Revisiting prostacyclin: new directions in pulmonary fibrosis and inflammation

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The study by Kern Lovgren et al., the current article in focus (Ref. 6, see p. L144 in this issue), provides an insight into important functions for an underappreciated ligand-receptor pair, prostacyclin (PGI2) and its receptor (IP) in the complex environment of inflammation and fibrosis. In endothelial cells, PGI2 is synthesized by the sequential action of cyclooxygenase-2 (COX-2) and a single membrane-bound enzyme, prostacyclin synthase. When PGI2 is released from cells it acts on IP to transduce its effects. The role of PGI2 has been traditionally associated with cardiovascular disease, where a balancing act between endothelial cell-derived PGI2 and platelet-derived thromboxane competes to regulate platelet aggregation on endothelial cells. Recent studies are now shedding light on a much more complex role for PGI2 in regulating inflammation and fibroblast proliferation, and they also emphasize a role for the position of eicosanoids in the fibrotic process.

Idiopathic pulmonary fibrosis (IPF) is a progressive disease of unknown etiology that leads to death in the absence of lung transplantation. Due to progressive fibrosis, the lungs cannot effectively exchange gas and lose dynamic compliance. Previous studies have emphasized the role of prostaglandin E2 (PGE2) as a downregulatory molecule that is protective for the pathology of IPF and in the pathobiology of fibrosis (5, 7–10, 12). PGE2 was synthesized at significantly lower levels in the fibroblasts of patients with IPF compared with fibroblasts isolated from patients with lung cancer. In addition, the induction of COX-2 was defective in fibroblasts from IPF patients (12). The observation that COX-2 knockout mice were protected from bleomycin-induced fibrosis (1) supported this concept, or so it seemed. The current study reemphasizes the role of PGI2, rather than PGE2, as an antiproliferative molecule in the setting of bleomycin-induced pulmonary fibrosis. The different conclusions between these two studies may be explained by the difference in experimental approaches. Using the bleomycin model of pulmonary fibrosis in mice, Kern Lovgren and coworkers (6) confirmed that COX-2-deficient mice showed clear protection against pulmonary fibrosis. On the basis of the studies of the role of PGE2 in the regulation of fibroblasts, they set out to test this hypothesis in vivo. Surprisingly, when they used knockout mice for the biosynthetic enzyme that synthesizes PGE2 (microsomal prostaglandin E2 synthase 1) to eliminate pulmonary PGE2 synthesis, they found that neither a change in pulmonary fibrosis nor a decrease in lung function was detected, even though the bleomycin-induced increase in pulmonary PGE2 formation was eliminated. These results imply that PGE2 was not the protective prostanooid in this model. PGE2 mediates its actions via a series of receptors (EPs), and this has been correlated with the responses of fibroblasts to PGE2 in pulmonary fibrosis (9, 10).

To confirm that PGE2 was not a mediator of pulmonary fibrosis in this model, the investigators probed the induction of pulmonary fibrosis in knockouts for the relevant EP2 and EP4 receptors. In these mice, there was no change in the response to bleomycin compared with wild-type controls, eliminating PGE2 as playing a significant protective role in bleomycin-induced pulmonary fibrosis. Because PGI2 has a single receptor, the use of IP knockout mice provides a definitive role for PGI2 and establishes a new paradigm for antiproliferative COX-2-derived eicosanoids in pulmonary fibrosis, shifting the emphasis from PGE2 to PGI2 in controlling lung fibrosis and proliferation.

Does PGE2 play a role in the biology of pulmonary fibrosis and IPF? The answer is we don’t know. Although the data from the Koller laboratory have the distinct advantage that it was generated in vivo, the model of bleomycin-induced pulmonary fibrosis is a response to injury induced by the addition of specific chemical agent. The human disease, although of unknown etiology, will possess different and common pathobiological features with the bleomycin model. Thus, although PGE2 does not play a role in the bleomycin model of pulmonary fibrosis, it is reasonable to suspect that it may play an important role in the human disease.

The work by Kern Lovgren and coworkers leads the way to potential novel strategies for therapeutic approaches to treatment of IPF. PGI2 analogs have successfully been used in the treatment of pulmonary arterial hypertension (e.g., Refs. 2, 3). Because these compounds are already in clinical use, there are now grounds for proposing the use of these compounds in trials for treatment of IPF.

The role of PGI2 in inflammation, though, is not one-sided. Recent studies by Honda et al. (4) have shown that IP−/− mice actually demonstrated an improvement in the severity of collagen-induced arthritis compared with controls. In fact, a PGI2 analog induced IL-6 in synovial fibroblasts, and wild-type mice showed increased levels of IL-6 in the inflamed joint during the progression of arthritis. Why PGI2 mediates an overall proinflammatory response in one setting and plays a counterinflammatory role in another is a critical question in understanding the biology of this molecule. Possibilities include the different strains of mice in which these experiments were performed, the differential coupling of IP in different tissues, and finally, the different cells that are critical within each model. These two series of experiments emphasize the importance of probing the differential functions of receptor-ligand pairs in vivo within different settings.

The current study by Kern Lovgren and coworkers also takes a novel approach to evaluating the bleomycin-induced model of fibrosis. This is the alteration of two critical parameters of airway function, static compliance and tissue elastance. Because decreases in these parameters are critical components of human IPF and are evidence of the severity of the disease,
measuring them in mice provides the first study linking pathology and airway dysfunction.

Finally, how should we think of eicosanoids in fibrosis and inflammation? Perhaps the best way is as a biochemical rheostat. In the model of bleomycin-induced fibrosis, eicosanoids by themselves cannot initiate a proliferative response in fibroblasts or the deposition of extracellular matrix. In the case of collagen-induced arthritis, eicosanoids cannot initiate joint inflammation and destruction. However, depending on the specific eicosanoid and receptor pair, these molecules can provide a powerful amplification or dampening mechanism. In the case of bleomycin-induced pulmonary fibrosis, the leukotrienes (11) may function as an amplifier of the process, whereas PGI2 may function as a dampener. Because of these properties, eicosanoids remain important therapeutic targets in multiple inflammatory settings.

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