Blood supply via microvessels in the heart is a critical determinant of the fate of heart failure patients, especially in the case of the hypertrophied heart. Disruption of coordinated cardiomyocyte growth and blood supply can eventually lead to the transition from cardiac hypertrophy into heart failure. Treatment that increase blood supply in an ischemic area through angiogenesis have thus been examined in order to prevent the development of heart failure.

Asahara, et al first reported a population of circulating cells named endothelial progenitor cells (EPCs), which are bone marrow-derived cells with properties of endothelial cells as well as progenitor cells. This cell type is known to contribute to both angiogenesis and vasculogenesis and thereby improving blood supply. A number of clinical trials have been conducted using EPCs as an angiogenic therapy. However, the results of these studies vary because of the differences in given study design or other factors. Among them, the impaired function and the poor survival rate of engrafted EPCs are the two most important factors that may preclude consistent results. The former has been reported to be associated with disease progression in diabetic mellitus or heart failure, and the latter with a harsh microenvironment where cells are transplanted. To overcome these problems, genes encoding survival factors that have been tested in numerous clinical trials for the treatment of ischemic disease.

Although these results provide some evidence that EPC treatment may be of benefit in treating ischemic disease, the problems remain unresolved due to uncertain mechanisms that cause EPC dysfunction and damage.

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Bai, et al shed light on mechanical stretch, an important contributor to the development of cardiac hypertrophy and heart failure, which elicits EPC dysfunction through induction of apoptosis and inhibition of proliferation and migration, ultimately leading to angiogenic failure. Bai, et al first isolated CD133+CD34+EPCs from human umbilical cord blood and validated EPC characteristics, including uptake of acetylated low-density lipoprotein, lectin binding, and expression of endothelial cell markers, CD31, and von Willebrand Factor (vWF). Cells were then subjected to mechanical stretch, a well-established model of mechanical stress in the pressure-overloaded heart. Protein expression profiles revealed that mechanical stretch induced an increase in the pro-apoptotic factor Bax and a decrease in the anti-apoptotic factor Bcl2. Accordingly, induction of apoptosis and inhibition of proliferation were observed in the stretched EPCs. Angiogenic ability of EPCs assessed by a migration assay using a Boyden chamber, and a tube formation assay in Matrigel, demonstrated that these two important components of angiogenesis were impaired in cells that had been subjected to mechanical stretch. The discovery of a notable decrease of VEGF expression in mechanically stretched EPCs led Bai, et al to examine VEGF endocytosis as a mechanism by which EPCs lose their angiogenic properties. As the importance of endocytosis in VEGFR signaling and angiogenesis has been reported in the developing eye, Bai, et al performed immunostaining for VEGFR to determine if the endocytosis of VEGFR was relevant to the mechanical stretch-induced inhibition of angiogenesis. Under normal conditions, EPCs indeed demonstrated an accumulation of VEGFR in the perinuclear region, indicating activation of VEGFR signaling via endocytosis. However, this accumulation of VEGFR was abrogated by mechanical stretch, implying a mechanical stress-induced inhibition of VEGFR endocytosis. Atypical protein kinase (aPKC) is a known negative regulator of Dab2-dependent VEGFR endocytosis. The inhibition of aPKC promotes angiogenesis through the acceleration of VEGFR endocytosis and subsequent signal transduction. Bai, et al treated EPCs with an aPKC inhibitor (aPKCi) to test if alterations in VEGFR endocytosis impacted EPC-led angiogenesis. Treatment with aPKCi partially reversed the impaired accumulation of VEGFR in EPCs and, consistently, reversed the reduction in tube formation. Interestingly, this restoration of angiogenesis did not coincide with a recovery of VEGF protein expression, suggesting that the VEGFR signal reactivation was independent of the presence of VEGF. In summary, these data identify mechanisms by which mechanical stress, an aggravating factor of heart failure, induces a reduction of VEGFR endocytosis, which in turn results in impaired VEGFR signal transduction and subsequent angiogenesis. This dysfunctional property of EPC can be partially reversed by inhibition of aPKC, indicating that the targeted improvement of VEGFR endocytosis may be a potent method to promote angiogenesis and could contribute to the prevention of heart failure development (Figure).

CD34+CD133+ EPCs are a potent angiogenic cell type that have been tested in numerous clinical trials for the treatment of ischemic disease. Although these results provide some evidence that EPC treatment may be of benefit in treat-
tion.
iogenesis are considerably insufficient after cell transplan-
ting. Accordingly, the survival of engrafted cells and subse-
quent angiogenesis are considerably insufficient after cell trans-
plantation. When potentially therapeutic cells are introduced into ischemic tissues, the trans-
planted cells are exposed to an extremely harsh, pro-apoptotic
microenvironment with persistent ischemia and mechanical
stress produced by a continuously beating myocardium. Ac-

ron environment where the cells were transplanted. When potentially therapeutic cells are intro-
duced into ischemic tissues, the transplanted cells are exposed to an extremely harsh, pro-apoptotic

However, some issues remain to be overcome. The first is
that Bai, et al did not clarify which isoform of aPKCs was acti-
vated by mechanical stress, or which isoform of VEGF/VEG-
FR was involved.9 Another issue would be the controver-
ry of mechanical stress-induced impairment of angiogenesis. Liang,
et al reported that skin undergoing long-term cyclical mechani-
cal expansion, associated with activated hypoxia-inducible fac-
tor-1a and VEGF expression, had enhanced activation of
CD34⁺CD133⁺ endothelial progenitor cells and improved an-

Despite the existence of dozens of clinical trials imple-
menting EPC transplantation, relatively few advances have
been made in demonstrating whether this therapy is truly ben-
eficial for heart failure patients. Therefore, further studies are
required to elucidate the full mechanisms for maximizing EPC
survival and producing functional blood vessels in the treat-
ment of heart failure.

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Figure. Mechanism proposed by Bai, et al in which endothelial progeni-
tor cells lose angiogenic properties in response to mechanical stress.9
