

MEETING ABSTRACT

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The D-type prostanoid (DP) receptor enhances the signaling of chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2)

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Background

Prostaglandin (PG) D₂ is substantially involved in allergic responses and signals via the seven-transmembrane-spanning/G protein-coupled receptors, chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) and D-type prostanoid (DP) receptor. While the proinflammatory function of CRTH2 is well recognized and CRTH2 is hence considered as an important emerging pharmacotherapeutic target, the role of the DP receptor in mediating the biological effects of PGD₂ in allergic inflammation has remained unclear.

Methods

The cross-talk of CRTH2 and DP receptors was investigated using both a recombinant HEK293 cell model and human eosinophils in Ca²⁺ mobilization assays, co-immunoprecipitation and radioligand binding assays.

Results

We show that CRTH2 and DP receptors modulate each other's signalling properties and form CRTH2/DP heteromers without altering their ligand-binding capacities. We find that the DP receptor amplifies the CRTH2-induced Ca²⁺ release from intracellular stores and, coincidentally, forfeits its own signalling potency. Moreover, desensitization or pharmacological blockade of the DP receptor hinders CRTH2-mediated signal transduction. Pharmacological blockade of G $\alpha_{q/11}$ proteins abolishes the Ca²⁺ response to both CRTH2 and DP agonists,

while inhibition of G α_i proteins selectively attenuates the CRTH2-mediated response but not the DP signal.

Conclusions

Our data demonstrate the capacity of DP receptors to amplify the biological response to CRTH2 activation. Therefore, the CRTH2/DP heteromer may not only represent a functional signalling unit for PGD₂ but also a potential target for development of heteromer-directed therapies to treat allergic diseases.

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