Chapter 2
Overview of Arrestin Mediated Signaling with Receptors and Non-receptor Binding Partners

Ya Zhuo and Candice S. Klug

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/theronine 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

[1]Various 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).

Y. Zhuo · C.S. Klug (✉)
Department of Biophysics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
e-mail: candice@mcw.edu

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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 rhodospin'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 Schioth 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_2AR) 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 κB (NF-κB) targeted gene expression through IκB 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_2AR 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 Zemmel 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.

References

Abraham DM, Davis RT, Warren CM, Mao L, Wolska BM, Solaro RJ, Rockman HA (2016) β-Arrestin mediates the Frank-Starling mechanism of cardiac contractility. Proc Natl Acad Sci 113:14426–14431

Attramadal H, Arriza JL, Aoki C, Dawson TM, Codina J, Kwatra MM, Snyder SH, Caron MG, Lefkowitz RJ (1992) Beta-arrestin2, a novel member of the arrestin/beta-arrestin gene family. J Biol Chem 267:17882–17890

Baldwin JM, Schertler GFX, Unger VM (1997) An alpha-carbon template for the transmembrane helices in the rhodopsin family of G-protein-coupled receptors. J Mol Biol 272:144–164

Benovic JL, Kühn H, Weyand I, Codina J, Caron MG, Lefkowitz RJ (1987) Functional desensitization of the isolated beta-adrenergic receptor by the beta-adrenergic receptor kinase: potential role of an analog of the retinal protein arrestin (48-kDa protein). Proc Natl Acad Sci 84:8879–8882

Bockaert J, Philippe Pin J (1999) Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J 18:1723–1729

Breitman M, Kook S, Gimenez LE, Lizama BN, Palazzo MC, Gurevich EV, Gurevich VV (2012) Silent scaffolds. J Biol Chem 287:19653–19664

Brown MD, Sacks DB (2009) Protein scaffolds in MAP kinase signalling. Cell Signal 21:462–469

Bruchas MR, Macey TA, Lowe JD, Chavkin C (2006) Kappa opioid receptor activation of p38 MAPK is GRK3- and arrestin-dependent in neurons and astrocytes. J Biol Chem 281:18081–18089

Burack WR, Shaw AS (2000) Signal transduction: hanging on a scaffold. Curr Opin Cell Biol 12:211–216

Carman CV, Benovic JL (1998) G-protein-coupled receptors: turn-ons and turn-offs. Curr Opin Neurobiol 8:335–344

Celver J, Vishnivetskiy SA, Chavkin C, Gurevich VV (2002) Conservation of the phosphate-sensitive elements in the arrestin family of proteins. J Biol Chem 277:9043–9048

Charest PG, Terrillon S, Bouvier M (2005) Monitoring agonist-promoted conformational changes of β-arrestin in living cells by intramolecular BRET. EMBO Rep 6:334–340

Cherezov V, Rosenbaum DM, Hanson MA, Rasmussen SGF, Thian FS, Kobilka TS, Choi H-J, Kuhn P, Weis WI, Kobilka BK, Stevens RC (2007) High-resolution crystal structure of an engineered human β2-adrenergic G protein-coupled receptor. Science 318:1258–1265

Chol K-Y, Satterberg B, Lyons DM, Elion EA (1994) Ste5 tethers multiple protein kinases in the MAP kinase cascade required for mating in *S. cerevisiae*. Cell 78:499–512

Christopoulos A, Christopoulos G, Morfis M, Udawela M, Laburthe M, Couvineau A, Kuwasako K, Tilakaratne N, Sexton PM (2003) Novel receptor partners and function of receptor activity-modifying proteins. J Biol Chem 278:3293–3297

Coffa S, Breitman M, Hanson SM, Callaway K, Kook S, Dalby KN, Gurevich VV (2011) The effect of arrestin conformation on the recruitment of c-Raf1, MEK1, and ERK1/2 activation. PLoS ONE 6:e28723

DeFea KA (2007) Stop that cell! β-arrestin-dependent chemotaxis: a tale of localized actin assembly and receptor desensitization. Ann Rev Physiol 69:535–560

