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Review

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Stem cells for the treatment of heart failure

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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 common clinical practice. To fill this gap, it is critical to first validate the hypothesis that the grafted stem cells primarily act by harnessing endogenous repair pathways. The confirmation of this mechanism would have three major clinically relevant consequences: (i) the use of cardiac-committed cells, since even though cells primarily act in a paracrine manner, such a phenotype seems the most functionally effective; (ii) the optimization of early cell retention, rather than of sustained cell survival, so that the cells reside in the target tissue long enough to deliver the factors underpinning their action; and (iii) the reliance on allogeneic cells, the expected rejection of which should only have to be delayed since a permanent engraftment would no longer be the objective. One step further, the long-term objective of cell therapy could be to use the cells exclusively for producing factors and then to only administer them to the patient. The production process would then be closer to that of a biological pharmaceutical, thereby facilitating an extended clinical use.

1. Introduction

A recent meta-analysis including 31 randomized cell therapy trials in 1521 patients with heart failure has reported a clear benefit of this approach with regard to exercise capacity, left ventricular ejection fraction and quality of life [1]. This optimistic conclusion, however, needs to be tempered in light of two factors: the method used for assessing cardiac function and the blinded or unblinded nature of the trial. Namely, another almost as recent meta-analysis has also concluded to the benefit of cell therapy, but exclusively when the functional assessment was based on echocardiography which is known to be operator-dependent, whereas the benefit was no longer significant when the analyses of outcome were based on magnetic resonance imaging which provides more objective data [2]. Furthermore, the randomized trial mentioned above [1] indicates that the benefits of cell therapy in terms of mortality, functional improvement and increase in left ventricular ejection fraction are also no longer significant in the subgroup of trials which have been blindly analysed. These comments should not be interpreted as suggesting that there is no benefit to draw from cardiac cell therapy in the context of heart failure. They simply call for some caution, which is indeed consistent with the fact that if phase 2 clinical trials can give us a suggested way forward, they are not tailored to conclusively establish that the new therapy under investigation should be readily implemented in the clinics. In the case of the treatment of heart failure by stem cells, it is indeed not so surprising that the first wave of clinical trials have not yielded results matching the initial expectations which were definitely excessive. The likely main reason is that these early trials have been clouded by the uncertainty which then surrounded the optimal cell type to be used as well as the most efficient method of cell transfer. Lessons drawn from this early clinical experience, together with the numerous laboratory data [3], now allow better clarification of these issues and if these lessons can be appropriately translated in protocols which are in preparation or already operative, there is a reasonable hope that the second wave of clinical trials could be therapeutically more efficient, thereby allowing

clarification of the place of cell therapy within the already available therapeutic armamentarium.

These lessons primarily derive from a major change in the hypothesis which underpins the mechanism of action of the grafted cells. Initially, the objective of cell therapy was that the grafted cells integrate within the recipient myocardium and, through the replacement of dead cardiomyocytes by this new graft-derived tissue, contribute to improved contractile function. The consistent discrepancy between the very limited, not to say complete lack, of grafted cells still detectable after a few weeks and the maintenance of a functional benefit has led scientists to revisit this hypothesis and to focus on a primarily paracrine mechanism. According to this paradigm, cells act by secreting multiple factors which harness endogenous repair pathways contributing synergistically to improve cardiac function [4]. The activation of these pathways could induce a stimulation of angiogenesis and a reduction of fibrosis (both of which would qualify as *repair*), and even maybe an increase in the pool of contractile cardiomyocytes (the only event which would qualify as true *regeneration*), even though the origin of these putatively new cardiomyocytes (mobilization of endogenous quiescent cardiac stem cells, multiplication of mature cardiomyocytes, reestablishment of a cardio-angiogenic differentiation programme in epicardial cells) still remains unsettled.

This paracrine hypothesis, if it was unequivocally validated, has major practical consequences which are detailed below and which could really allow a dramatic improvement in the efficacy of cardiac cell therapy and allow it to fill the gap which still exists between well-controlled trials and a large-scale clinical use.

