Prostaglandins in chronic Inflammation; A new role revealed by receptor KO mice

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Abstract

Chronic inflammation is the basis of various chronic diseases including cancer and vascular diseases. Chronic inflammation is not a recurrent or protracted form of acute inflammation but is characterized by specific features such as infiltration of mononuclear cells, immune responses and tissue remodeling. Prostaglandins (PGs) such as PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and TXA_2 are well established as mediators of acute inflammation. They are synthesized and released in response to various, often noxious, stimuli, and exert their functions by acting on their cognate receptors expressed on the surface of neighboring cells. There are a family of eight types and subtypes of receptors for PGs, including PGD receptor (DP), EP1, EP2, EP3 and EP4 subtypes of PGE receptor, PGF receptor (FP), PGI receptor (IP) and TXA receptor (TP). We cloned cDNAs for these receptor, generated KO mice deficient in individual receptor, and examined their pathophysiological functions. These studies have not only clarified molecular mechanisms of PG-mediated acute inflammatory responses such as fever generation and pain sensitization but also have revealed that PGs collaborate with various cytokines, chemokines, and growth factors, and function in transition to and maintenance of chronic inflammation. In some cases, PGs form a positive feedback loop with other inflammatory mediators to amplify the inflammatory processes. For example, in collagen-induced arthritis, PGI_2-IP signaling collaborates with IL-1β in synoviocytes, and promotes inflammation by amplifying expression of various molecules including IL-6 and RANKL. PGs function also as a link to immune inflammation. In experimental allergic encephalomyelitis, PGE_2-EP2/4 signaling promotes inflammation by facilitating Th1 differentiation and Th17 expansion. In these circumstances, PGs amplify the action of cytokines by enhancing expression of their receptors, and thereby function as cytokine sensitizer. As for tissue remodeling, in bleomycin-induced lung fibrosis model, $PGF_{2\alpha}$ acts on lung fibroblasts independently of TGF-β, and promotes fibrosis by inducing expression of a set of fibrosis-associated genes including collagen. Thus, PGs function not only as mediators of acute inflammation but also appear to play an important role in chronic inflammation.