The Potential of Stem Cells in Regeneration of Damaged Heart

The mammalian heart has been considered for long time as a terminally differentiated organ incapable of regenerating after injury. In recent years, many evidences demonstrated that cardiomyocytes, during aging and after injury, are able to reentry in the cell cycle and promote cells renewal [Ahuja, 2007, Cardiac myocyte cell cycle control in development`, disease`, and regeneration].

In addition, it has been identified the presence of several endogenous or extra-cardiac progenitor cells (CPCs) population that, after myocardial infarction (MI), are able to proliferate and differentiate into the cardiac lineages [Forte, 2011, Cardiac cell therapy: the next (re)generation].

Cardiac damage occurring after an insult, mostly ischaemic, triggers a cascade of cellular events, eventually leading to fibrosis and maladaptive remodelling. None of the pharmacological intervention approved so far can rescue or reverse this phenomenon, and cardiovascular diseases are still the leading cause of death in the western world (Wang et al., 2016). The availabile pharmacological treatments are sympthomatic and none of them can reverse or rescue heart failure completely. Therefore for nearly 20 years cell therapy has been considered the road to pursue, and cellular approaches have been studied and developed (Marbán, 2018).

Cardiac cell therapy (CCT) is a therapeutic approach, based on isolation, expansion and injection of different population of adult stem cells, and seems to be a valid alternative to promote and support heart regeneration.

Since the seminal observations regarding the regenerative capacity of transplanted autologous skeletal myoblasts, research has explored different cellular populations which can be used effectively (at least in principle) as a therapeutic agent against cardiac adverse remodelling, acting via specific mechanisms to improve cardiac function (Reviewed in Pagano et al., 2018).

Many different types of adult SCs, distinguished by their origin and differentiation capacity, have been studied, e.g., multipotent bone marrow derived SCs (BM-SCs) (including hematopoietic (HSCs), mesenchymal (BM-MSCs), endothelial stem cells), mesenchymal SCs (MSCs), skeletal myoblasts, and cardiac SCs (CSCs))

In the last decades the results obtained in several clinical trials have demonstrated the therapeutic potential of the non-cardiac stem cell sources skeletal myoblast [Taylor, 1998. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation][Menasché, 2008, The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation], bone-marrow mononuclear cells [Orlic, 2001, Bone marrow cells regenerate infarcted myocardium] [Orlic, 2001, Bone marrow cells regenerate infarcted myocardium] [Jeevanantham, 2013, Clinical trials of cardiac repair with adult bone marrow-derived cells], and mesenchymal stem cells [Golpanian, 2016, Rebuilding the Damaged Heart: Mesenchymal Stem Cells`, Cell-Based Therapy`, and Engineered Heart Tissue] [Perin, 2015, A Phase II Dose-

Escalation Study of Allogeneic Mesenchymal Precursor Cells in Patients With Ischemic or Nonischemic Heart Failure]. However, many evidences underlined that resident CPCs, especially Cardiosphere-derived cells CDCs, represent the best candidate for cardiac regenerative medicine [Nguyen, 2016, Adult Stem Cell Therapy and Heart Failure`, 2000 to 2016: A Systematic Review].

Among all the adult progenitor cell types, only three are currently being tested as future cell-based commercial therapies: two of them are in phase III testing for heart failure (HF) with reduced ejection fraction and are i) autologous bone marrow mononuclear cells (CardiAMP trial, NCT02438306) and ii) allogeneic mesenchymal precursor cells (DREAM HF-1 trial, NCT02032004); one is being developed for various types of HF, including genetic disease associated HF, that is cardiosphere-derived cells (CDCs) (CADUCEUS trial NCT00893360 now closed and HOPE-2 trial, NCT03406780 still recruiting). In addition, CDCs are the unique cell populations yet used in clinical trials which can be qualify as cardiac progenitor cells (CPCs), being of intrinsic cardiac origin.

A recent editorial on Nature Biotechnology (‘A futile cycle in cell therapy’, 2017) highlighted the importance of rigorous description of cell mediated heart repair mechanisms before clinical translation, given the negative results obtained by the largest US clinical trial on bone marrow derived CD34+ cells (PreSERVE-AMI); the same attention should be given to the different delivery methods, each of which could give unique therapeutic advantage to a cell type or the other. The results of completed trials revealed that stem cells often fail to engraft and survive for long time periods after transplantation (Wernly et al., 2019), thus defining the best delivery method for preserving their viability and therapeutic capacity becomes crucial.

Many efforts have been made within the scientific community, aiming at potentiating the cellular products and describing the in vitro response to the milieu the cells would experience once transplanted. Yet, not as many addressed specifically what are the most suitable surgical delivery methods to be used for efficient usage of the specific cellular product.