2. Cardiac versus extra-cardiac cells

Even if they are still limited, the head-to-head experimental studies which have compared different cell types have established the functional superiority of those whose phenotype is close to that of the target tissue, i.e. of cells committed towards a cardiac lineage [5]. This superiority remains present even if the paracrine hypothesis is prevailing, as shown by the finding that the production of potentially cardio-protective growth factors is higher with cells derived from the right ventricle (cardiospheres) than with extra-cardiac cells derived from bone marrow or adipose tissue [6]. These observations justify the choice of cells currently tested in the second wave of clinical trials and which, in contrast to the cells used in the first era (skeletal myoblasts and bone marrow cells), adopt or try to get close to a cardiac phenotype. These cells include cardiospheres derived from a piece of right ventricular muscle obtained by a trans-jugular endomyocardial biopsy and which seem to be primarily composed of mesenchymal cells [7] or mesenchymal stem cells derived from the bone marrow but exposed to a cocktail of cardiopoietic factors designed to force them to express cardiac markers before their reinjection [8]. The same concern of using cells as close as possible to those which they are intended to rescue has dictated our choice to use human embryonic stem cells, the intrinsic pluripotency of which allows differentiation into multiple cell types including cardiomyocytes. Depending on the culture conditions, the cells can then be grafted at the early stage of progenitor cells (which is the option that we have selected for an initial

clinical trial) or later on, once they have completed their development into mature cardiomyocytes. A thorough discussion of the specific problems raised by these cells is beyond the frame of this review and suffice is to say that, from a clinical point of view, the major safety issue here is the purification of the final cell therapy product in order to ensure that it is no longer 'contaminated' by residual pluripotent cells which would have escaped the cardio-instructive signals and might then become tumorigenic [9].

3. Retention versus survival of cells

The transfer of cells in the heart can be achieved either by an intracoronary or by a direct intramyocardial approach. In the latter case, cells can be delivered from the 'inside', i.e. in the left ventricular endocardium by a percutaneous catheter, or from the 'outside', i.e. by transepical injections during a surgical procedure. Unfortunately, regardless of the method, and even though direct administration is the most efficient [10], a very large fraction of cells is lost during this transfer because of mechanical leakage (heartbeats which squeeze the myocardium) or wash-out through the venous and lymphatic systems. Furthermore, among the cells which have been initially retained in the myocardium, the majority are expected to die within the hours or days following the procedure because of multiple causes: hypoxia related to the poorly vascularized environment, inflammation, apoptosis due to the loss of cell-to-cell connexions and cell anchorage to an extracellular matrix, rejection if allogenic cells have been used. Consequently, multiple strategies have been developed to empower the survival of grafted cells. They are based on physical (for example, hypoxic preconditioning), pharmacological or genetic processes [11]. If these different approaches have occasionally been successful in experimental models, then their common complexity and the regulatory hurdles inherent in the use of some of the involved compounds have so far precluded their translation towards the clinics. However, in the light of the paracrine hypothesis mentioned above, the real interest of these pro-survival strategies deserves to be revisited. Namely, the benefit of the cells seems to be more related to their initial retention, which is a prerequisite for them to secrete the factors underpinning their effects. Once activated, the endogenous pathways seem to remain effective over time even though the trigger cells have disappeared. For this reason, it is probably critical to focus on the optimization of early engraftment in order that a sufficient number of cells remain present during a sufficiently long period of time for releasing the blend of biomolecules which underpin their paracrine effects. This is well illustrated by a study [12] which has compared the injection of mesenchymal stem cells, with or without encapsulation in alginate, in a rat model of myocardial infarction. Not surprisingly, retention of cells was higher 3 days after the procedure in the encapsulated group but after one week almost all cells had gone, regardless of whether they had been combined with alginate or not. Nevertheless, after one month, outcomes were significantly better with regard to left ventricular function, reduction in scar size and angiogenesis in the encapsulated group, thereby suggesting that it had been sufficient for the cells to be engrafted in large amounts early on after their delivery for inducing protective effects which had then remained sustained over time, even though the cells were no longer present in the target tissue.

