptor (AT1aR) as a model, found that exogenous arrestin-2 or -3 expression resulted in decreased agonist-stimulated phosphoinositide hydrolysis, yet increased ERK activation (Tohgo et al. 2002). This suggests that non-visual arrestins might inhibit G protein signaling through increased desensitization but increase ERK phosphorylation through an arrestin-dependent mechanism. By recruiting various protein partners including trafficking proteins and signaling molecules directly to the GPCR, non-visual arrestins can connect activated GPCRs to diverse signaling pathways, which leads to the phosphorylation of numerous intracellular targets (Xiao et al. 2007, 2010). Accumulated evidence has shown that this non-visual arrestin-mediated signaling regulates important cellular responses such as cell growth, differentiation, cytoskeleton rearrangement, chemotaxis, and apoptosis (DeWire et al. 2007). For example, one study found that the directed movement of lymphocytes towards chemokines is regulated specifically by GRK6-mediated phosphorylation and arrestin-3 binding to CXCR4 (Fong et al. 2002). Moreover, in the case of the apoptotic pathway, researchers found that in mouse embryonic fibroblasts arrestin-2 was necessary for the insulin-like growth factor-1 receptor (IGF1-R) stimulated pathway through phosphatidylinositol 3 kinase (PI3K) activation, which inhibits apoptosis (Povsic et al. 2003; Miller and Lefkowitz 2001).

Despite these efforts, the field is just beginning to understand the molecular mechanism of arrestin-mediated signaling. These pathways are regulated via non-visual arrestins by bringing signaling proteins within spatial proximity of each other, therefore facilitating protein-protein interactions. Non-visual arrestins often function as signaling scaffolds. Multiprotein complexes organized by arrestins were termed signalosomes (Shenoy and Lefkowitz 2003). Some of the best-characterized non-visual arrestin mediated signalosomes upon stimulation of different GPCRs induce RhoA-dependent stress fiber formation, inhibit nuclear factor κ B (NF- κ B) targeted gene expression through I κ B stabilization, induce ERK-dependent protein translation and antiapoptotic effects, and so on (Reiter et al. 2012).

Several types of signalosomes organized by non-visual arrestins promote the activation of MAP kinases of the three main subfamilies: ERK (Luttrell et al. 2001), JNK (McDonald et al. 2000), and p38 (Bruchas et al. 2006). Accumulated evidence suggests that both arrestin-2 and arrestin-3 can form a signaling complex with different GPCRs and MAPK cascade components, though a clear model of this

signaling complex has not been established (Burack and Shaw 2000; Pearson et al. 2001; Luttrell et al. 2001; DeFea et al. 2000b; Christopoulos et al. 2003; McDonald et al. 2000). In mammals, there are three major MAPK pathways: the extracellular signal-regulated kinase (ERK) signaling pathway, the c-Jun NH₂-terminal kinase (JNK) pathway and the p38 pathway. Each signaling cascade is composed of three kinase modules, where the kinases sequentially activate downstream component by phosphorylation. MAPKs regulate a diverse range of cellular responses induced by many different activators (Roux and Blenis 2004). Generally, there are two mechanisms that control the efficiency and specificity of MAPK signaling: recognition motifs and scaffolds that organize them into multiprotein complexes (Zeke et al. 2009; Brown and Sacks 2009). Several scaffold proteins that specifically organize the MAPK cascade components have been discovered, the classical examples of which are the Ste5 protein in yeast and the KSR (kinase suppressor of Ras) protein in mammals (Zeke et al. 2009; Brown and Sacks 2009). Ste5 specifically serves as a scaffold in yeast mating pathway by directly interacting with the kinase components of a particular MAPK cascade (Chol et al. 1994; Printen and Sprague 1994). Similarly, KSR proteins scaffold signaling modules of the ERK cascade and modulate signaling in the Ras-dependent signaling pathway (Therrien et al. 1996). The functions of these kinds of scaffold proteins are similar. They physically assemble the individual kinases and upstream regulators and control MAPK pathway localization within the cell. In addition, they can prevent MAPK signaling proteins from competing inputs. Most importantly, they are required for efficient signaling (Therrien et al. 1996; Garrenton et al. 2006; Morrison and Davis 2003; Good et al. 2011). Despite no sequence and size similarity to KSR and Ste5 protein, non-visual arrestins carry out a similar scaffolding function in the regulation of MAPKs (Shenoy and Lefkowitz 2003).

Recently, a number of studies have attempted to explore the mechanism of arrestin-dependent assembly of MAPKs and also the downstream consequences of arrestin-dependent signaling (Tohgo et al. 2002; Xiao et al. 2010; Luttrell and Gesty-Palmer 2010; Breitman et al. 2012; Seo et al. 2011; Coffa et al. 2011; Walters et al. 2009; Zhan et al. 2016; Wisler et al. 2015; Khoury et al. 2014). DeFea et al. (2000b) showed that agonist stimulation of protease-activated receptor (PAR2) results in the formation of a complex containing the activated receptor, arrestin-2, Raf-1, and phosphorylated ERK. Arrestin-3 has been found to scaffold an entire signaling module for JNK3 in response to GPCR signaling, such as AT1aR (McDonald et al. 2000). Another study using purified proteins has shown that ERK2 directly binds free arrestin-2 and arrestin-3, as well as receptor-associated arrestin-2 and arrestin-3 (Coffa et al. 2011). Moreover, they also found that in COS-7 cells arrestin-2 and -3 associated with receptors significantly enhanced ERK2 binding (Coffa et al. 2011). Another study based on immunoprecipitation assays found that both arrestin domains interact with all components of the two MAPK cascades (ASK1-MKK4-JNK3 and Raf-1-MEK1-ERK2), which suggests a model of arrestin-dependent assembly of the MAPK signaling module: arrestin binds all three kinases along its short axis with each kinase directly interacting with both domains of arrestin (Song et al. 2009). However, studies using the AT1aR and