DeFea KA, Vaughn ZD, O'Bryan EM, Nishijima D, Déry O, Bunnett NW (2000a) The proliferative and antiapoptotic effects of substance P are facilitated by formation of a β-arrestin-dependent scaffolding complex. Proc Natl Acad Sci 97:11086–11091

DeFea KA, Zalevsky J, Thoma MS, Déry O, Mullins RD, Bunnett NW (2000b) β-Arrestin-dependent endocytosis of proteinase-activated receptor 2 is required for intracellular targeting of activated Erk1/2. J Cell Biol 148:1267–1282

DeWire SM, Ahn S, Lefkowitz RJ, Shenoy SK (2007) β-arrestins and cell signaling. Ann Rev Physiol 69:483–510

Dore AS, Okrasa K, Patel JC, Serrano-Vega M, Bennett K, Cooke RM, Errey JC, Jazayeri A, Khan S, Tehan B, Weir M, Wiggin GR, Marshall FH (2014) Structure of class C GPCR metabotropic glutamate receptor 5 transmembrane domain. Nature 511:557–562

Fong AM, Premont RT, Richardson RM, Yu Y-RA, Lefkowitz RJ, Patel DD (2002) Defective lymphocyte chemotaxis in β-arrestin2- and GRK6-deficient mice. Proc Natl Acad Sci 99:7478–7483

Fredriksson R, Lagerström MC, Lundin L-G, Schiöth HB (2003) The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol Pharmacol 63:1256–1272

Gáborik Z, Jagadeesh G, Zhang M, Spät A, Catt KJ, Hunyady L (2003) The role of a conserved region of the second intracellular loop in AT1 angiotensin receptor activation and signaling. Endocrinology 144:2220–2228

Garrenton LS, Young SL, Thorner J (2006) Function of the MAPK scaffold protein, Ste5, requires a cryptic PH domain. Genes Dev 20:1946–1958

Good MC, Zalatan JG, Lim WA (2011) Scaffold proteins: hubs for controlling the flow of cellular information. Science 332:680–686

Gurevich VV, Gurevich EV (2004) The molecular acrobatics of arrestin activation. Trends Pharmacol Sci 25:105–111

Gurevich VV, Gurevich EV (2012) Synthetic biology with surgical precision: targeted reengineering of signaling proteins. Cell Signal 24:1899–1908

Gurevich VV, Gurevich EV (2013) Structural determinants of arrestin functions. In: Luttrell LM (ed) The Molecular Biology of Arrestins. Progress in molecular biology and translational science, vol 118. Elsevier, Oxford, pp 57–92

Gurevich EV, Benovic JL, Gurevich VV (2002) Arrestin2 and arrestin3 are differentially expressed in the rat brain during postnatal development. Neuroscience 109:421–436

Gurevich EV, Benovic JL, Gurevich VV (2004) Arrestin2 expression selectively increases during neural differentiation. J Neurochem 91:1404–1416

Gurevich VV, Hanson SM, Song X, Vishnivetskiy SA, Gurevich EV (2011) The functional cycle of visual arrestins in photoreceptor cells. Prog Retin Eye Res 30:405–430

Gurevich EV, Tesmer JJ, Mushegian A, Gurevich VV (2012) G protein-coupled receptor kinases: more than just kinases and not only for GPCRs. Pharmacol Ther 133:40–69

Hepler JR, Gilman AG (1992) G proteins. Trends Biochem Sci 17:383–387

Hoffmann C, Zürn A, Bünemann M, Lohse MJ (2008) Conformational changes in G-protein-coupled receptors—the quest for functionally selective conformations is open. Br J Pharmacol 153:S358–S366

Hua T, Vemuri K, Pu M, Qu L, Han GW, Wu Y, Zhao S, Shui W, Li S, Korde A, Laprairie RB, Stahl EL, Ho JH, Zvonok N, Zhou H, Kufareva I, Wu B, Zhao Q, Hanson MA, Bohn LM, Makriyannis A, Stevens RC, Liu ZJ (2016) Crystal structure of the human cannabinoid receptor CB1. Cell 167(750–762):e714

