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Current trends in PGE2 targeting for anti-inflammatory therapy.

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Prostaglandin E2 (PGE2) is an eicosanoid lipid mediator that significantly participates in the pathogenesis of many inflammatory diseases. PGE2 is produced when arachidonic acid is released from the plasma membrane by phospholipases and metabolized by two cyclooxygenases (COX-1 and COX-2) and three specific isomerases, mPGES-1, mPGES-2, and cPGES. The most widely used nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetaminophen, ibuprofen, celecoxib, have proven efficacy in the treatment of inflammation, pain and fever by blocking COX activity and thus reducing the generation of PGE2 in injured tissues and the central nervous system [1,2]. However, due to the coincident depression of gastrointestinal homeostatic efficiency of PGE2 and thromboxin A2 (TxA2), and the inhibition of the cardiovascular protective effects of prostacyclin (PGI2), these drugs cause serious gastrointestinal and cardiovascular adverse events, such as ulcer, GI bleeding, myocardial infarction and heart failure [3]. Thus, pathway elements downstream of the COX enzymes in the biosynthetic-response of PGE2, the terminal synthases and receptors, are considered as novel, more specific targets for the treatment of inflammation and pain [4,5].

Among the three terminal synthases, mPGES-1 is often functionally coupled with COX-2 and serves as the primary source of inflammatory PGE2 synthesis. Inhibition of mPGES-1 has displayed similar efficacious effects to NSAIDs in several rodent models of analgesia and global depletion of mPGES-1 in mice appeared to have beneficial cardiovascular effects due to the product rediversion to cardioprotective PGI2 [6]. However, the development of mPGES-1 inhibitors is still complicated. Firstly, in addition to PGE2, PGI2 mediates, sometimes dominates, inflammatory pain in some animal models. So although substrate rediversion to PGI2 offers cardioprotection; it also compromises the analgesic efficacy of mPGES-1 inhibitors in some conditions. Secondly, the consequences of mPGES-1 deletion vary amongst cell types. Most recently, we reported that deletion of mPGES-1 in the vasculature and myeloid cells differentially modulates inflammatory response in cardiovascular system, where enzyme inhibition in macrophages restrains while in vascular cells unalters or aggregates atherogenesis or vascular injury response [7,8]. Our studies implied that, albeit that pursuing of macrophage targeted therapeutic strategies is to be challenging, macrophage mPGES-1 acts as a preferable drug target for anti-inflammatory therapy which might substantially avoid the dark sides of COX-2 inhibition and refine the therapeutic efficacy of global mPGES-1 shooting. However, whether such an approach actually would conserve the analgesic efficacy expected of NSAIDs needs to be deeply verified.

PGE2 acts on four specific G-protein-coupled receptors subtypes, termed EP1–4. Targeting the four receptors is being pursued as alternative approach to COX-2 inhibitors in the development of analgesics as well [9]. Various EP agonists and antagonists have been developed to clarify the role of each receptor, however, the safety profile of these new targets is unknown. In particular, enhanced expression of EPs has been observed in many clinical and experimental cardiovascular diseases, their importance in blood pressure regulation, atherosclerosis, aneurysm formation, myocardial ischemia and myocarditis has been diversely implied [10]. Thus, further exploration of both the analgesic efficacy and the cardiovascular risks of these EP antagonists is also extensively required.

Taken together, NSAIDs are the most regular used analgesic, anesthetic and anti-inflammatory drugs in the world. However, many of the users are seniors who already likely to have varying degrees of heart diseases. Thus, even a small incremental risk of cardiovascular events attributable to NSAIDs has been of concern. Therefore, it is in an urgent need to develop a class of drugs that afford pain relief and have cardiovascular efficacy. Targeting macrophage mPGES-1 and probably the four PGE2 receptors might serve as promising strategies for the development of

the next generation anti-inflammatory drugs. We wish to take this opportunity to encourage researchers to continue contributing to our understanding of the role of prostaglandins and other pathogenic factors in inflammation and to discover more specific and effective strategies for anti-inflammatory therapy.

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