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Prostaglandin E_2 and Polyenylphosphatidylcholine: Stiff Competition for the Fibrotic Complications of Inflammatory Bowel Disease?

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Although considerable progress has been made in the treatment of inflammatory bowel disease (IBD), more than 75 % of patients with Crohn's disease still require surgery at least once in their lifetime, usually for strictures and bowel obstruction. These often reflect intestinal fibrosis, a common histopathologic feature of IBD [1]. Although intestinal fibrosis is traditionally considered a consequence of excessive chronic inflammation, treatment with anti-tumor necrosis factor-α and other immunomodulatory drugs, which effectively ameliorate bowel inflammation, has unfortunately done little to curb the incidence of fibrotic complications. This observation has motivated investigators to reconsider the mechanisms that lead to intestinal fibrosis in an effort to identify alternative therapeutic approaches [2]. In this issue of *Digestive Diseases and Sciences*, Baird et al. [3] report on the anti-fibrotic potential of prostaglandin E_2 (PGE_2) and polyenylphosphatidylcholine (PPC).

The initial glimmer of our current recognition that PGE_2 is critical to the homeostasis of the gastrointestinal (GI) tract dates to 1938, when acetylsalicylic acid, or aspirin, was first reported to cause gastric hemorrhage [4], which in 1955 was attributed to its potential to promote erosive gastritis [5]. The roots of our mechanistic understanding for these observations derive from two Nobel Prize-winning discoveries, namely the purification and structural characterization of prostaglandins by Sune Bergström and Bengt Samuelsson, and the subsequent discovery by John Vane that aspirin inhibited the enzymatic production of prostaglandins. Today, it is recognized that abundant production of PGE_2 by the constitutively active cyclooxygenase-1 in gastric epithelial cells is critical to their protection from a harsh acidic environment. It is now appreciated that PGE_2 promotes epithelial integrity in other parts of the GI tract and indeed in other organs. That PGE_2 protects against epithelial injury is evident from its anti-apoptotic effects in a mouse model of radiation colitis [6]. Although PGE_2 is classically thought of as a pro-inflammatory molecule, this reputation largely reflects its actions on the microvasculature, but—interestingly—its effects on leukocytes are predominantly suppressive, as exemplified by its contribution to immune tolerance in the gut [7]. The increased risk of Crohn's disease associated with the use of aspirin and other NSAIDs [8] may therefore be explained by the loss of both the anti-inflammatory and epithelial-protective actions of PGE_2.

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Returning to the challenge of curbing fibrotic responses, significant data—mostly from studies of the lung, liver, kidney, and skin—support the hypothesis that PGE_2 exerts anti-fibrotic effects independently of its anti-inflammatory and epithelial-protective actions. This reflects that PGE_2 can also inhibit nearly all aspects of fibroblast activation via its ability to increase intracellular cyclic AMP [9]; in vivo administration of PGE_2 can prevent lung fibrosis in mouse models [10]. The paper by Baird and colleagues reports for the first time that exogenous administration of PGE_2 ameliorated intestinal fibrosis in the commonly employed 2,4,6-trinitrobenzene sulfonic acid (TNBS) murine model. The authors also examined the effects of PGE_2 on intestinal fibroblasts in vitro, and like fibroblasts from other organs, PGE_2 directly inhibited fibroblast proliferation and collagen production. Since in this in vivo study PGE_2 was co-administered with TNBS, it inhibited intestinal inflammation as well. This experimental design, therefore, fails to distinguish whether PGE_2 is capable of actually reversing preexisting intestinal fibrosis or whether it merely limits the inflammatory damage that culminates in fibrosis. As noted earlier, an independent anti-fibrotic effect is essential if we are to argue that PGE_2 is superior to existing immunomodulatory drugs used to treat IBD. Although its recognized direct inhibitory effects on fibroblast functions would predict that this would be the case, a proof-of-principle experiment would require its administration later in the disease model when intestinal fibrosis is already established.

What about PPC? PPC is a mixture of polyunsaturated phosphatidylcholine (PC) molecules derived from plant-based extracts that has primarily been used for the treatment of liver disease [11]. PC, an essential component of the lipid membrane bilayers of all cells, contributes to the integrity of the mucosal barrier of epithelial cells, including those lining the GI tract. The observation that mucosal PC content is diminished in patients with IBD [12] prompted early-stage clinical trials that suggest that exogenous PPC is potentially beneficial for IBD patients [13]. Baird and colleagues reported that PPC inhibited intestinal inflammation and fibrosis elicited by TNBS to the same degree as did PGE_2, consistent with prior reports of the inhibitory effects of PPC on alcohol-induced cirrhosis in vivo [11] and on collagen synthesis by hepatic stellate fibroblast-like cells in vitro [14]. The parallel actions of PPC and PGE_2 led to the hypothesis that the actions of PPC may be mediated by PGE_2, which was not supported by the observation that colonic tissue concentrations of PGE_2 did not increase with systemic administration of PPC. A more rigorous approach to this question might be to test whether the protective actions of PPC are abolished either by pharmacologic or genetic inhibition of PGE_2 biosynthesis or by antagonism or deletion of its receptors. It is alternatively possible that PPC could initiate the production of other anti-inflammatory, anti-fibrotic eicosanoids that increase intracellular cyclic AMP (e.g., prostaglandin D_2 or I_2) that the authors did not measure. As was noted above for PGE_2, addressing the question of whether PPC can attenuate intestinal fibrosis in this model independent of its effects on inflammation is also worthy of future study. Certainly, this work provides justification for additional exploration of PPC as potential therapy in IBD.

While acknowledging the promise of PGE_2 and PPC in treating intestinal fibrosis, questions and challenges still remain. In the study by Baird and colleagues, PGE_2 was administered orally, which brings to mind an oral analog of PGE_2, misoprostol (Cytotec®), which has long been available to protect the stomach from NSAID-induced injury but whose use is

notably limited by accompanying diarrhea. A potential strategy to circumvent this limitation would be to take advantage of the functional specificity mediated by individual receptors for PGE_2. There are four such E prostanoid receptors, termed EP1–EP4, with differing cellular distribution and signal transduction mechanisms; only EP2 and EP4 signal via increased cyclic AMP. Increases in intestinal motility are mediated by EP1 and EP3 [15], whereas a selective EP4 agonist protects against colitis manifestations in a mouse model while enhancing epithelial survival and regeneration [16]. Selective agonists of EP2 and/or EP4 may thus offer the promise of anti-inflammatory, epithelial-protective, and anti-fibrotic actions—ideal for IBD—without the unwanted side effects inherent to PGE_2 itself or its receptor-nonselective analogs like misoprostol. One further possible challenge that might be anticipated is resistance to the beneficial effects of PGE_2, as has been identified in other fibrotic disorders [17]. Finally, we would be remiss if we failed to acknowledge the well-recognized ability of PGE_2 to promote tumorigenesis in the colon [18] and elsewhere—an important issue for IBD patients. It appears that several EP receptors may contribute to tumorigenesis at different stages of the disease. Therefore, a better understanding of whether and how the potential benefits of selective EP agonists can be harnessed without promoting tumor formation would be essential going forward. The question of whether PPC promotes tumorigenesis in this setting would also be important to answer. The promising results that Baird and colleagues present in this issue suggest that the answers to these questions are worth pursuing.

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