Huang W, Manglik A, Venkatakrishnan AJ, Laeremans T, Feinberg EN, Sanborn AL, Kato HE, Livingston KE, Thorsen TS, Kling RC, Granier S, Gmeiner P, Husbands SM, Traynor JR, Weis WI, Steyaert J, Dror RO, Kobilka BK (2015) Structural insights into micro-opioid receptor activation. Nature 524:315–321

Jaakola V-P, Griffith MT, Hanson MA, Cherezov V, Chien EYT, Lane JR, Ijzerman AP, Stevens RC (2008) The 2.6 angstrom crystal structure of a human A2A adenosine receptor bound to an antagonist. Science 322:1211–1217

Kenakin T (2013) New concepts in pharmacological efficacy at 7TM receptors: IUPHAR review 2. Br J Pharmacol 168:554–575

Kendall RT, Luttrell LM (2009) Diversity in arrestin function. Cell Mol Life Sci 66:2953–2973

Khoury E, Nikolajev L, Simaan M, Namkung Y, Laporte SA (2014) Differential regulation of endosomal GPCR/beta-arrestin complexes and trafficking by MAPK. J Biol Chem 289: 23302–23317

Kovoor A, Celver J, Abdryashitov RI, Chavkin C, Gurevich VV (1999) Targeted construction of phosphorylation-independent β-arrestin mutants with constitutive activity in cells. J Biol Chem 274:6831–6834

Lagerstrom MC, Schioth HB (2008) Structural diversity of G protein-coupled receptors and significance for drug discovery. Nat Rev Drug Discov 7:339–357

Lefkowitz RJ, Shenoy SK (2005) Transduction of receptor signals by ß-arrestins. Science 308:512–517

Lohse MJ, Hoffmann C (2014) Arrestin interactions with G protein-coupled receptors. Handb Exp Pharmacol 219:15–56

Lohse M, Benovic J, Codina J, Caron M, Lefkowitz R (1990) Beta-arrestin: a protein that regulates beta-adrenergic receptor function. Science 248:1547–1550

Lohse MJ, Nikolaev VO, Hein P, Hoffmann C, Vilardaga J-P, Bünemann M (2008) Optical techniques to analyze real-time activation and signaling of G-protein-coupled receptors. Trends Pharmacol Sci 29:159–165

Luttrell LM, Gesty-Palmer D (2010) Beyond desensitization: physiological relevance of arrestin-dependent signaling. Pharmacol Rev 62:305–330

Luttrell LM, Ferguson SSG, Daaka Y, Miller WE, Maudsley S, Della Rocca GJ, Lin F-T, Kawakatsu H, Owada K, Luttrell DK, Caron MG, Lefkowitz RJ (1999) β-Arrestin-dependent formation of β2 adrenergic receptor-Src protein kinase complexes. Science 283:655–661

Luttrell LM, Roudabush FL, Choy EW, Miller WE, Field ME, Pierce KL, Lefkowitz RJ (2001) Activation and targeting of extracellular signal-regulated kinases by β-arrestin scaffolds. Proc Natl Acad Sci 98:2449–2454

