A growing body of evidence outlines the key roles of circulating endothelial progenitor cells (EPCs) in vascular repair and angiogenesis. Several mechanisms have been proposed to explain the beneficial effects of EPCs. It was reported that EPCs participate in the reendothelialization process after arterial injury. However, under pathological conditions such as diabetes mellitus, hypertension, dyslipidemia, and aging, the functional capacities of EPCs appear to be impaired. Thus, it is of clinical importance to elucidate the molecular signaling that ameliorates EPC function.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Kawabe et al report that prostaglandin I$_2$ (PGI$_2$) improves EPC function via a PGI$_2$ receptor, which is termed IP receptor. Like many other lipid mediators of the eicosanoid family, PGI$_2$ is produced by the PGI$_2$ synthase coupled to cyclooxygenase (COX) system. COX involves either COX-1 or COX-2, depending on the cell type and the biological context. Although numerous articles have shown the antiplatelet and vasodilating properties of PGI$_2$, the beneficial effects of this lipid molecule on EPCs and reendothelialization have not yet been investigated.

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To gain insights into the role of the PGI$_2$-IP axis in the regulation of EPC function, the authors performed bone marrow transplantation (BMT) from the IP$^{-/-}$ or IP$^{+/+}$ donor mice into the IP$^{+/+}$ or IP$^{-/-}$ recipients prior to wire-mediated endovascular injury. Previous studies had shown that neointima (NI) formation induced by arterial injury was enhanced in mice holding a ubiquitous deficiency in IP expression. Data from the present work strongly suggest that such a phenotype could principally result from delayed reendothelialization due to impaired function of EPCs. Although the number of circulating EPCs increased in the IP$^{-/-}$ mice, EPCs from IP$^{-/-}$ mice displayed poor adhesion to the denudated endothelium and impaired migration capacities in vivo (Figure). These adhesion defects induced by the disruption of IP were further confirmed by in vitro studies, which revealed that IP$^{-/-}$ EPCs had decreased expression of β1, β3, and α5 integrin subunits with poor binding capacity to fibronectin, which is supposed to be an important component of extracellular matrices during vascular healing. Moreover, IP$^{-/-}$ EPCs seemed to display diminished proliferation capacities in vitro, which could also account for the delayed reendothelialization observed in vivo.

The investigators further demonstrated that selective disruption of IP in bone marrow resulted in enhanced NI formation. The NI in the BMT (IP$^{-/-}$ → IP$^{+/+}$) mice was comparable to that in the BMT (IP$^{-/-}$ → IP$^{-/-}$) mice. Interestingly, the NI in the BMT (IP$^{+/+}$ → IP$^{-/-}$) mice was significantly more than that in the BMT (IP$^{+/+}$ → IP$^{+/+}$) mice, suggesting that IP expression in tissues other than bone marrow could also participate in regulation of NI formation. In that respect, the authors propose that the PGI$_2$-IP system in the vascular cells would be potentially involved in the pathogenesis of NI formation. In fact, the expression of IP in the arterial wall was previously shown to play a key role in vascular remodeling. In addition, adipose tissues may represent another tissue, whose deficiency in IP expression could affect arterial remodeling. PGI$_2$ was reported to promote adipocyte differentiation through its extracellular binding to IP on preadipose cells. Recent studies suggested that perivascular and visceral adipose tissues have positive and negative effects on vascular homeostasis and repair. It is plausible that adipose tissues, particularly perivascular and visceral adipose tissues in IP$^{-/-}$ mice, are phenotypically and functionally modified, leading to enhanced NI formation.

Moreover, PGI$_2$ inhibits platelet-endothelium interaction. Abou-Saleh et al reported that the secretion of PGI$_2$ by EPCs could similarly inhibit platelet-EC interaction and thereby prevent platelet activation by blocking translocation of platelet P-selectin and activation of glycoprotein IIb/IIIa. It is of interest in the overall setting of a potential beneficial role of PGI$_2$ in the regulation of VEGF and EPCs under atherothrombotic conditions.

Hence, these studies suggest an important role for PGI$_2$ in vascular remodeling through IP expression in arterial wall cells, EPCs, and other blood cell types. However, the broad effects of PGI$_2$ do not only result from the variety of cell types in which it is expressed or it acts on; these effects also emanate from the different signaling cascades that indicate that PGI$_2$ may be involved within the same cell type. In the present study, extracellular PGI$_2$ influenced EPC functions through the IP pathway. In contrast, others reported that intracellular PGI$_2$ could stimulate proangiogenic activities of EPCs through the peroxisome proliferator–activated receptor δ pathway but not through that of IP. Moreover, Hatae et al demonstrated how the balance between activation of peroxisome proliferator–activated receptor δ and IP pathways...
by PGI$_2$ regulates apoptosis in an opposite fashion within the same cell. In the study by Kawabe et al, $^3$ it was reported that EPCs from IP$^{-/-}$ mice formed fewer and smaller colonies than those from wild-type mice due to decreased proliferation of EPCs on fibronectin. It could also be of interest to further explore whether these observations in IP$^{-/-}$ EPCs may partly arise from increased apoptosis, which could be triggered by the activation of the PGI$_2$–peroxisome proliferator–activated receptor δ pathway over the inactivated PGI$_2$-IP pathway. Last, recent evidence$^{16}$ of a direct implication of PGI$_2$ in the regulation of intracellular miRNA sheds further light on the complexity of PGI$_2$–mediated cellular signaling.

In conclusion, the study by Kawabe et al$^3$ reveals a key role for the PGI$_2$-IP axis in the regulation of EPCs. Stimulation of the PGI$_2$-IP system may hold a promise as a therapeutic strategy to limit NI formation after vascular injury by accelerating reendothelialization.

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**Disclosures**

None.

**References**


When Endothelial Progenitor Cell Says I2 Shall Limit Neointima Formation!
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