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Review Article

Stem Cell-Mediated Medicine for the Cardiovascular Disease

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Stem cell-based studies have investigated to evaluate the potential of therapeutic effects for the treatment of cardiovascular disease. That is, myocardial and vascular regeneration have been initially proposed as mechanism of action in stem cell biology. These approaches can be broadly classified as regenerative therapy (direct therapy) and trophic effect (indirect therapy). The regenerative therapies involve cell transplantation, reprogramming of fibroblasts, and activation of cardiomyocytes or vascular cells, namely differentiated cells derived from adult or pluripotent embryonic stem cells. The regenerative cells are functioned as the alternative of damaged native cells to restore pathophysiological feature. Because very few cells are actually incorporated long-term into the myocardium or vessel wall, it has become the biggest problem for the translational researches to engraft stem cells. In the trophic studies, stem cells are usually used in undifferentiated state. It is a well-known process for repair and preservation of cardiovascular function by the alteration of stem cell niche (microenvironment). Stem or progenitor cells can secrete many growth factors, a broad variety of cytokines, and chemokines and can function as cell-cell mediator between damaged cells in the reparative process [1-4]. Furthermore, there are reported that mesenchymal stem cells (MSCs) under hypoxic condition have effects on the restoration of injured tissue and the preservation of cardiovascular function by several factors [5,6]. Although the ability of stem cell transplantation for the tissue repair of cardiovascular disease has been broadly studied, yet the potentials of trophic therapies for the indirect restoration of stem cells are unclear.

Hwang et al. provides new insights into the role of the paracrine molecules secreted from MSCs on arrhythmogenicity in rats with myocardial infarction (MI). It suggests that the hypoxic environment surrounding MSCs in the myocardium affects released growth factors or cytokines, and these secreted molecules determine the arrhythmogenic substrate of the surrounding myocardium. Furthermore, paracrine factors derived from hypoxic conditioned stem cells are expected to have remarkable beneficial effects for acute MI or ischemic myocardium [6]. This same group represents the hypoxic paracrine effect on the ion channels and proteins related to intracellular Ca^{2+} levels in infarcted myocardium [7]. These proteins such as L-type Ca2+ channel, sarcoplasmic reticulum Ca^{2+} ATPase, Na^{+}/K^{+} ATPase, and calmodulin, are associated with the positive regulation of Ca^{2+} homeostasis. In contrast, paracrine factors derived from neighbor cells also have a positive effect on stem cell function. At site of MSC transplantation, endothelial colony-forming cells (ECFCs) circulating in peripheral blood can contribute to the formation of new vasculature functioned as paracrine mediators prior to the establishment of blood perfusion [8]. The regenerative potential of MSCs can be strengthened by secreting ECFC-derived critical angiocrine factors via platelet-derived growth factor (PDGF)-BB (PDGF-BB)/PDGF-β signaling.

In cardiovascular system, several cell types including cardiomyocytes, endothelial cells, smooth muscle cells, and

cardiac fibroblast need a well-controlled intra-/extracellular interactions to support the harmonization of signaling pathway. To regulate definitely cellular communication in multiple cell types, cells can release various vesicles into their environment or other cells [9]. Especially, 40~1000 nm size of microvesicles and exosomes have an influence on cardiovascular communication. Lai et al. demonstrates that purified exosomes of MSCs derived from adult bone marrow can reduce infarct size in a mouse MI model [10], and can rapidly prevent adverse remodeling via multiple cardioprotective PI3K/Akt pathways [11]. In hypoxic pulmonary hypertension, exosomes derived from conditioned media of MSCs have robust biological functions including anti-inflammatory and therapeutic effects through inhibition of hypoxic STAT3 signaling [12]. Furthermore, they show that, potentially through epigenetic mechanisms involving microRNA (miR) signaling including miR-17 superfamily and miR-204, exosomes can modulate long-lasting effects on physiological relevance.

In stem cell biology, miRs play a crucial role in the regulation of cell fate and the contribution of tissue repair and regeneration. Using miRs as specific regulator of stem cells can provide mechanistic insights and their crosstalk between miRs and cells [13]. It is known that a specific mechanism of cell-cell genetic exchange has been delivered various RNAs by exosomal transfer. MiR communication has been also occurred in the stem cell and the different tissue/cell-specific microvesicle/exosome microenvironment [14,15]. The microvesicles of GATA-4-overexpressed MSCs express high levels of miR-221, and induce cardioprotection via the inhibition of p53 upregulated modulator of apoptosis (PUMA) [16]. In human c-kit positive cardiac stem cells, miR-499 controls cell fate by traversing gap junction, connexin 43. This phenomenon is named 'mircrine'. Furthermore, an improvement of ventricular function and a positive effect on cardiac performance are shown in the ischemic myocardium by mircrine mechanism [17].

Stem cell-mediated medicine, i.e. paracrine effect, microvesicles/exosomes, and miRs, may be accepted as an attractive source in cardiovascular tissue repair and regeneration. Although stem cell therapy holds promise in the near future, there are many difficulties on current usage including physiological efficiency, delivery, safety, and so on. In addition, further preclinical and clinical investigation is necessary to determine the in vivo distribution and functional relevance. On the basis of the preliminary reports, current studies should be advanced in terms of functional enhancement of stem cells by applying genetic modification, conditional change, and precondition before sample collection from cells. The specific research of cell communication and its mechanism based on stem cell-mediated medicine may help to restore better cardiovascular disease by the understanding of their biological functions.

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