EDITORIAL

Open Challenges and New Perspectives in Cardiac Regenerative Medicine

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Cardiac regenerative medicine for heart failure has become a consolidated research field in the past 20 years. Despite the time and effort put by the scientific community into a deeper understanding of the regenerative potential of the heart and its mechanisms, healing an injured heart is still an open challenge. Cell therapy has played an important role in the progression of cardiac regenerative medicine, although many other areas have significantly pushed the field forward, mostly related to cell reprogramming and cell cycle re-entry strategies. Different cardiac and non-cardiac cell populations endowed with specific regenerative/therapeutic potential have been characterized, and the biological mechanisms responsible for the observed beneficial effects are being studied in both preclinical and clinical settings. The present collection of review articles explores several topics, which can significantly affect the way cardiac regenerative medicine, including cardiac cell therapy, will follow its future steps, and possibly advance towards an increase of its therapeutic benefit.

The very initial expectation in the field of cell therapy was a quite straightforward prevision: transplanted undifferentiated cells with cardiogenic potential would replenish the pool of cadiomyocytes lost after an injury by direct differentiation. This expected easy picture has been gradually overcome in favor of a more complex one, involving the interplay between cell populations, a-cellular factors, and the cardiac microenvironment as a whole. With this view, also the development of finely designed biotechnological and bioengineering strategies and tools needs space.

Besides transplantation of regenerative progenitors from many sources, strategies of direct *in situ* reprogramming of resident cells to an undifferentiated state have been progressively explored (see review by Li TS *et al.*). This approach gives the double advantage of exploiting the abundance of stromal cells in the heart, while targeting a population contributing to damage and fibrosis, which is fibroblasts. In line with a vision of cell therapy devoid of direct involvement of exogenous cell sources in new tissue generation, many recent and current research studies are investigating indirect paracrine mechanisms of intervention on the damaged myocardium. These mainly include preserving cell viability and function of stressed myocytes, sustaining angiogenesis, counteracting detrimental activation of fibrosis and adverse remodeling, and activating endogenous repair. Indeed, the more potent the beneficial paracrine effect, either through enhanced cell engraftment or paracrine signals potentiation, the more effective the improvement in cardiac function observed in preclinical studies (see review by Davis DR).

As anticipated, tissue repair and regeneration involve a balance and crosstalk amongst many players and pathways. Thus, cardiac regenerative medicine requires continuous insight into endogenous biological and pathogenetic mechanisms. Myocardial injury is associated, together with other factors, with deranged protein homeostasis and mitochondrial dysfunction, both significantly contributing to cell senescence (see review by Beltrami AP *et al.*). This phenomenon involves not only parenchymal cells, but also many other cell types that can mediate impairment or reduction of reparative capacity, such as pericytes, stromal cells, and epicardial cells. The latter, in particular, are significantly involved in cardiac development and repair (once activated) for their paracrine communication with the myocardium (see review by Limana F *et al.*). However, the equilibrium between pro-regenerative and pro-fibrotic signaling still requires clarification.

An important topic involved in the cardiac muscle repair scenario is intra- and inter-cellular signaling mediated by non-coding RNAs (ncRNAs). They are regulators of cardiac muscle development and homeostasis, with altered ncRNA expression reported to affect the physiology of all different cardiac cell types, including cardiomyocytes and stromal cells (see review by Ballarino M *et al.*). Importantly, both short and long ncRNA can be secreted either as free molecules or transported by extracellular vesicles, and act as mediators of paracrine signaling in cardiac regenerative medicine applications.

Cell-free approaches represent a promising frontier, and the strategy seems fully supported by the accredited paracrine hypothesis for therapeutic cell action. Exosomes represent a class of vesicles recently explored as cell products for cardiac regeneration, collected through the secretome of specific reparative cell types, or artificially loaded with desired molecules. The use of a-cellular products, retaining nonetheless potent biological activity, may overcome several limitations intrinsic to cell

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therapy, such as immunological concerns, and may allow standardized production. Similarly, another carrier system holding great promise is biomimetic nanoparticles that fuse biological and fabricated components to improve therapeutic efficiency, tissue targeting, and allow controlled release of their content (see review by Cheng K *et al.*).

A lot has been done to understand what is needed to fix the damaged cardiac muscle, to prevent or, at least, limit its deterioration after injury, but one of the major challenges in cardiac repair remains the identification of the most effective advanced therapeutic product. Whether cell-based or a-cellular, delivered through injection, cardiac patches or within matrix cocoons, cellular and/or biotechnological therapies seem highly promising options for treating heart failure. A strong interdisciplinary drive, involving cellular and molecular biology, bioengineering, and biomaterials, is already pushing some of these strategies, either alone or in combination, towards rapid clinical translation (see review by Gambini E *et al.*). The complexity of the regenerative therapy approach currently stimulates challenging experimental settings, as well as the exploration of fields such as nanotechnology. This opens new and exciting perspectives in the design of novel efficient and feasible therapeutic options for treating heart failure patients in the near future.

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