Ma P, Zemmel R (2002) Value of novelty? Nat Rev Drug Discov 1:571–572
Maeda T, Imanishi Y, Palczewski K (2003) Rhodopsin phosphorylation: 30 years later. Prog Retin Eye Res 22:417–434
Mahoney JP, Sunahara RK (2016) Mechanistic insights into GPCR-G protein interactions. Curr Opin Struct Biol 41:247–254
Mancini AD, Bertrand G, Vivot K, Carpentier É, Tremblay C, Ghislain J, Bouvier M, Poitout V (2015) β-Arrestin recruitment and biased agonism at free fatty acid receptor 1. J Biol Chem 290:21131–21140
McBee JK, Palczewski K, Baehr W, Pepperberg DR (2001) Confronting complexity: the interlink of phototransduction and retinoid metabolism in the vertebrate retina. Prog Retin Eye Res 20:469–529
McDonald PH, Chow CW, Miller WE, Laporte SA, Field ME, Lin FT, Davis RJ, Lefkowitz RJ (2000) β-arrestin 2: a receptor-regulated MAPK scaffold for the activation of JNK3. Science 290:1574–1577
Miller WE, Lefkowitz RJ (2001) Arrestins as signaling molecules involved in apoptotic pathways: a real eye opener. Sci STKE 2001:pe1
Miller WE, Maudsley S, Ahn S, Khan KD, Luttrell LM, Lefkowitz RJ (2000) β-arrestin1 interacts with the catalytic domain of the tyrosine kinase c-SRC. J Biol Chem 275:11312–11319
Morrison DK, Davis RJ (2003) Regulation of MAP kinase signaling modules by scaffold proteins in mammals. Ann Rev Cell Dev Biol 19:91–118
Noma T, Lemaire A, Naga Prasad SV, Barki-Harrington L, Tilley DG, Chen J, Le Corvoisier P, Violin JD, Wei H, Lefkowitz RJ, Rockman HA (2007) β-arrestin-mediated β1-adrenergic receptor transactivation of the EGFR confers cardioprotection. J Clin Investig 117:2445–2458
Oakley RH, Laporte SA, Holt JA, Barak LS, Caron MG (1999) Association of β-arrestin with G protein-coupled receptors during clathrin-mediated endocytosis dictates the profile of receptor resensitization. J Biol Chem 274:32248–32257
Oakley RH, Laporte SA, Holt JA, Caron MG, Barak LS (2000) Differential affinities of visual arrestin, βarrestin1, and βarrestin2 for G protein-coupled receptors delineate two major classes of receptors. J Biol Chem 275:17201–17210
Oakley RF, Laporte SA, Holt JA, Barak LS, Caron MG (2001) Molecular determinants underlying the formation of stable intracellular G protein-coupled receptor-β-arrestin complexes after receptor endocytosis. J Biol Chem 276:19452–19460
Palczewski K, Kumasaka T, Hori T, Behnke CA, Motoshima H, Fox BA, Trong IL, Teller DC, Okada T, Stenkamp RE, Yamamoto M, Miyano M (2000) Crystal structure of rhodopsin: a G protein-coupled receptor. Science 289:739–745
Pearson G, Robinson F, Beers Gibson T, Xu B-E, Karandikar M, Berman K, Cobb MH (2001) Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev 22:153–183
Pierce KL, Premont RT, Lefkowitz RJ (2002) Seven-transmembrane receptors. Nat Rev Mol Cell Biol 3:639–650
Povsic TJ, Kohout TA, Lefkowitz RJ (2003) β-arrestin1 mediates insulin-like growth factor 1 (IGF-1) activation of phosphatidylinositol 3-kinase (PI3K) and anti-apoptosis. J Biol Chem 278:51334–51339
Printen JA, Sprague GF (1994) Protein-protein interactions in the yeast pheromone response pathway: Ste5p interacts with all members of the MAP kinase cascade. Genetics 138:609–619
Reiter E, Ahn S, Shukla AK, Lefkowitz RJ (2012) Molecular mechanism of beta-arrestin-biased agonism at seven-transmembrane receptors. Annu Rev Pharmacol Toxicol 52:179–197
Roux PP, Blenis J (2004) ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiol Mol Biol Rev 68:320–344
Seifert R, Dove S (2009) Functional selectivity of GPCR ligand stereoisomers: new pharmacological opportunities. Mol Pharmacol 75:13–18
Seo J, Tsakem EL, Breitman M, Gurevich VV (2011) Identification of arrestin-3-specific residues necessary for JNK3 kinase activation. J Biol Chem 286:27894–27901

Shenoy SK, Lefkowitz RJ (2003) Multifaceted roles of beta-arrestins in the regulation of seven-membrane-spanning receptor trafficking and signalling. Biochem J 375:503–515

Shenoy SK, McDonald PH, Kohout TA, Lefkowitz RJ (2001) Regulation of receptor fate by ubiquitination of activated β2-adrenergic receptor and β-arrestin. Science 294:1307–1313

Shukla AK, Wodak SJ (2016) Editorial overview: multi-protein assemblies in signaling. Curr Opin Struct Biol 41:v–vii

