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General review

Stem cells for the treatment of heart failure

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ABSTRACT

Stem cell-based therapy is currently tested in several trials of chronic heart failure. The main question is to determine how its implementation could be extended to standard clinical practice. To answer this question, it is helpful to capitalize on the three main lessons drawn from the accumulated experience, both in the laboratory and in the clinics. Regarding the *cell type*, the best outcomes seem to be achieved by cells the phenotype of which closely matches that of the target tissue. This argues in favor of the use of cardiac-committed cells among which the pluripotent stem cell-derived cardiac progeny is particularly attractive. Regarding the *mechanism of action*, there has been a major paradigm shift whereby cells are no longer expected to structurally integrate within the recipient myocardium but rather to release biomolecules that foster endogenous repair processes. This implies to focus on early cell retention, rather than on sustained cell survival, so that the cells reside in the target tissue long enough and in sufficient amounts to deliver the factors underpinning their action. Biomaterials are here critical adjuncts to optimize this residency time. Furthermore, the paracrine hypothesis gives more flexibility for using allogeneic cells in that targeting an only transient engraftment requires to delay, and no longer to avoid, rejection, which, in turn, should simplify immunomodulation regimens. Regarding *manufacturing*, a broad dissemination of cardiac cell therapy requires the development of automated systems allowing to yield highly reproducible cell products. This further emphasizes the interest of allogeneic cells because of their suitability for industrially-relevant and cost-effective scale-up and quality control procedures. At the end, definite confirmation that the effects of cells can be recapitulated by the factors they secrete could lead to acellular therapies whereby factors alone (possibly clustered in extracellular vesicles) would be delivered to the patient. The production process of these cell-derived biologics would then be closer to that of a pharmaceutical compound, which could streamline the manufacturing and regulatory paths and thereby facilitate an expended clinical use.

In a recent meta-analysis of 31 randomized cell therapy trials in heart failure which included 1521 patients, exercise capacity, left ventricular ejection fraction and quality of life were found to be improved in the treated patients [1]. However, this positive appraisal of outcomes should be interpreted cautiously because in several of these studies, cardiac function was assessed by echocardiography which is less objective than magnetic resonance imaging [2] while the aforementioned benefits in terms of mortality, functional improvement and increase in left ventricular ejection fraction were no longer significant when the analysis was restricted to the subgroup of blinded trials. Nevertheless, there are some encouraging signals and the challenge is now to use the large experimental and clinical database [3] as a building block to design more effective protocols, with regard to the selection of cell type, the modalities of cell transfer and the optimization of cell engraftment. Importantly, to be successful, the development of such protocols first requires a more thorough understanding of the mechanism of action of the transplanted cells.

1. Mechanistic considerations

Initially, the objective of cell therapy was the integration of transplanted cells within the recipient myocardium with the assumption that their electrical coupling with host cardiomyocytes should translate into a mechanical contribution of the cellular graft to contractile function. Over time, a major change in the mechanistic paradigm has occurred in that cells are now

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increasingly thought to primarily act as non-necessarily contracting reservoirs of a wide array of biomolecules which harness endogenous repair pathways [4]. This paracrine mechanism involves multiple targets (stimulation of angiogenesis; attenuation of fibrosis, inflammation and apoptosis; recruitment of tissue-resident stem/progenitor cells), which synergistically contribute to improved tissue protection and an attendant preservation of cardiac function. Three major lines of evidence support this paracrine hypothesis. First, the literature is replete with studies that consistently demonstrate a sharp discrepancy between the scarcity of sustained cell engraftment and the maintenance of a functional benefit, thereby making highly unlikely that the minute amounts (if any) of still detectable cells can account for the preservation of left ventricular function and geometry and thus rationalizing an alternate mechanism of action than a cell-autonomous contractile effect [5]. Second, while intramyocardially injected embryonic stem cell (ESC)-derived cardiomyocytes have been shown to couple with host cardiomyocytes, such was not the case when the same cells were delivered under the form of an epicardial patch [6]. Nevertheless, several studies have shown that cell-loaded epicardial patches were functionally more effective than injected cells, thereby supporting the idea that electro-mechanical integration is not a prerequisite for a successful outcome. Third, cells are known to release a wide blend of biomolecules acting on key signaling pathways such as those mentioned above. In particular, elegant studies based on 14 carbon dating and stereology have documented a very low, albeit existing, turn-over of cardiomyocytes during adulthood [7], thereby making conceivable that such a process could be boosted by appropriate cues, such as those provided by cell-secreted factors. Alternatively, the paracrine mobilization of endogenous quiescent cardiac stem cells or even the restoration of a cardio-angiogenic differentiation program in epicardial cells might underpin the increase of endogenous contractile elements such as that reported after intramyocardial delivery of ESC [8].

