Since Asahara et al discovered endothelial progenitor cells (EPCs) in 1997,1 extensive studies have been conducted in an attempt to not only clarify and characterize these cells, but also to utilize EPC-containing products (ie, bone marrow-derived cells) for therapeutic angiogenesis.2 Initially, the favorable effects of blood flow recovery in ischemic tissue were believed to be from the incorporation of EPCs into endothelial cells,3 but additional studies have shown that EPCs mediate angiogenesis by paracrine effects.4,5 However, both the optimal definition and characterization of EPCs remain controversial. A number of factors have been shown to modulate the functions of EPCs.6,7

Recently, prostacyclin (prostaglandin [PG] I₂) was shown to play an important role in EPC-mediated angiogenesis, in addition to its wide range of vasoprotective effects that include vasoilation, inhibition of platelet aggregation, and smooth muscle cell proliferation.8 However, the precise mechanism of action of PGI₂ in EPC-mediated angiogenesis is not yet clear. He et al9 showed that cyclooxygenase (COX) enzymatic activity, and the subsequent production of PGI₂, enhances EPC-mediated angiogenesis by the PPARδ pathway. They showed that activation of the COX-1/PGI2/PPARδ pathway in EPCs resulted in the independent, direct differentiation of EPCs into endothelial cells through a PGI₂-specific receptor, IP.

Kawabe et al showed that removal of IP from EPCs caused their dysfunction10 and following that study, the same group, including Aburakawa et al, have described the critical role of the PGI₂/IP signal in EPC-mediated angiogenesis.11 In this issue of the Journal, the authors compare the effects of PGI₂/IP signaling in bone marrow and non-bone marrow tissues on blood flow recovery in hindlimb ischemia, using a bone marrow transplantation model in genetically IP-deficient mice. They observed that IP-deficient mice, after receiving a bone marrow transplant of wild-type cells, initially showed decreased blood flow, compared with wild-type mice in the hindlimb ischemia model; the decreased blood flow completely recovered within 30 days of the induction of hindlimb ischemia. In contrast,

**Prostacyclin**

– A Potential New Target for Endothelial Progenitor Cell-Mediated Angiogenesis –

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**Figure.** Novel effect of PGI₂ on EPC proposed by Aburakawa et al.11 PGI₂ upregulates integrins on EPC in an autocrine or paracrine manner directly through its specific receptor IP. PGI₂, prostaglandin I₂; EPC, endothelial progenitor cell; EC, endothelial cell.
wild-type mice receiving a bone marrow transplant of IP-deficient cells showed continual blood flow impairment. The authors also show that this impairment could be completely recovered by intramuscular injection of wild-type EPCs, but not IP-deficient EPCs. These results strongly suggest that the PGI2-specific receptor, IP, present on EPCs, was essential for angiogenesis in a mouse model of hindlimb ischemia. Histologically, they also observed that the recipients of wild-type EPCs had more arterioles, in addition to capillaries, at the ischemic site and that many of the transplanted EPCs differentiated into pericytes, which may explain the ischemic improvement following stimulation of PGI2.

These novel findings were strengthened by an ex vivo experiment that demonstrated other factors, such as the pro-angiogenic factors derived from skeletal muscle, could be excluded. In an aortic ring assay, Aburakawa et al showed enhanced angiogenesis following treatment with wild-type EPCs, but not IP-deficient EPCs. In addition, they showed that both a COX inhibitor, indomethacin, and an IP-selective antagonist could attenuate the in vivo and ex vivo enhancement of angiogenesis by wild-type EPCs.

Because this same group had previously shown that expression levels of integrin family members were decreased in IP-deficient EPCs, they examined whether or not the impairment of the angiogenic effects of IP-deficient EPCs was related to defects in integrin expression. They used siRNA to knockdown integrin β1 (Intβ1-KD) in wild-type or IP-deficient EPCs. Interestingly, the angiogenic effects of Intβ1-KD wild-type EPCs were attenuated to the level of IP-deficient EPCs in both the in vivo and ex vivo experiments. This finding suggests that the PGI2/IP pathway in EPCs functions as an angiogenic factor through the accumulation of EPCs in ischemic tissue as a consequence of integrin β1 expression (Figure).

This study provides novel insight into the mechanism of PGI2/IP-dependent angiogenesis in EPCs. Although a number of clinical studies have used EPCs to induce therapeutic angiogenesis, the “optimal therapeutic protocol” has yet to be described, mainly because of the lack of knowledge regarding EPCs. Additional studies are needed to clarify the biology of EPCs, including their definition, characterization, and therapeutic mechanisms.

References