Song X, Coffa S, Fu H, Gurevich VV (2009) How does arrestin assemble MAPKs into a signaling complex? J Biol Chem 284:685–695

Therrien M, Michaud NR, Rubin GM, Morrison DK (1996) KSR modulates signal propagation within the MAPK cascade. Genes Dev 10:2684–2695

Tohgo A, Pierce KL, Choy EW, Lefkowitz RJ, Luttrell LM (2002) β-Arrestin scaffolding of the ERK cascade enhances cytosolic ERK activity but inhibits ERK-mediated transcription following angiotensin AT1a receptor stimulation. J Biol Chem 277:9429–9436

Tohgo A, Choy EW, Gesty-Palmer D, Pierce KL, Laporte S, Oakley RH, Caron MG, Lefkowitz RJ, Luttrell LM (2003) The stability of the G protein-coupled receptor-β-arrestin interaction determines the mechanism and functional consequence of ERK activation. J Biol Chem 278:6258–6267

Walters RW, Shukla AK, Kovacs JJ, Violon JD, DeWire SM, Lam CM, Chen JR, Muehlbauer MJ, Whalen EJ, Levkowitz RJ (2009) β-arrestin1 mediates nicotinic acid-induced flushing, but not its antilipolytic effect, in mice. J Clin Investig 119:1312–1321

Wei H, Ahn S, Shenoy SK, Karnik SS, Hunyady L, Luttrell LM, Lefkowitz RJ (2003a) Independent β-arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2. Proc Natl Acad Sci 100:10782–10787

Wei H, Ahn S, Shenoy SK, Karnik SS, Hunyady L, Luttrell LM, Lefkowitz RJ (2003b) Independent β-arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2. Proc Natl Acad Sci USA 100:10782–10787

Wisler JW, Harris EM, Raisch M, Mao L, Kim J, Rockman HA, Lefkowitz RJ (2015) The role of beta-arrestin2-dependent signaling in thoracic aortic aneurysm formation in a murine model of Marfan syndrome. Am J Physiol Heart Circ Physiol 309:H1516–H1527

Wu B, Chien EYT, Mol CD, Fenalti G, Liu W, Katritch V, Abagyan R, Brooun A, Wells P, Bi FC, Hamel DJ, Kuhn P, Handel TM, Cherezov V, Stevens RC (2010) Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. Science 330:1066–1071

Xiao K, McClatchy DB, Shukla AK, Zhao Y, Chen M, Shenoy SK, Yates JR, Lefkowitz RJ (2007) Functional specialization of β-arrestin interactions revealed by proteomic analysis. Proc Natl Acad Sci 104:12011–12016

Xiao K, Sun J, Kim J, Rajagopal S, Zhai B, Villén J, Haas W, Kovacs JJ, Shukla AK, Hara MR, Hernandez M, Lachmann A, Zhao S, Lin Y, Cheng Y, Mizuno K, Ma'ayan A, Gygi SP, Lefkowitz RJ (2010) Global phosphorylation analysis of β-arrestin-mediated signaling downstream of a seven transmembrane receptor (7TMR). Proc Natl Acad Sci 107: 15299–15304

Yang S, Ben-Shalom R, Ahn M, Liptak AT, van Rijn RM, Whistler JL, Bender KJ (2016) Beta-arrestin-dependent dopaminergic regulation of calcium channel activity in the axon initial segment. Cell Rep 16:1518–1526

Yin J, Mobarec JC, Kolb P, Rosenbaum DM (2015) Crystal structure of the human OX2 orexin receptor bound to the insomnia drug suvorexant. Nature 519:247–250

Zeke A, Lukács M, Lim WA, Reményi A (2009) Scaffolds: interaction platforms for cellular signalling circuits. Trends Cell Biol 19:364–374

Zhan X, Stoy H, Kaoud TS, Perry NA, Chen Q, Perez A, Els-Heindl S, Slagis JV, Iverson TM, Beck-Sickinger AG, Gurevich EV, Dalby KN, Gurevich VV (2016) Peptide mini-scaffold facilitates JNK3 activation in cells. Sci Rep 6:21025