G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) ion channels are transmembrane proteins involved in a vast range of biologic processes by mediating acute and adaptive cellular responses to diverse stimuli.1-3 GPCRs are ubiquitously expressed 7-transmembrane receptors that finely tune cellular functions by activating a heterotrimeric G protein-dependent cascade of acute (in seconds) and long-term signals (e.g., Gq-PLCβ-DAG-PKC and Gαs-AC-cAMP-PKA signaling pathways).1,4 In addition to activating G proteins, GPCRs also transduce extracellular signals by activating arrestin-mediated cell responses, such as hydrolysis of cAMP or kinase cascade signals known as the second wave of GPCR signaling (＞2–3 minutes).5,6 However, whether arrestin also contributes to acute GPCR function remains largely unknown. TRP channels are a superfamily of Ca2+-permeable cation nonselective channels that play critical roles in various sensory functions, such as thermosensation, mechanosensation, pain, itch, and chronic inflammatory sensation.2,7 TRP channels cannot only be directly activated by various chemical, mechanical and thermal stimuli, but also function as major effectors of GPCRs downstream of G protein-dependent signal transduction pathways.1-3,8 In this highlighted study, Liu and colleagues5 unexpectedly identified a new β-arrestin-1-mediated, G protein-independent, fast communication between GPCR and TRPC3, which substantially contributes to acute catecholamine secretion following AT1R activation.5

With the specific G protein or β-arrestin-1 biased AT1R agonists and knockout mice models, Liu et al.5 found that not only the Gq-PLCβ-mediated pathway but also β-arrestin-1-biased agonism are capable of stimulating acute catecholamine secretion from adrenal chromaffin cells. Surprisingly, unlike the notion that the activation of Gq-PLCβ mediates secretion through IP3R sensitive intracellular Ca2+ store, the β-arrestin-1-dependent mechanism is specifically and critically dependent on the extracellular Ca2+ influx through the plasma membrane. Liu et al.5 then screened a series of channel blockers and found that the AT1R-β-arrestin-1-mediated Ca2+ influx was through TRPC3 at the plasma membrane, which was confirmed by using the TRPC3−/−/TRPC6−/−/TRPC7−/− mice. The activation of TRP channels by GPCRs has been reported previously, but they are mainly dependent on G protein signal pathways, leading to changes in the membrane expression and/or activation threshold of TRP channels.1-3,5,7 The finding that AT1R-β-arrestin-1 specifically activates TRPC3 is interesting and totally different from the canonical Gq-PLCβ pathway that often shows a non-selective modulation of several distinct TRP channels.1,2 Since β-arrestin-1 may mediate coupling of AT1R and TRPC3 by a direct functional complex formation or through an indirect cascade signaling pathway, Liu et al.5 thus performed co-immunoprecipitations, bioluminescence resonance energy transfer experiments, and patch clamp recordings.
The results indicate that AT1R recruits β-arrestin-1 to the plasma membrane and promotes the formation of AT1R-β-arrestin-1-TRPC3 complex in a quick manner, thus leading to the direct opening of TRPC3 channels. A detailed structural-functional analysis revealed that β-arrestin-1 interacts with the TRPC3 C-terminal via its C-terminal region and interacts with the SH3 domain of PLCγ through its poly-proline P1 region. Upon activation, the simultaneous interaction of β-arrestin-1 with TRPC3 and PLCγ forms a scaffold to directly open TRPC3 channels, which then mediates extracellular Ca\(^{2+}\) influx and triggers catecholamine secretion. The direct activation of TRPC3 by AT1R-β-arrestin-1 is striking, because it may provide a novel synergistic function of GPCRs and TRP channels in acute cellular responses. In addition, β-arrestin-1 and TRPC3 activation also underlies the mAChR-mediated catecholamine secretion from chromaffin cells, indicating a general role of the GPCR-β-arrestin-1-TRPC3 in acute cellular responses to extracellular stimuli.

Taken together, Liu et al.\(^5\) revised the conventional thinking of how GPCRs regulate channel activities and in doing so shed light on the clinical treatment of heart failure. This work revealed that in addition to the classic G protein-TRP channel axis, β-arrestin-1 can also mediate acute physiologic responses via direct binding to and thus activating TRPC3 channels (Fig. 1). The newly identified AT1R-β-arrestin-1-TRPC3 mode of secretion should be a paradigm-shift work in the field of GPCR signaling and arrestin functions, and will have a broad implication in understanding cellular responses to environmental stimuli under both physiologic and pathological conditions.

**Disclosure of potential conflicts of interest**

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