Mesoangioblasts — A Newcomer in Cell-Based Treatment Strategy for Cardiovascular Disease? —

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For decades, several autologous cells have been considered as candidates for a cell-based strategy to rescue and repair damaged tissue in cardiovascular disease. Mesenchymal stem cells (MSCs), which were discovered on culture plates in 1970 as a rare population of progenitor cells in the bone marrow, may be one of the candidates. MSCs are capable of not only replicating as undifferentiated cells, but also differentiating into bone, muscle, adipose, endothelial cells, smooth muscle cells, and cardiomyocytes. Expressing CD73, CD90, and CD105, and lacking CD34, CD45, HLA-DR, CD14 or CD11b, CD79a, or CD19 on the cell surface are needed to define the cells as MSCs. It is currently considered that MSCs originate not only in bone marrow but also in adipose tissue, gut, lung, liver, dental pulp, heart, and so on. In animals, injected MSCs have been reported to play roles in cardioprotection, neovascularization, antifibrosis, and stimulation of endogenous cardiac stem cell proliferation and differentiation.

Recently, transendocardial injection of MSCs into patients with left ventricular dysfunction caused by chronic ischemic cardiomyopathy has reduced the infarct size and improved the myocardial function regionally. However, a cell-processing center, which entails huge cost to build and maintain, is crucial for preparing MSCs, suggesting difficulties in their clinical application (Figure).

Endothelial progenitor cells (EPCs), which were identified in 1997 as a population of hematopoietic cells circulating in the peripheral blood, may also be a candidate. EPCs are capable of differentiating into mature endothelial cells in vitro and playing roles in neovascularization of ischemic tissues and re-endothelialization of injured vessels in vivo, suggesting progeny of hemangioblasts. EPCs are generally cultured from bone marrow- and peripheral blood-derived mononuclear cells (MNCs). Expressing CD133, CD34, VEGF-receptor 2 (KDR/Flk-1), and low intensity CD45 (CD45dim) on the cell surface is widely acceptable to define cultured or non-cultured MNCs as EPCs; however, the method for identification and characterization of EPCs is still controversial. Nevertheless, injections of bone marrow- and peripheral blood-derived MNCs, which are phenotypically defined as EPCs, have improved the clinical condition in patients with ischemic coronary artery disease and peripheral artery disease. Bone marrow- and peripheral blood-derived MNCs are possibly a feasible clinical application compared with MSCs because a cell-processing center is unnecessary for preparing MNCs (Figure).
In 2002, Minasi et al reported that dorsal aorta-derived multipotent and self-renewing cells differentiated into most mesodermal tissues such as connective tissues, myoblasts, blood, cardiovascular and lymphatic systems. The cells were identified as a subset of MSCs co-expressing hemangioblastic markers CD34, KDR/Flik-1, and Kit, possibly revealing 2 sides of MSCs and EPCs. They were named mesoangioblasts (MABs) and then isolated from human heart and peripheral blood. The isolated MABs expanded clonally and differentiated into endothelial cells, smooth muscle cells, and cardiomyocytes. In animals with myocardial infarction, injected MABs have generated new expanded clonally and differentiated into endothelial cells, for their clinical application as well as for MSCs.\(^5\) Moreover, in animals with ischemic limbs, injected MABs have augmented neovascularization in the limbs and increased blood perfusion in the ischemic limbs.\(^12\) MABs may be a new candidate for a cell-based strategy to rescue and repair damaged tissue in cardiovascular disease; however, a cell-processing center is again crucial for obtaining MABs, suggesting difficulties for their clinical application as well as for MSCs (Figure).

In this issue of the Journal, Hata et al report a human study in which systemically administered heparin increased the levels of plasma hepatocyte growth factor (HGF) and colony-forming units of MABs that were cultured with peripheral blood-derived MNCs. They have called the colony-forming cells “circulating MABs” and concluded that these circulating MABs are mobilized from the heart via HGF stimulation. Surprisingly, although the colony of circulating MABs was generated in exactly the same manner as the generation of EPCs with peripheral blood-derived MNCs, the colony expressed CD73 and lacked CD34 and CD45 on the surface, showing the characteristics of MSCs. Further studies to solve this mystery will be needed before clinical application of circulating MABs. Nevertheless, this study suggests important roles of heparin and HGF in obtaining a large number of MABs from the peripheral blood. Systemically administered granulocytc-colony stimulating factor has induced mobilization of EPCs from the bone marrow in patients with ischemic cardiovascular disease.\(^14\)\(^15\) A stronger response of EPC mobilization has brought better outcomes for patients with myocardial infarction.\(^6\) If it becomes possible to obtain MABs without a cell culturing process, systemic administration of heparin will be surely easy and useful for obtaining a large number of MABs from the peripheral blood for the desired cell-based strategy to rescue and repair damaged tissue in cardiovascular disease.

Implantation of autologous MSCs or EPCs may be a promising strategy to rescue and repair damaged tissue in cardiovascular disease with ischemia.\(^4\) However, despite decades having passed since the discovery of these cells, the expected strategy has not yet been standardized. One reason may be the remaining open questions about origin, phenotype, character, ability, localization, role, extraction, and usage of the cells.\(^3\)\(^7\)\(^8\) The area of research for MABs is quite primitive, but should be progressed unhurriedly and carefully to ensure favorable clinical use on the basis of abundant fundamental research.

References