Arrestins as signaling modulators: the plot thickens. Focus on “Arrestins 2 and 3 differentially regulate ET\textsubscript{A} and P2Y\textsubscript{2} receptor-mediated cell signaling and migration in arterial smooth muscle”

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ARRESTINS ARE PROTEINS THAT bind to G protein-coupled receptors (GPCRs) to affect their functions. There are four mammalian arrestins, which are cytosolic proteins that undergo a global conformational change upon binding to a GPCR. The nomenclature for arrestin subtypes is as follows, with common alternative names in parentheses: arrestin-1 (visual arrestin), arrestin-2 (β-arrestin-1), arrestin-3 (β-arrestin-2), and arrestin-4 (cone arrestin). Arrestins were initially discovered on the basis of their roles in ligand-induced desensitization of GPCRs. Agonist-bound GPCRs are selectively phosphorylated by members of the G protein receptor kinase (GRK) family of kinases, thereby creating binding sites for arrestins. The arrestin-bound GPCR is unable to couple to its G proteins, resulting in desensitization. However, work performed in the past few years has gradually illuminated the multifunctionality of arrestins as scaffolding proteins in cell signaling, as discussed below.

The article in this issue by Morris and colleagues (6) provides an excellent example of how our knowledge of the role of arrestins is evolving. Morris and coworkers first show that two different arrestin subtypes (arrestin-2 and arrestin-3) have differential effects in regulating desensitization of two different GPCRs (P2Y\textsubscript{2} purinergic and ET\textsubscript{A} endothelin receptors) in a single cell type (primary rat aortic smooth muscle cells). The authors then go on to show that the two arrestins have different effects on agonist-mediated cell migration, in ways distinct from their effects on desensitization. The authors also addressed the role of GRKs in pathways that lead to vascular remodeling, showing that GRK2 is critical for cell migration. Taken together, the results nicely illustrate yet another rapidly emerging level of complexity in cell physiology.

The specificity of different GPCRs for different arrestins has previously been demonstrated in several model systems. In 2008, Hoffmann and coworkers (2) showed that different P2Y receptor subtypes interact preferentially with different arrestins. In another example, Li and colleagues (3) demonstrated that arrestin-2 regulates protease-activating receptor 4 (PAR4)-induced responses in platelets, but not responses to ADP alone. In a more general way that relates to cellular regulation, the role of arrestins has provided a molecular explanation for “ligand-directed” or “biased” signaling, as recently reviewed. The differential recruitment of arrestins to GPCRs in response to receptor occupation by different ligands is responsible for some of the differential cellular effects of these ligands. This phenomenon is important with respect to understanding the action of drugs that target the cardiovascular system and particularly the heart (1). Advances in our understanding of the roles of arrestins and GRKs is anticipated to improve the therapeutic profile of existing classes of pharmacologic agents, as well as to provide new targets for therapeutic intervention by novel agents. Thus, the fact that Morris and colleagues examined the roles of arrestins in vascular smooth muscle, with an emphasis on mechanisms of vascular remodeling, is complementary to work done on the heart, and lends itself to future translational approaches toward improved therapy of cardiovascular disease.

The ability of arrestins to act as scaffolding proteins for signal transduction, independent of their effects on receptor desensitization, was recently reviewed (4). These types of effects are termed “G protein-independent” because arrestin-GPCR complexes are generally dependent on ligand-induced GPCR activation but are independent of G proteins and are relatively stable. The GPCR-bound arrestin functions as a scaffold in that it is able to recruit various catalytically active proteins to the complex. In this respect, arrestins are conceptually analogous to the Src homology-2 (SH2) domain-containing proteins that bind to activated receptor tyrosine kinases. Proteins that are recruited by arrestins include Src family tyrosine kinases, phosphodiesterases, phosphatases, and components of MAPK cascades. Importantly, the epithelial growth factor receptor (EGFR) can be transactivated via GPCR-arrestins. The assembly of the GPCR-arrestin-enzyme complex in a discrete location is envisioned to modulate signaling in a...
spatial manner and is thus part of a theme in the current literature on signal transduction. The study by Morris and colleagues placed particular emphasis on arrestin-mediated activation of p38 and ERK MAPK pathways, since these are known to be important for vascular remodeling. G protein-dependent and -independent pathways for arrestin function are depicted in Fig. 1.

A particularly tantalizing aspect of the arrestin saga concerns the abilities of these proteins to regulate cytoskeletal function by serving as protein scaffolds (7). The first mechanism involves arrestin-mediated recruitment of cofilin. Actin filaments are severed by cofilin, at the leading edge of the cell, in a manner that promotes cell migration. A second mechanism is that arrestins can regulate the function of the small GTPases RhoA and RalA, which are important for cytoskeletal reorganization and cell migration. A third way in which arrestins can regulate migration is by sequestering the MAPKs ERK1/2 to the leading edge of cells. Consistent with this emerging story line, the study by Morris and colleagues exemplifies how arrestins can differentially regulate cell migration in vascular smooth muscle cells. The authors also demonstrate an essential role for GRK2 in migration; again there are several mechanisms that may be responsible. The roles of arrestins and GRKs in cell migration were a focal point here because vascular remodeling requires migration of arterial smooth muscle cells.

The physiological roles of arrestins continue to expand in interesting ways. The roles of arrestins in cardiac function and pathology have been reviewed by Tilley (8). Elegant evidence has been provided to indicate that arrestin-mediated EGFR transactivation is beneficial in the heart, in that this pathway suppresses cardiac hypertrophy and is thus protective against heart failure. Morris and coworkers address the role of GPCRs in vascular hypertrophy and hypertension, which is a novel emphasis. The authors are judiciously cautious in their discussion of whether arrestins are beneficial or harmful, overall, in the cellular events underlying hypertension. Further analysis of the roles of arrestins and GRK in vascular remodeling, and the mechanisms involved, is clearly warranted.

With respect to another aspect of cell physiology, β-arrestin-1 knockout in mice was recently shown to increase obesity and decrease insulin sensitivity (9). This clearly makes β-arrestin-1 a “good guy” for most of us. Stay tuned for the next installments in this fast-paced field!

DISCLOSURES

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REFERENCES