Stimulation and modulation of inflammatory mast cell responses by prostaglandin receptors

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Prostaglandins (PGs) play roles in various types of inflammatory diseases by exerting their pro-inflammatory actions. Particularly, PGE₂ has been reported to work as one of the pro-inflammatory mediators during the pathological processes in various peripheral tissues. The actions of PGE₂ are mediated by four PGE receptor subtypes, EP1, EP2, EP3, and EP4: EP1 receptor is coupled to intracellular Ca²⁺ mobilization, EP2 and EP4 are coupled to stimulation of adenylate cyclase, and EP3 is coupled mainly to inhibition of adenylate cyclase. Both pharmacological and genetic analyses have clarified which EP subtype are involved in each of PGE₂ actions (Narumiya S, Sugimoto Y, et al. Physiol. Rev. 79: 1193, 1999; Sugimoto Y, and Narumiya S. J. Biol. Chem. 282: 11613, 2007). For instance, EP3 receptor is involved in inflammation-associated fever generation, and EP1 is involved in thermal hyperalgesia. However, until recently, it was unknown which EP subtypes mediates PGE₂-induced inflammatory response, such as enhancement of vasopermeability, edema formation and leukocyte infiltration. In order to clarify these points, we employed arachidonate-induced and PGE₂-elicited dermatitis models and examined the effect of each EP gene disruption on this model. Finally, we uncovered that PGE₂-EP3 signaling triggers acute inflammatory responses by mast cell activation in the skin (Morimoto K, Shirata N, et al. J. Immunol. 192: 1130, 2014). In addition to the roles of PGE₂-EP3 signaling in mast cell activation, we would like to discuss on potential roles of PGI₂ in the modulation of inflammatory mast cell responses.