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EDITORIAL

Cardiac Progenitor Cell-Derived Extracellular Vesicles: a Rising Star for Cardiac Repair and Regeneration

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Cardiovascular diseases represent a significant cause of death and disability worldwide [1]. Myocardial infarction (MI), among other cardiovascular diseases, causes massive cardiomyocyte loss and scar formation in place of dead myocardial tissues, thus leading to adverse cardiac remodeling and heart failure. Current treatments for cardiac ischemic injury mainly focus on limiting the cardiomyocyte death and suppressing the fibrogenic response caused by tissue damage, but cannot achieve a restoration of lost cardiac tissues. Therefore in many cases of heart attack, even with proper treatments, the infarction will cause severe cardiac remodeling, cardiac output decline, and eventually heart failure. True cellular replacement and myocardial restoration is always the ultimate goal of the treatment for MI.

One approach for salvage of functional myocardium is transplantation of exogenous stem cells. Various sources of stem cell candidates have been tested in animal models, among which heart-derived progenitor cells hold particular potential [2, 3]; however, the poor long-term survival of the exogenous cells in stem cell therapy causes controversy in mechanism behind the beneficial effects despite the promising preclinical outcomes. Actually, the majority, if not all, of the transplanted cells are not able to differentiate to cardiomyocytes in vivo. Consequently, the paracrine hypothesis is more and more supported that cardiac progenitor cells stimulate myocardial repair through secreting paracrine factors such as growth factors, cytokines, and chemokines. Extracellular vesicles (EVs) are nano-sized, lipid bilayer membrane, vesicles produced by almost all types of cells and widely existing in body fluids, including plasma, saliva, urine, and cerebrospinal fluid. Accumulating results have provided evidence of EVs mediating salutary effects of stem cell therapy on ischemic cardiovascular diseases, making them encouraging cell-free therapeutic agents.

In a recent study of human cardiac progenitor cell (hCPC)-derived extracellular vesicles (hCPC-EVs), Maring and coworkers investigated the effect of hCPC-derived EVs on short-term cardiac recovery in MI murine model [4]. They blocked secretion of EVs from hCPCs by knocking down Rab27A, which has been found crucial in the EV secretion pathway in multiple cell types. Injection of normal hCPCs into the border area could decrease post-MI infarct size, while injection of Rab27A-knockdown hCPCs did not exhibit a notable reduction of infarct size compared to vehicle control, suggesting EVs secreted by hCPCs are likely to be the major contributor to the cardioprotective effect of transplanted hCPCs. Subsequent study on the effect of cell-free hCPC-derived EVs further supported this observation. Moreover, hCPC-derived EVs were found to be uptaken by cardiomyocytes and endothelial cells and induced pro-proliferative and pro-angiogenic actions. Maring et al. reported an encouraging increase of the proliferation of cardiovascular cells, including cardiomyocytes and endothelial cells, simultaneously with an upregulation of yes associated protein (YAP) and endoglin after EV injection in comparison to control group. Stimulation of cardiomyocyte proliferation results in repair of injured myocardium and preservation of cardiac function, which is an important step towards cardiac recovery. Besides, neovascularization is for sure critical for both preservation of influenced cardiomyocytes and regeneration of new cells in ischemic cardiac injury. Better vascularization around

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the infarct area should be benefit to cardiomyocyte proliferation and myocardium restoration.

Despite that promising results were provided for the potential utility of hCPC-EVs as regenerative therapeutic candidates towards MI, several aspects had better be considered and improved in future work. First of all, Ki67 is not the only marker for evaluating cardiomyocyte proliferation, since most Ki67-positive cardiomyocytes will not divide into two functional cardiomyocytes and will stay binuclear after the duplication of their nuclei [5]. True newborn cell percentage should be quantified and compared between control and EV-treated myocardial tissues. Additionally, only short-term pro-angiogenic potential of hCPC-EVs has been accessed in this study, which revealed the hCPC-EVs and endothelial cell communication; however, we cannot confirm the formation of new vessels and their benefit on cardiomyocytes before the actual neovascularization is observed.

Taken together, the work of Maring et al. shows that injection of EVs derived from hCPCs can reduce MI-induced infarct size by their pro-proliferative and pro-angiogenic effect. Secreted EVs are the major contributor to the protective effect of transplanted cardiac progenitor cells. EVs are relatively stable under various physiological conditions and can be stored long term, making them a promising new tool for cardiac repair and regeneration.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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