A precise characterization of the cell-released factors purportedly accounting for their benefits still remains elusive but there is an increasing body of evidence that these factors could be clustered in extracellular vesicles. Extracellular vesicles encompass particles of different sizes, primarily exosomes (<100 nm), which are formed through a three-step process (invagination of the plasma membrane producing endocytic vesicles, inward budding of the endosomal membrane giving rise to multivesicular bodies and fusion of these bodies with the plasma membrane), and shedding microvesicles (up to 300 nm) which originate from the outward budding of cytoplasmic protrusions. They cargo a wide array of biomolecules, including microRNAs, proteins (more than 4000 different proteins and 700 different RNAs have been described so far [9]), lipids and genetic material that they can horizontally transfer to target cells, thereby activating cytoprotective pathways [10] as exemplified by the ability of cardiosphere-derived extracellular membrane vesicles to alter the phenotype of fibroblasts and endow them with angiogenic and cardioprotective properties [11]. Extracellular vesicles are thus thought to be major players in the intercellular communication network and their role as mediators of the effects of cell therapy is primarily based on the observations of their reparative effects made in different disease states (reviewed in [12]), including myocardial infarction [13–15], and showing that they can largely recapitulate the benefits of transplanted cells. Likewise, in preliminary studies, we have documented that the preservation of postinfarct function afforded by human ESC-derived cardiac progenitor cells could be equaled by delivery of the extracellular vesicles collected from those same cells. Because microRNAs, known to regulate endogenous repair [16], comprise a large fraction of the extracellular vesicular package, some of them have been identified as playing a key role in vesicle-induced tissue protection [14,15,17]. However, it is rather likely that the protective effects of the vesicles arise from the mix of the molecular payload that they shuttle and it might actually be therapeutically counterproductive to deconstruct the vesicular content. Interestingly, exosome-mediated transfer of biomolecules to target cells has been reported to occur within a relatively short time frame [18] which would be consistent with the protective effects of transplanted cells despite their fast clearance. In the context of a paracrine mechanism of action, vesicles feature advantages over conditioned media, which contain large molecules unlikely to cross cell membranes as well as over the delivery of defined factors which only target a single signaling pathway. Confirmation that the use of vesicles alone could successfully substitute for cells would have major clinically-relevant advantages with regard to manufacturing, streamlining of the regulatory path and final costs. Several questions, however, must still be answered before riping towards this cell-based but cell-free therapy, including the confirmation that biomolecules alone can fully substitute for cell contact-dependent signals, the identification of the most functionally effective vesicles (exosomes, microvesicles or their mix), the assessment and extent of their potential immunogenicity, the phenotype of the parent cells they should be retrieved from (as the vesicular content varies with the cell of origin) and, ultimately, the characterization of their most "active" ingredients in the perspective of the possible synthesis of biomimetic compounds.

A key question, however, is to assess whether the endogenous repair capacity which has been convincingly demonstrated in animal models is relevant to the human, chronically diseased heart. From this standpoint, encouraging signals are provided by two studies. Thus, Cheng et al. [19] have reported that cardiospheres retrieved from patients with advanced heart failure retained their ability to ameliorate left ventricular dysfunction of infarcted mouse hearts. In another study, mechanical unloading by a left ventricular assist device in patients with heart failure has been shown to result in an increased number of cardiomyocytes at the time the system was removed to proceed with transplantation [20]. Put together, these data support the idea that even though the naturally occurring repair mechanisms of the human heart are insufficient to compensate for the massive loss of cardiomyocytes resulting from extensive infarcts, they still may be amenable to therapeutic interventions targeted at their upregulation.

2. Clinically-relevant considerations

2.1. Cell phenotype

Assuming that the grafted cells primarily act as biofactories, the next question is whether their phenotype makes a difference, i.e., given the fact that multiple cells types secrete multiple factors, one can wonder whether cells could be easily exchangeable with, ultimately, similar outcome. Such does not seem to be the case in that the studies which have compared different cell types have consistently demonstrated the superiority of cardiac-committed cells (c-*kit*$^+$ or Sca-1$^+$ cardiac stem cells, cardiospheres, induced pluripotent stem cell [iPSC]-derived cardiomyocytes) over cells not committed to a cardiac lineage such as bone marrow mononuclear cells, mesenchymal stem cells (MSC) or skeletal myoblasts [21–28] (Table 1). Of note, the superiority of cardiac-committed cells could be evidenced on the basis of various end points such as better engraftment, reduced extent of infarction and fibrosis, increase in angiogenesis, improvement of cardiac function and even mitigation of ventricular arrhythmias. Furthermore, the better outcomes associated with cardiac-committed cells were also demonstrated in terms of paracrine factor production [26] with a differential