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Activation at a distance：new paradigm of β−arrestin dependent pathways drive mitogen−activated protein kinase signaling

Rezon YANUAR and Akihiko TANIMURA

Division of Pharmacology, School of Dentistry, Health Sciences University of Hokkaido

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G protein−coupled receptors (GPCRs) are the largest and most diverse family of signaling protein in human genome, which regulates of many human physiologies such as pain perception, chemotaxis, cardiovascular action, metabolism, fluid secretion, etc. (Lefkowitz, 2000 ; Syrovatkina et al., 2016). It has been well known that the activation of GPCR triggers the interaction with G proteins to promote dissociation of the Gα−subunit and Gβγ−subunit from receptor and activate effector enzymes such as adenylate cyclase (AC) that converts ATP to cyclic AMP (cAMP) and phospholipase C which associated with intracellular Ca^{2+} release. In addition to these classical pathways, mitogen−activated protein kinases (MAPKs) are also known to be activated via GPCRs system through the recruitment of β−arrestin (βArr).

βArr was first identified as a molecule involved in the desensitization of GPCR. Later studies revealed that βArr has three functions : internalization of GPCR, desensitization of G protein−mediated signaling, and formation of scaffold to activate MAPK cascade (DeWire et al., 2007). The MAPKs are a family of serine/ threonine kinases that regulate cell functions including proliferation, gene expression, differentiation, cell survival, apoptosis, and secretion. Three major unit of MAPKs has been classified in mammalian cells, i.e., ERKs, JNKs, and p38 (Pearson et al., 2001). It became clear that βArr can activate ERK/MAPKs by scaffolding Src, Raf 1, MKK1, and ERK1/2 (Luttrell et al., 2001). Furthermore, the involvement of the epidermal growth factor receptor (EGFRs) can be functionally transactivated by GPCRs mediated via−βArr, also strongly contribute for ERK1/2 activation (Noma et al., 2007).

As the “key” of internalization, role of βArr has been elucidated. The activated βArr are recruited to accumulates in clathrin−coated structure (CCSs) through interaction with the β2 adaptin subunit of adaptor protein−2 (AP−2) which facilitate the clathrin−mediated endocytosis (CME) process (Laporte et al., 2000). In addition to this endocytosis−mediated activation of MAPKs, recent study revealed that βArr traffics to CCSs separately from its activating GPCR and promotes MAP kinase activation from CCSs before endocytic scission. The previous understanding is based on the principle that βArr operates in obligate physical complex with an activated GPCR and its signaling activity requires endocytosis of the formed complex (Fig. 1A). The new aspect is called ’activation at a distance’ (Fig. 1B), where βArr traffics to CCSs separately from its activating GPCR and promotes MAP kinase activation from CCSs before endocytic scission (Eichel et al., 2016).

Eichel at al., reported difference behavior of β1− and β2−adrenergic receptor (β1−, β2−AR) during the agonist−induced activation of ERK1/2 using the total internal reflection fluorescence microscopy (TIR−FM). It was demonstrated that βArr was robustly recruited and colonized with clathrin, while β1−ARs are remained distributed in the plasma membrane even after the activation. Addition of CGP20712A, a highly selective β1−AR antagonist blocks the recruitment of βArr to CCSs, suggesting that the ability of β1−AR to promote trafficking of βArr to CCSs without moving receptors themselves. It was also shown that while βArr−2 extensively overlapped with plasma membrane CCSs, there was no detectable recruitment of Golgi elements or endosomes appear (Eichel et al., 2016). Moreover, the addition of dynamin−dependent endocytic routes blocker, Dyngo−4a, did not inhibit β1−AR−elicit ERK1/2 activation (Eichel et al., 2016). Together, these results showed a new aspect of βArr mechanism, that βArr could traffic to CCSs separately from its activating GPCR and promotes MAPKs

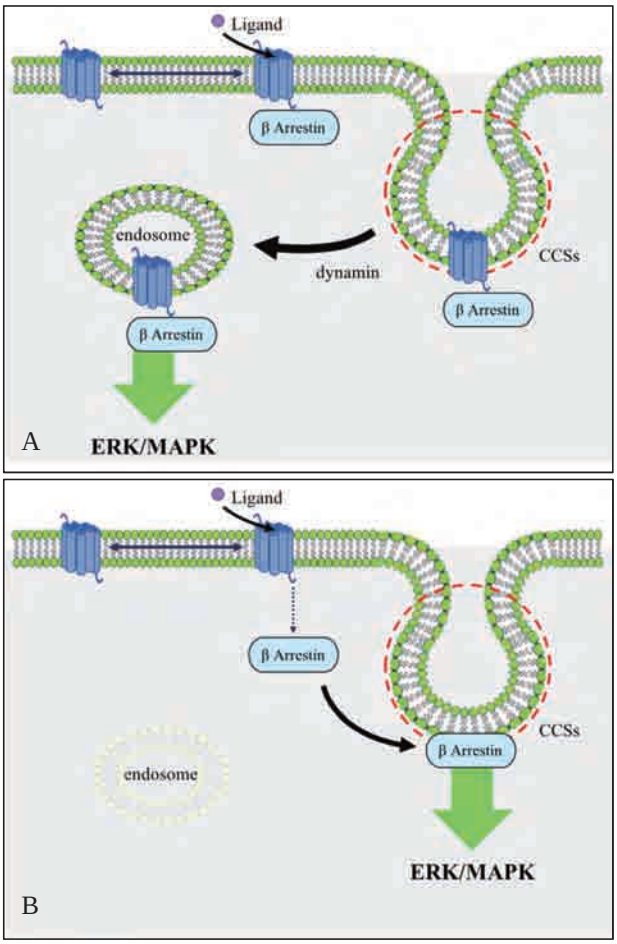

Figure 1. A schematic illustration of β−arrestin (βArr) function, based on the classical βArr activation (A) and the new aspect is called 'activation at a distance' (B).
(A) An activation of receptor by a ligand induces the recruitment of βArr to clathrin coated structures (CCSs), as well of the activated receptor. The complex of GPCR−βArr−CCSs could operates to promotes ERK/MAPKs activation and its signaling activity requires endocytosis.
(B) An activation of receptor by a ligand induces the recruitment of βArr to clathrin coated structures (CCSs), without colocalization of the activated receptor. The complex of βArr−CCSs could operates to promotes ERK/MAPKs activation.

activation before the endocytic process.

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