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Cross-talk of PGD_2 receptors: the DP receptor modulates signaling and trafficking of CRTH2

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Background

Prostaglandin (PG) D_2 is substantially involved in allergic inflammation and signals via the seven transmembrane (7TM) spanning/G protein-coupled receptors (GPCRs) chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) and D-type prostanoid (DP) receptor. Both receptors are co-expressed in eosinophils among other immune cells and have emerged as therapeutic targets in allergic diseases. While a proinflammatory function of the CRTH2 receptor is well recognized, the role of the DP receptor in allergic inflammation, however, remains unclear. As it has been shown for many other 7TM/GPCRs, we believe that intermolecular cross-talk occurs between CRTH2 and DP receptors which might be essential for receptor function and regulation.

Material and methods

Intracellular Ca^{2+} release in HEK293 cells stably expressing CRTH2 (HEK-CRTH2), DP (HEK-DP) or both receptors (HEK-CRTH2+DP) was examined by Fluid Excitation (FLEX). Ca^{2+} flux in human eosinophils was measured by FLEX and flow cytometry. Agonist-induced receptor internalization was determined by confocal imaging and flow cytometry. Receptor interaction studies were performed by co-immunoprecipitation.

Results

The DP receptor is dominantly involved in mediating Ca^{2+} mobilization following CRTH2 activation. Agonist-induced DP receptor desensitization, which is a rapid mechanism to shut down cellular responses, also blocked CRTH2 signaling. Binding of the DP antagonist to its receptor abolished the cross-activation of the DP receptor by CRTH2. Co-immunoprecipitation studies revealed the formation of CRTH2/DP heteromers which might explain the pharmacological interaction between CRTH2 and DP receptors.

Conclusions

For the first time we show that the DP receptor seems to function as an interface molecule which translates the activation of the CRTH2 receptor to intracellular signal transduction pathways.

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