



Published in final edited form as:

*Circulation*. 2012 June 12; 125(23): 2818–2820. doi:10.1161/CIRCULATIONAHA.112.110726.

## Prostaglandin E2 in Remote Control of Myocardial Remodeling

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### Keywords

bone marrow mononuclear cells; Editorials; myocardial infarction; prostaglandins

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 survived acute MI, heart undergoes a remodeling process characterized by changing in size, shape, structure, and function. The progressive ventricular dilation, wall thinning, 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 due to fibrosis. Therefore inflammatory response has to be precisely controlled and timely resolved to avoid adverse remodeling in the post-infarct heart<sup>1,2</sup>. As a result, modulating inflammatory response has been considered a potential therapeutic approach to preserve and recover heart function after MI<sup>3,4</sup>. A great deal of effort has been made to understand the cellular and molecular mechanisms of inflammatory response following MI<sup>2,5-8</sup>.

Prostaglandins (PGs) are a group of 20-carbon lipid metabolites derived from arachidonic acids through a cascade of cyclo-oxygenases (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<sup>9-11</sup>. mPGES-1 (microsomal prostaglandin E2 synthase-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<sup>12</sup>.

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**Conflict of Interest Disclosures:** None

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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<sup>13</sup>. More relevant to heart, PGE2, among other PGs, can regulate cardiomyocytes hypertrophy<sup>14, 15</sup> and remodeling<sup>16</sup>. In an earlier study by Degousee et al, systemic ablation of mouse *Ptges* gene promoted pathological remodeling in left ventricle after MI<sup>17</sup>. 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 vs. other cell types.

A report by the same group in this issue provided a more definitive answer by clarifying the crucial role of bone marrow derived leukocyte in the cardiac remodeling after MI<sup>18</sup>. Taking advantage of a well established bone-marrow transplant approach, the authors established two chimera wildtype 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 since this phenotype is similar to what is observed in the mouse model of systemic inactivation of mPGES-1<sup>17</sup>. 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 due to the induction of mPGES-1 activity in cardiac fibroblasts<sup>18</sup>.

These observations have unveiled a mechanism of cardiac remodeling orchestrated by leukocytes remotely generated in bone marrow (Figure 1). Although implication of inflammatory response in cardiac remodeling is not new and there has been a growing interest for the crosswalk between bone marrow and heart failure<sup>19</sup>, this report has added a new molecular link involving mPGES-1 from bone marrow derived leukocytes<sup>18</sup>. 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<sup>17</sup>, 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 BM derived leukocytes in myocardial remodeling<sup>18</sup>. 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 myocardium is lower in the mPGES-1 deficient mice than that of the wildtype controls<sup>17</sup>

while higher in *BM*<sup>-/-</sup> mice than that of *BM*<sup>+/+</sup> mice<sup>18</sup>. Yet, under both circumstances, hearts developed more left ventricular (LV) dilation, worse LV systolic and diastolic function, and higher LV end-diastolic pressure following MI. These results highlight the confounding factors involved in the pathological remodeling in heart. One possibility is that the direct causes of such adverse myocardium remodeling are not limited to PGE2 or PGE2 downstream signaling alone in cardiomyocytes. Prostaglandins biosynthesis is not regulated in a linear fashion but rather by a convoluted network of reactions. In fact, the deficiency of mPGES-1 activity, systemically or in BM 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<sup>16</sup>. 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.

