Editorial Commentary

The exosomes carry new hope for cardiac regeneration

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Coronary artery disease (CAD) is the number one cause of death in developed countries (1,2). In the UK alone, there are 2 million people with CAD and 188,000 require treatment for a myocardial infarction (MI) each year. Because of the limited regenerative capacity of the human heart (3), an acute MI causes permanent damage that may ultimately result in heart failure (HF). The management of chronic HF has improved considerably in recent years but, at the same time, healthcare and social costs have rocketed. Therefore, there is an urgent need for new strategies potentially transforming palliative care into curative therapy.

Cardiovascular regenerative medicine is an exciting and rapidly expanding field of research that aims to improve the treatment of CAD through novel healing modalities, such as gene therapy, stem cell therapy, and tissue engineering. Clinical trials using skeletal myoblasts, bone marrow-derived cells and mesenchymal stem cells (MSCs) have shown feasibility and initial evidence of efficacy (4-6). However, the mechanisms underpinning the benefit of cell therapy remain matter of debate among scientists and clinicians. The direct participation of transplanted cells in vascular and cardiac repair has been toughly disputed (7,8). The prevalent view among the scientific community is that factors secreted by exogenous cells are pivotal in promotion of tissue healing and can also incite resident cells to change their secretome (9,10). Stem cells secrete potent combinations of trophic factors that help cardiac repair and regeneration at multiple points, such as supporting cardiomyocyte viability, differentiation of resident stem/progenitor cells, and angiogenesis, while modulating inflammatory and pro-fibrotic responses (9,11-13).

A recent study from Qiao *et al.* indicates that microRNA-21-5p dysregulation in exosomes derived from patients with HF compromises the regenerative potential of these secreted vesicles thereby resulting in delayed recovery in a murine model of MI (14). The authors also reported that other microRNAs contained in the exosomes can contribute in the observed adverse effects (14). This microRNA has been implicated in cardiac remodeling, including the induction of fibrosis (15), though this observation was not confirmed by others (16). MI is associated with recruitment of circulating monocytes. Importantly, microRNA-21-5p is the microRNA most represented in macrophages and its downregulation has been associated with induction of atherosclerosis, plaque instability, and vascular inflammatory reaction (17). Mechanistically, the lack of microRNA-21 in macrophages upregulated the expression of the target mitogen-activated protein kinase kinase 3, thereby leading to the activation of the p38-CHOP and cJNK signaling pathways; the ultimate effect being the induction of macrophage apoptosis (17). Moreover, ablation of microRNA-21 in macrophages reduces the clearance of apoptotic cells, which is key for the resolution of inflammation. This means that downregulation of the microRNA can lead to unresolved inflammation in the injured tissue (17). It would be interesting to understand if macrophages from patients with HF have a deficit in microRNA-21 and this contributes to an imbalance between inflammation and angiogenesis. In addition, the microarray used by the authors did not include some microRNAs that are contained in the soluble fraction of the stromal cell secretome. For instance, stromal cells-secreted microRNA-132 acts as a paracrine inducer of cardiac

repair (18). *In vitro* studies demonstrated that microRNA-132 activates vascular growth while inhibiting myofibroblast differentiation into collagen-producing fibroblasts, these effects being mediated by suppression of Ras-GTPase activating protein and methyl-CpG-binding protein 2 (18). In infarcted hearts of mice with coronary artery ligation, intra-myocardial delivery of human pericytes, which belong to the perivascular stromal cell population, reportedly improved indexes of cardiac contractility, reparative neovascularization, and interstitial fibrosis, but these benefits were negated to the same pericytes transfected with anti-microRNA-132 (18).

The study by Qiao *et al.* provides important cumulative evidence supporting the theory that stromal cells have a potential in regenerative medicine and that their secretome can be a source of curative agents. It remains to be elucidated whether the failure of this endogenous mechanism has any relevance in the pathogenesis and progression of HF. Moreover, the authors highlight that their findings may account for the modest benefit of patients' autologous cell therapies reported in recent clinical trials. Certainly, this possibility should be taken in consideration. However, the experimental approach they have adopted consisted in the transfer of exosomes genetically modified to inhibit or overexpress the microRNA-21. Since the observed defect was discovered in HF patients, the obvious experimental recipient would have been mice with chronic HF rather than MI. Despite of the above incongruence, this excellent study contributes in the advancement of potential mechanisms of cardiac repair and may have an impact in the generation of new exosome-based therapies.

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