When the cells are delivered through a catheter, this optimization can rely on dedicated delivery devices, molecules enhancing homing of cells towards ischaemic areas or incorporation of the cells into resorbable biomaterials which can increase the viability of cells during the early postengraftment period and specifically allow them to be shielded from deformation by extensional flow experienced during needle injection [13]. For surgical applications, it seems more effective to use an epicardially delivered patch rather than multiple injections. These patches, in which cells have been incorporated, feature several advantages: greater retention of cells, preservation of their viability due to their attachment to a self-secreted matrix, mechanical strengthening of the diseased wall, and the potential to act as a platform for releasing drugs or growth factors previously incorporated in the patch material [14].

4. Autologous versus allogeneic cells

The advantages of autologous cells are well recognized: availability, absence of immune or ethical issues. However, with accumulated experience, their limitations have also been acknowledged: interindividual variability of cell function, making difficult the consistent yield of a well-standardized cell therapy product; logistical complexity when cells have to be shipped from the collection centre to a core facility for processing (this situation is already common and will become increasingly frequent because of the stringent regulatory constraints pertaining to the so-called Advanced Therapy Medicinal Products); and cost of customized quality controls. Conversely, allogeneic cells derived from cell banks, which have been extensively qualified for their functionality, sterility and cytogenetic stability, overcome these hurdles. An additional advantage is that such cells are readily available whenever necessary, as an 'off-the-shelf' product. Obviously, the expected limitation of allogeneic transplantation is the rejection of the grafted cells. However, in the light of the paracrine hypothesis already mentioned, this issue also needs to be revisited since the objective may no longer be to avoid rejection by a life-long immunosuppressive treatment, with its well-known side effects, but only to delay it in order to allow, once again, for cells to be present in sufficient amounts and for a sufficient period of time to load the target tissue with their cardioprotective factors before being cleared by the immune system of the host. Support for this hypothesis comes, in particular, from a study which has compared the effects of cardiospheres in relation to their allo-, xeno- or syngeneic origin [15]. Eight days after the injection of cells in the infarcted myocardium of rats, retention was found to be equivalent between allo- and syngeneic cells; not unexpectedly, however, after three weeks, cell engraftment was still high in the syngeneic group, whereas most of the allogeneic cells had disappeared because of rejection. However, after six months, the functional benefits were similar in the two groups, suggesting that an initially high rate of cell engraftment had been effective enough to trigger endogenous pathways, the protective effects of which had then remained

operationally sustained despite the lack of a persistent cell engraftment. Should this scheme be validated, it would have a real clinical relevance by leading to a major simplification of the immunosuppressive treatment. Namely, regardless of its modalities (drugs or induction of tolerance, for example, by co-transplantation of mesenchymal stem cells or specific antibodies), this treatment could be of short duration, with a subsequently favourable shift of the risk-to-benefit ratio.

5. Cells versus factors

If factors released by the grafted cells are still incompletely characterized, then several studies yet suggest that they might be clustered into microparticles released by those cells. These microparticles represent an important means of intercellular communication, in particular because they carry multiple physiologically active biomolecules, and particularly micro-RNAs able to modulate gene expression in the target cells. Depending on their size, these vesicles include exosomes (up to 100 nm) and microvesicles which are larger. The task then is to assess whether it would be possible to replace cells by their sole secretion products. Indeed, the beneficial effect of the administration of mesenchymal stem cell-derived microvesicles has already been established in a murine model of myocardial ischaemia [16]. Likewise, preliminary studies from our laboratory suggest the functional equivalence between injection of human embryonic stem cell-derived cardiac progenitors and injection of microvesicles derived from the same batch of cells. This functional equivalence now needs to be confirmed by additional studies. It is also important to determine which is the optimal parent cell the vesicles should be derived from and to more extensively characterize the vesicle content accounting for their cytoprotective effect. If it really turned out that the benefit of stem cell transplantation can be recapitulated by the exclusive administration of their secretome, one might consider a new paradigm of 'cell-free cell therapy', whereby cells could be exclusively used *in vitro* for producing the factors which would then be the only therapeutics given to the patient. Such a novel form of biotherapy would have the major advantage of streamlining technical, ethical, economical and regulatory processes and thus overcome many hurdles associated with conventional cell therapy. One important consequence of such an approach could be to make it accessible to a larger number of patients suffering from heart failure who have exhausted conventional therapies and are therefore in need of new therapeutic options.

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