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Preface: Changing Paradigms for G-Protein–Coupled Receptor Signaling

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G-protein–coupled receptors (GPCRs) are a large family of cell surface receptors that are activated by extracellular stimulus or a ligand leading to conformational change transducing the signal into the cell. Conformational change in the GPCR activates heterotrimeric G-protein that couples to a plethora of downstream signaling effectors generating secondary messengers and a cognate response. Termination of signal is mediated by phosphorylation of activated GPCRs by GPCR kinases (GRKs), protein kinase A (PKA), and protein kinase C (PKC) followed by β -arrestin binding that interdicts and inhibits effector signaling. This represents the classical paradigm of GPCR signaling and desensitization. However, increasing evidence shows that the diverse set of signals generated by GPCRs cannot be explained within the context of canonical signaling pathway suggesting mechanisms beyond the classical paradigm. Given that noncanonical signaling pathways may become significant players in various conditions, it is critical to understand the mechanistic underpinnings as they may not fit the traditional paradigm. In recognition of the changing conceptual understanding of GPCR activation and signaling, this review series titled “Changing paradigms for GPCR signaling” brings together a compendium of articles appreciating the noncanonical signaling mechanisms that could play key roles in determining GPCR responses in physiology and pathology. The review articles in this series are based thematically on transactivation mechanisms and their impact on cardiac function, cross-talk between diverse receptor pathways that titrates GPCR responses, and finally unappreciated roles for GRKs and β -arrestin in mediating novel signals in addition to their classical role in terminating signals emanating from activated GPCRs.

Apart from the classical activation of G-proteins after ligand binding, GPCRs are able to recruit epidermal growth factor receptor (EGFR) as a downstream signaling partner in mediating signals. This phenomenon of co-opting and activating a receptor tyrosine kinase for enhancing downstream signals after GPCR stimulation represents transactivation. Increasing evidence shows that transactivation of EGFR can be mediated by many GPCRs, indicating that this mechanism could be integral in providing diversity to downstream signaling. Although studies show that transactivation could play a beneficial role in cardiac hypertrophic responses, more studies are required to detail the effects of EGFR activation. In this context, the review by Grisanti et al, on “Cardiac-GPCR-mediated EGFR transactivation: Impact and therapeutic implications” provides an in-depth discussion on the current understanding of EGFR transactivation with a focus on angiotensin II, urotensin II,

and β -adrenergic receptors systems. This in-depth article is followed by a comprehensive review on the mechanistic underpinnings on transactivation process. A quintessential step in the process of transactivation involves generation of the agonist to activate receptor tyrosine kinase after GPCR stimulation. A key step involves activation of extracellular proteases that cleave and release agonists for transactivation. The review by Schafer and Blaxall on “G protein coupled receptor-mediated transactivation of extracellular proteases” discusses the activation of extracellular proteases such as A Disintegrin and Metalloproteases and matrix metalloproteinases after GPCR stimulation. Studies show that activation of extracellular proteases provides for increasing the diversity and reach of signals initiated after GPCR stimulation including activation of EGFRs, transforming growth factor β receptor, or protease-activated receptors. These 2 reviews encompass insightful discussion on the activation of unique yet myriad of downstream signals in addition to canonically activated G-protein–dependent pathways.

Traditionally, it is believed that GPCR activation leads to termination of the signals by desensitization mediated by phosphorylation through kinases (GRKs, PKA, and PKC). GPCR phosphorylation (mediated by GRKs, PKA, and PKC) that occurs in response to its cognate agonist is termed as homologous desensitization, whereas heterologous desensitization happens by indiscriminate phosphorylation (mediated by PKA and PKC) of stimulated and unstimulated GPCRs. A quintessential component of this classical mechanism is the requirement of a GPCR agonist to modulate and/or predispose the response of other GPCRs to their ligands. However, in addition to these classical mechanisms of desensitization, proinflammatory cytokine-like tumor necrosis factor α (TNF α) is known to modulate function of beta-adrenergic receptor (β AR), a prototypical GPCR. Recent studies show that TNF α can directly mediate desensitization of β ARs through GRK2 even in the absence of β AR ligands. The mechanisms of this noncanonical desensitization and its implications are discussed indepth in the review “Pro-inflammatory cytokines mediate GPCR dysfunction” by Mohan et al. This kind of noncanonical regulation of GPCR function has significant clinical implications as proinflammatory cytokine TNF α is elevated in many comorbid conditions, including hypertension, diabetes, obesity, and dyslipidemia which are significant cardiovascular risk factors. Adding to this layer of noncanonical regulation of β ARs, recent studies have further shown that insulin receptor (a receptor tyrosine kinase) forms a complex with β 2AR and initiates β 2AR desensitization through both GRK and PKA. Discussion on the mechanistic underpinning is comprehensively covered in the review “Cross-talk between insulin signaling and GPCRs” by Fu et al. These noncanonical mechanisms that alter β AR signaling would directly impact cardiac function and its innate ability to respond to increasing demands with mechanical overload.

It is well known that ligand-bound GPCR is phosphorylated by GRKs, leading to recruitment of β -arrestin which physically interdicts further G-protein coupling resulting in receptor desensitization. Nonetheless, accumulating evidence has shown that GRKs apart from performing the coordinated role of phosphorylating the receptor can also noncanonically phosphorylate nonreceptor targets and regulate signaling mechanisms in a kinase-independent manner. The recognition that such noncanonical function of GRKs has critical implications in cardiac function is discussed in the review titled “Non-canonical

roles of GRKs in cardiovascular signaling” by Schumacher and Koch with a focus on GRK2 and GRK5 (which are members of the GRK family). Similar to GRKs, β -arrestin binding to phosphorylated GPCRs to mediate desensitization is considered its classical function but quickly additional roles for β -arrestin in endocytosis and endosomal signaling were identified. However, the most exciting nonclassical role identified for β -arrestin is its ability to activate new kinase-dependent signaling. Intense studies have to lead to the identification of β -arrestin-dependent G-protein-independent signaling from an activated GPCR which is considered to be beneficial compared with the G-protein-dependent signaling. In-depth discussion on this intriguing role of β -arrestin in mediating noncanonical G-protein-independent signaling is presented in the review by Jean-Charles et al, titled “GPCR signaling via β -arrestin-dependent mechanisms.”

Finally, I thank the authors for submitting such high-quality reviews that embrace the theme on “Changing Paradigms for GPCR Signaling.” A noteworthy aspect of these in-depth reviews is to showcase the idea that the cellular system uses the same set of classical molecules and yet can mediate noncanonical effects. Such effects are executed by simply altering the signaling network, thereby resulting in cellular responses beyond the framework of classical regulation. Our hope with this series is to highlight the yet, unappreciated aspects of GPCR signaling that may not fit the classical paradigm but could become the basis for future therapeutic strategies given that >30% of the current drugs target GPCRs.