co-immunoprecipitation described a different model of arrestin-3 mediated assembly of MAPKs: MEK1 indirectly binds arrestin-3 through contacts with Raf and ERK, whereas the latter two kinases directly bind arrestin-3 (DeWire et al. 2007). In addition to the investigation of the physical interactions within arrestin-dependent signalosome, there are many studies focusing on the physiological responses resulting from arrestin-dependent ERK activation. It has been found that arrestin-mediated ERK activation results in retention of active ERK in cytosolic endocytic vesicles, instead of trafficking into the nucleus (Lefkowitz and Shenoy 2005; Luttrell et al. 2001; Tohgo et al. 2003). In the cytoplasm, ERK in this arrestin-mediated signalosome can phosphorylate non-nuclear substrates that regulate possible physiological effects on cell motility, chemotaxis, and apoptosis (Wei et al. 2003a; Tohgo et al. 2002; Luttrell et al. 2001).

Rhodopsin-like GPCRs were functionally divided into broad classes based on the stability of the arrestin-receptor complex (Oakley et al. 2000). Class A receptors such as β_2 AR form weak and transient complexes with non-visual arrestins, so that they do not constrain ERK activity within endosomes. Instead, active ERK immediately dissociates from the signalosome and translocates into the nucleus, while the receptors are rapidly recycled to the plasma membrane (Christopoulos et al. 2003). In contrast, Class B receptors such as AT1aR form stable receptor-arrestin complexes so that active ERK1/2 remains associated with the receptor in endocytic vesicles and likely phosphorylates cytosolic substrates (Lefkowitz and Shenoy 2005; Luttrell et al. 2001; Oakley et al. 1999, 2000; Kendall and Luttrell 2009; Wei et al. 2003b). It appears that arrestin dependent ERK activation is mainly generated by Class B receptors and does not have the typical nuclear ERK functions, however, the precise downstream targets largely remain unknown. Furthermore, the key that determines receptor affinity for the two non-visual arrestins and the lifetime of the receptor-arrestin complex is the distinct phosphorylation sites, most notably in the C-termini of the receptors (Tohgo et al. 2003; Oakley et al. 2000; Rh et al. 2001). Interestingly, one study showed that swapping the C-termini between class A and class B receptors changes their non-visual arrestin binding behavior (Lohse and Hoffmann 2014).

There are many human disorders associated with excessive signaling by various GPCRs. Mutations in GPCRs can cause acquired and inherited diseases such as retinitis pigmentosa (RP), nephrogenic diabetes insipidus, severe fertility disorders, and even carcinomas (Lagerstrom and Schioth 2008; Ma and Zimmel 2002). It is hypothesized that the excessive signaling of GPCRs can be dampened by enhanced arrestins, which were designed to bind active unphosphorylated GPCRs with high affinity (Kovoor et al. 1999; Celver et al. 2002; Gurevich and Gurevich 2013). It has been widely found that excessive MAPK signaling results in many severe pathological processes such as cancer. Non-visual arrestins play an important role in regulating different MAPK pathways; a clear understanding of the mechanisms of arrestin-dependent assembly of MAPKs into a signaling complex is very important and promising for the development of therapies that selectively manipulate MAPK cascades. Although there have been models and various studies (DeWire et al. 2007; Coffa et al. 2011; Song et al. 2009) focusing on

arrestin-dependent assembly of MAPKs, mechanisms of the signaling complex still remain largely unexplored. It is very likely that scaffold proteins adopt more sophisticated mechanisms in regulating the signaling network, such as using cooperative or allosteric assembly of components. Moreover, one of the most important features of signaling complexes is their dynamic nature. Dynamic conformational changes are always involved in the formation and dissociation of multiple protein complexes. Advanced biophysical and biochemical techniques have allowed us to obtain both static structural information and monitor the signaling events in a time-resolved fashion to probe the dynamics of interactions between components of signaling complexes (Shukla and Wodak 2016).

It is well known that all cellular behaviors, such as proliferation, differentiation, apoptosis, migration, etc., are mediated and regulated by signaling events that are driven by protein-protein interactions. Targeting individual protein-protein interactions has been proposed to have great therapeutic potential (Gurevich and Gurevich 2012). For example, if we could selectively disrupt or enhance individual protein-protein interactions, we may be able to force cancer cells to stop proliferating or “tell” dying neurons to stay alive by manipulating corresponding signaling pathways. Therefore, the ability to modulate protein-protein interactions in a desired manner may help us to cure some of the severe diseases instead of just managing the symptoms, although there are a lot of challenges that need to be addressed. A comprehensive understanding of structural and functional properties of signaling proteins is essential to develop signaling biased proteins with modified structure and functions. In fact, arrestin proteins are likely to be a perfect target to test this idea because non-visual arrestins function as important signaling scaffolds in the cell through interactions with numerous signaling proteins.

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