Prostaglandin E2 in Remote Control of Myocardial Remodeling

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Despite the advance in treatment of acute myocardial infarction (MI) with timely reperfusion of ischemic myocardium, coronary artery disease remains a leading cause of morbidity and mortality worldwide. In patients who have survived acute MI, the heart undergoes a remodeling process characterized by changing in size, shape, structure, and function. The progressive ventricular dilation, wall thinning, and fibrosis, together with loss of contractile function, lead to life-threatening heart failure and arrhythmia. Therefore, understanding the process of pathological remodeling in post-MI hearts is of paramount importance.

It is well established that inflammatory response is elicited by MI and contributes significantly to cardiac remodeling. At the onset of MI injury, inflammatory leukocytes produced in bone marrow are mobilized and infiltrate the myocardium from circulation. The locally targeted leukocytes can be beneficial to wound healing by removing dead cells and matrix debris. However, prolonged inflammation may also contribute to additional cell death and scar formation as a result of fibrosis. Therefore, inflammatory response has to be precisely controlled and resolved in a timely fashion to avoid adverse remodeling in the postinfarct heart. As a result, modulating inflammatory response has been considered a potential therapeutic approach to preserve and recover heart function after MI. A great deal of effort has been made to understand the cellular and molecular mechanisms of inflammatory response after MI.

Prostaglandins (PGs) are a group of 20-carbon lipid metabolites derived from arachidonic acids through a cascade of cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases. Prostaglandin E2 (PGE2) is one of the most abundant species, with an important role in both promotion and resolution of inflammation. Microsomal prostaglandin E2 synthase-1 (mPGES-1) encoded by Ptges gene is the major terminal prostaglandin synthase of PGE2. Genetic inactivation of Ptges gene in mice led to attenuated inflammation, reduced pain, less brain ischemia/reperfusion injury, and atherosclerosis. Therefore, inhibiting PGE2 synthase and downstream receptors is viewed as a viable alternative strategy to COX-2 inhibition for inflammatory diseases.

In addition to inflammation, PGE2 can exert other effects depending on receptor subtypes, cell type, and the context of its activation. More relevant to heart, PGE2, among other PGs, can regulate cardiomyocytes hypertrophy and remodeling. In an earlier study by Degousee et al, systemic ablation of mouse Ptges gene promoted pathological remodeling in left ventricle after MI. Reduced PGE2 in mPGES-1-deficient mice resulted in more severe ventricle dilation and worse cardiac function after MI. Therefore, PGE2 produced in infarct heart appears to have a beneficial effect in post-MI myocardial remodeling. In the same study, Degousee et al also found that the transient induction of the mPGES-1 protein observed in the post-MI heart was mainly produced from inflammatory cells recruited to infarct zone and peri-infarct region of the heart. Therefore, bone marrow–derived inflammatory cells may be an important source of PGE2 that attenuates pathological remodeling in post-MI heart. However, this observation is correlative based on immunohistochemistry, and there is no direct evidence to support the relative contribution of PGE2 from bone marrow–derived leukocytes versus other cell types.

A report by the same group in this issue of Circulation provided a more definitive answer by clarifying the crucial role of bone marrow–derived leukocyte in the cardiac remodeling after MI. Taking advantage of a well-established bone marrow transplant approach, the authors established two chimera wild-type female mouse lines reconstituted with bone marrow from either Ptges+/+ (BM+/+) or Ptges−/− (BM−/−) male mice. By performing MI on these chimera mice followed by functional and molecular studies, the specific contribution of PGE2 produced from bone marrow–derived leukocytes to post-MI myocardial remodeling was evaluated. As shown in their study, inactivation of mPGES-1 in bone marrow–derived leukocytes led to a more severe pathological remodeling and worse function. This is within expectation because this phenotype is similar to what is observed in the mouse model of systemic inactivation of mPGES-1. It was quite unexpected, however, when they observed that local inflammation was enhanced in the infarct area in the BM−/− mice and an even higher level of PGE2 was detected in the myocardium post infarct, possibility as a result of the induction of mPGES-1 activity in cardiac fibroblasts.
These observations have unveiled a mechanism of cardiac remodeling orchestrated by leukocytes remotely generated in bone marrow (Figure). Although implication of inflammatory response in cardiac remodeling is not new and there has been a growing interest in the crosswalk between bone marrow and heart failure, this report has added a new molecular link involving mPGES-1 from bone marrow–derived leukocytes. It is interesting to note that even though the recruitment of bone marrow–derived leukocytes is largely confined within the infarct zone and peri-infarct area, the impact of prostaglandin PGE2 produced from these cells on cardiac remodeling can be observed throughout the myocardium. However, the current report only demonstrated the necessary role of PGE2 production from bone marrow–derived leukocytes in myocardial remodeling. It remains to be determined whether the PGE2 produced from these cells is sufficient to deliver a beneficial effect to post-MI heart. An obvious experiment would be to establish chimera mice of Pges−/− genotype but reconstituted with Pges+/− bone marrow, and to determine whether post-MI myocardial remodeling can be ameliorated. Clearly, more work is needed to establish the role of prostaglandins, especially PGE2, in mediating the remote control of myocardial remodeling by bone marrow–derived leukocytes.

From these studies, another interesting paradox emerges: both lower and higher levels of PGE2 are associated with worse cardiac remodeling and function. PGE2 level in the remote control of myocardial remodeling by bone marrow–derived leukocytes, led to significant changes in the overall prostaglandin profiles in the myocardium. It is likely that the combined effects of all prostaglandin species are ultimately responsible for the myocyte hypertrophy and remodeling. Additional animal models with targeted manipulation of PG receptors in myocytes would be needed to sort out the specific and direct contribution from different PG species.

Another interesting observation from these studies is the cross-talk between bone marrow–derived leukocytes and other different cell types in myocardium. Elevated PGE2 was observed to be produced in the resident cardiac fibroblasts in the BM−/− hearts. Although the functional significance of this observation is unclear, the result indicates an active interaction between bone marrow–derived cells and other cardiac resident cells beyond cardiomyocytes. Because these cardiac cells such as fibroblasts also contribute significantly to myocardial remodeling, PGE2 may exert its effect though regulation on these cells. Indeed, prostaglandin-mediated cross-talk may also impact on vascular remodeling, progenitor/stem cell mobilization, and differentiation. The study presented in this report provides an excellent model system and outstanding opportunity to further investigate these questions.

The clinical significance of mPGES-1 function goes beyond its possible role in MI or heart failure. COX-2 inhibitors were once used mainly as anti-inflammatory and pain medicine by millions of people worldwide. However, after elevated cardiovascular risk was linked this class of nonsteroidal anti-inflammatory drugs, a major effort has been shifted to target mPGES-1 as an alternative to COX-2. In light of the study reported here, however, it is clear that we also need to better understand the role of mPGES-1 and its product PGE2 in the pathological progression of heart diseases. If the critical role of mPGES-1 in the remodeling of the left ventricle after MI is also implicated in human patients as suggested from these mouse studies, an mPGES-1 selective inhibitor may also have an adverse effect on myocardium remodeling and long-term mortality of the post-MI patients. It is, therefore, highly prudent to evaluate the safety profile of this class of drugs, especially for any potential cardiovascular risks.

**Disclosures**

None.

**References**


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