Endothelial progenitor cells (EPCs), which were identified in 1997 as a population of hematopoietic cells circulating in the peripheral blood, have been reported to originate from bone marrow and to play roles in neovascularization of ischemic tissues and re-endothelialization of injured vessels. As it is now possible to obtain EPCs by culturing bone marrow- and peripheral blood-derived mononuclear cells, it has been expected to treat damaged tissues in cardiovascular disease using “cell therapy” by injection of such mononuclear cells or cultured EPCs. Actually, there are many reports that intramuscular and intravascular injections of these cells have improved the clinical condition in patients with ischemic cardiovascular diseases. However, the outcomes have not exceeded initial expectations, possibly contributing to why present cell therapy with EPCs has not yet been generalized.

EPCs are considered to play a role in neovascularization of ischemic tissue through a multistep process comprising the following neovascularization-related capacities of the cells: chemotaxis and adhesion to mature endothelial cells; migration and invasion to the intracellular space in adjacent endothelial cells; and secretion of cytokines to stimulate sprouting of new capillaries from preexisting arteries. Thus, the efficacy of cell therapy by injection of EPCs may depend on the neovascularization-related capacities of the injected cells. It has been reported that such capacities of EPCs are impaired in patients with dyslipidemia, diabetes mellitus, chronic kidney disease, coronary artery disease (CAD), and congestive heart failure. It has been also reported that impaired migration capacity of chronic ischemic cardiomyopathy patient-derived EPCs in vitro closely correlates with impaired neovascularization capacity of the cells in vivo. Unsatisfactory clinical outcomes following cell therapy with EPCs may be the result of using EPCs with impaired neovascularization-related capacities. Accordingly, ex vivo pretreatment of the impaired capacities for cell injection may improve the unsatisfactory clinical outcomes (Figure).

It has been reported that ex vivo pretreatment of cardiovascular disease patient-derived EPCs with endothelial nitric oxide synthase enhancer, ultrasound, and platelet-derived microparticles augmented the neovascularization-related capacities of the EPCs in vitro. Moreover, in rodents with ischemic hindlimbs, cell therapy by intramuscular or intravenous injection of such ex vivo pretreated EPCs augmented the neovascularization of the ischemic limbs in comparison with cell therapy by injection of untreated EPCs. Hypoxia-induced oxidative stress accelerated apoptosis of EPCs that were injected into ischemic limbs. The loss of viable EPCs in the ischemic tissue led to insufficient effect of augmenting neovascularization by the EPCs. However, pretreatment of the EPCs by transfection of small interfering ribonucleic acid (RNA) targeted against FOXO4 for augmenting the anti-apoptosis capacity of the cells increased the number of viable EPCs in the ischemic tissue and thereby restored the deficient effect.

In this issue of the Journal, Li et al report on the possibility of pretreating ischemic cardiomyopathy patient-derived EPCs by transfection of microRNA (miRNA/miR)-126-3p. MicroRNAs (miRNAs), which were first discovered in Caenorhabditis elegans in 1993, are an emerging class of highly conserved, short, single-stranded, non-coding RNAs (20–25 nucleotides) that negatively regulate gene expression at the posttranscriptional level by inhibiting messenger RNA translation or promoting messenger RNA degradation. Specific miRNAs have a key role in various cell biological processes (e.g., cell differentiation, cell proliferation, and apoptosis) and pathological processes (e.g., cardiovascular disease, inflammatory disease, and cancer). In order to use miRNAs as a therapeutic tool, it will be necessary to specify the detailed spectra of the more than 500 types of miRNAs that have so far been discovered in mammalian genomes. With regard to EPCs, 68 types of miRNAs, including miRNA-126-3p, were expressed in healthy cord blood- and CAD patient’s peripheral blood-derived EPCs. In diabetic patient-derived EPCs, miRNA-126 regulated the colony-forming capacity, proliferation capacity, and migration capacity. A low expression of miRNA-126 in patients with ischemic cardiomyopathy was associated with an increased risk of cardiovascular death and decreased survival time of patients. Downregulated expression of miRNA-126 in cardiovascular disease patient-derived EPCs might reduce the neovascularization-related capacities of the cells and worsen the prognosis of the patient.

Li et al transfected lentiviral vectors expressing miRNA-126-3p into ischemic cardiomyopathy patient-derived EPCs
and overexpressed the miRNA in the cells. The miRNA-126-3p overexpressing EPCs showed enhancement of migration capacity and tube-like structure generating capacity. Cytokine production in the cells was desirably upregulated for stimulating neovascularization and suppressing inflammation. Intramuscular injection of the cells into the heart of mice with ischemic cardiomyopathy improved cardiac function. Survival rate of the injected cells increased. Although the survival time of the mice was not prolonged significantly, ex vivo pretreatment of EPCs by overexpressing miRNA-126-3p may be a promising strategy to enhance the effect of cell therapy with cardiovascular disease patient-derived EPCs. To bring the strategy into reality, it will be necessary to solve some problems regarding the use of lentiviral vectors and secure a cell-processing center at great expense for providing pretreated EPCs safely and consistently.

References