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Muscarinic receptors belong to G protein−coupled receptor (GPCR) class and consist of five subtypes (M_1−M_5) (Pronin et al., 2017). Activations of M_1 and M_3 receptors have been known to induces Gq protein (G_q)−mediated activation of phospholipase C_β (PLC_β), leading to hydrolysis phosphatidylinositol 4,5−bisphosphate (PIP_2) to inositol 1,4,5−triphosphate (IP_3) and diacylglycerol (DAG). IP_3 then activates IP_3 receptors in the endoplasmic reticulum to evokes Ca^{2+} mobilization (Lin et al., 2008). Agonists of muscarinic receptor pilocarpine (Pilo) and carbachol (CCh) have been known to activate salivary secretions through the activation of G_q−mediated Ca^{2+} mobilization.

It has also been reported that muscarinic receptor agonists induced phosphorylation of ERK (pERK) (Lin et al., 2008 ; Pronin et al., 2017). In 2008, Lin et al demonstrates that CCh−induced pERK was attenuated by the prolonged PMA−treatment. On the other hand, Pilo−induced pERK was PMA−insensitive and was inhibited by Src inhibitor (PP2) and EGFR inhibitor (AG−1478). These results indicate that the CCh− and Pilo−induced pERK was mediated by PKC and Src−mediated transactivation of EGFR (Src−EGFR pathway), respectively. An involvement of $G_{\beta\gamma}$ in the Pilo−mediated Src activation has been speculated in this paper (Lin et al., 2008). Recently, Pronin et al. also reported similar Src−dependent pERK by Pilo (Pronin et al., 2017). Unlike the previous paper by Lin et al, this paper suggests an involvement of β−arrestin (βA) on the Src−EGFR pathway.

βA has been known to attenuate G protein signaling by the receptor desensitization. Recent findings for the involvement of βA in the activation of G protein−independent pathways, such as the MAP kinase pathway (MAPK), have attracted attention. One of βA signaling functions is scaffolding of MAPK cascades. βA also known to induce G protein−independent pERK through the activation of Src (Azzi et al., 2003). These current knowledges support the involvement of βA on the Pilo−induced transactivation of EGFR.

As indicated above, GPCR signaling is bimodal, the G protein−mediated and the βA−mediated pathways. Pronin et al. demonstrated that Pilo−induced pERK was almost completely eliminated by PP2. In contrast, more than 55% oxotremorine−M−induced pERK was still occurred even in the presence of the saturating concentration PP2, and the remaining pERK was completely blocked by PKC inhibitors (Pronin et al., 2017). These results suggest that Pilo act as bias agonist, an agonist selectively stimulates either G protein or βA pathway.

It has been known that MAPK/ERK regulate many critical signaling pathways such as cell proliferation, differentiation, apoptosis. However, functions of muscarinic receptor−mediated MAPK/ERK pathways in salivary cell are yet to clearly defined. Recently, Minagi et al. reported long−term administration of Pilo showed upregulation of M_3 receptor expression (Minagi et al., 2018). It is possible that Pilo−activated MAPK/ERK play a role in the upregulation of M_3 receptor, and this idea needs to explored.

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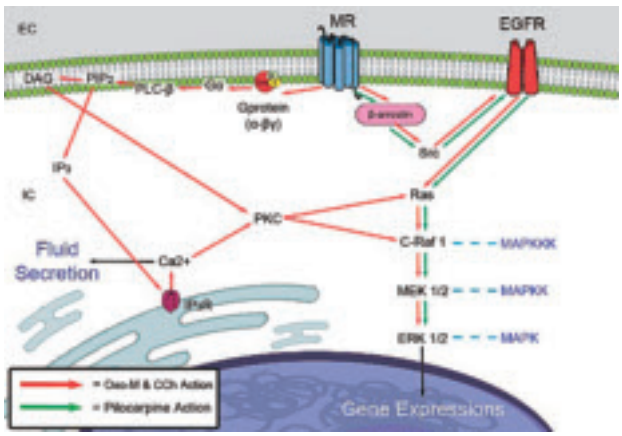

Figure 1. Schematic illustration of signaling pathways involved in Pilo−, Oxo−M−, and CCh−induced activation of MAPK/ERK pathway.