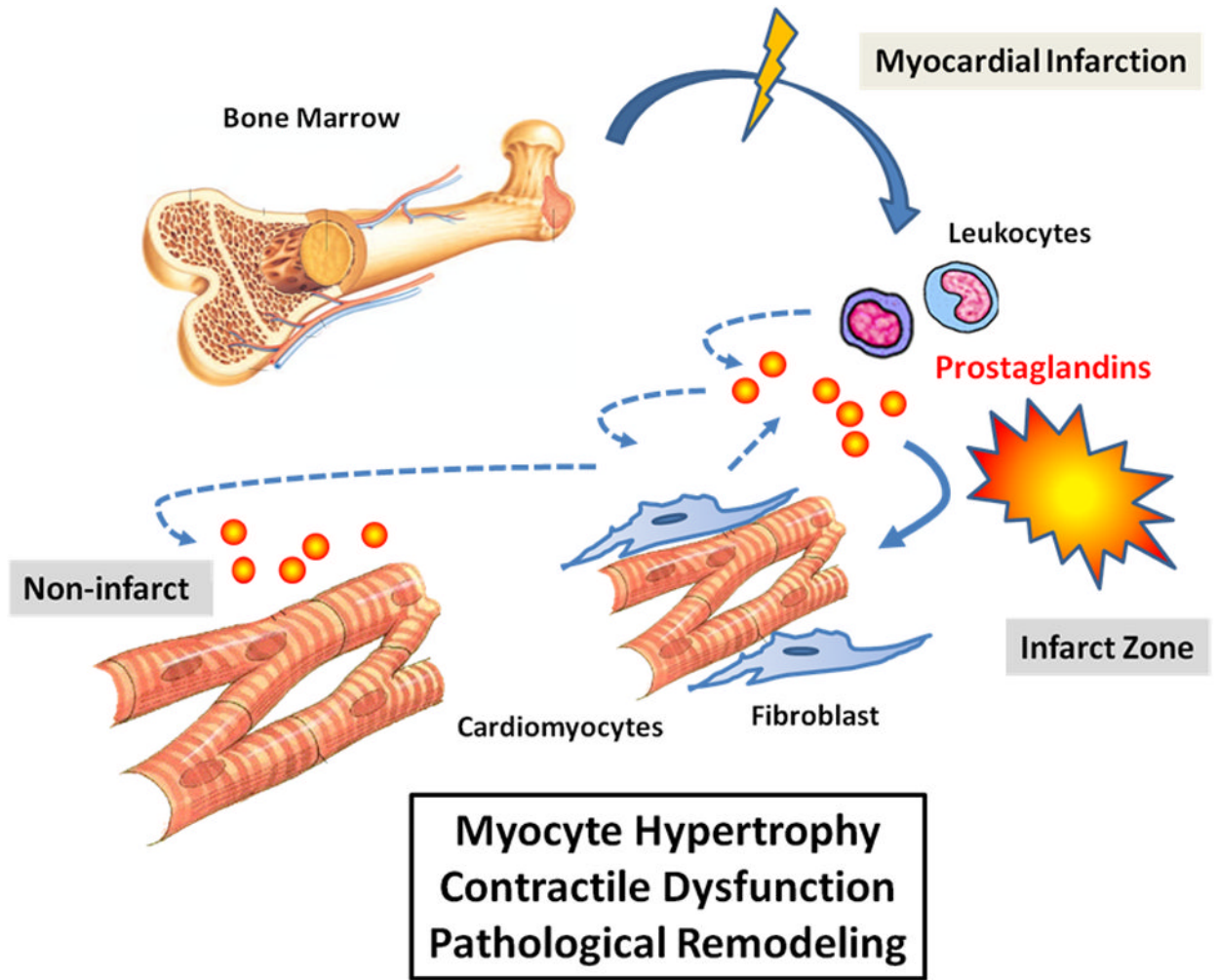
Another interesting observation from these studies is the cross-talk between BM derived leukocytes and other different cell types in myocardium. Elevated PGE2 was observed to be produced in the resident cardiac fibroblasts in the *BM*<sup>-/-</sup> hearts<sup>18</sup>. Although the functional significance of this observation is unclear, the result indicates an active interaction between BM derived cells and other cardiac resident cells beyond cardiomyocytes. As these cardiac cells such as fibroblasts also contribute significantly to myocardial remodeling, PGE2 may exert its effect through regulation on these cells. Indeed, prostaglandin mediated cross-talk may also impact on vascular remodeling, progenitor/stem cell mobilization and differentiation<sup>2021</sup>. 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 non-steroidal 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 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 risks of cardiovascular incidents.

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**Figure 1.** Illustration of Prostaglandin-E2 from bone marrow derived leukocytes in myocardial remodeling after myocardial infarction.