Letter by Li and Hong Regarding Article, “Cross Talk of Combined Gene and Cell Therapy in Ischemic Heart Disease: Role of Exosomal MicroRNA Transfer”

To the Editor:

We read with great interest the article by Ong et al., who demonstrated that codelivery of cardiac progenitor cells (CPCs) with a minicircle plasmid carrying hypoxia-inducible factor-1 into the ischemic myocardium can improve the survival of transplanted CPCs. Their data revealed that hypoxia-inducible factor-1 was able to modulate the local niche and transform it from a hostile ischemic milieu into a hospitable environment for transplanted stem cells. Specifically, they showed that minicircle plasmid carrying hypoxia-inducible factor-1 was taken up by cardiac endothelial cells, which secreted exosomes that were internalized by the CPCs. The exosomes were enriched for miR-126 and miR-210, which induced a glycolytic switch in CPCs. The switch to the glycolytic state allows the CPCs to adapt to hypoxic stress. This study revealed a critical role for exosomes as a communicator in cardiovascular regeneration.

Exosomes are nanosized membrane vesicles that can mediate cellular-, tissue-, and organ-level communication by transporting proteins, mRNAs, and microRNAs. This is a normal process that occurs in most cell types, and it can be altered under various pathologic conditions, such as myocardial infarction. A growing body of evidence suggests that exosomes can be used as both diagnostic markers and therapeutic tools for the treatment of various diseases. Exosomes harvested from either plasma or cells of an autologous source are nonimmunogenic and, thus, can be used to deliver therapeutic compounds, such as small interfering RNAs targeting specific genes for a therapeutic purpose.

A recent study by Bang et al. demonstrated that cardiac fibroblast-derived exosomes induce cardiomyocyte hypertrophy via a paracrine mechanism, and exosomes are the cell communicator between fibroblasts and cardiomyocytes. Moreover, it has been shown that exosomes released from local tissue may enter the circulation and alter the function of cells of a distant site as the tissue communicator. It would be interesting to know whether hypoxia-inducible factor-induced exosomes from cardiac endothelial cells could activate cells from bone marrow to enhance cardiac regeneration.

In summary, the work of Ong et al. established the role of exosomes in altering the local niche as the cell–cell communicator. Additional studies on whether exosomes could alter distant niche, such as bone marrow, as the tissue–tissue communicator and whether direct delivery of exosomes containing miR-126 and miR-210 could improve cardiac regeneration are certainly warranted. These studies will pave the way to the development of a novel exosome-based diagnosis and therapies for cardiovascular diseases.

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Disclosures

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