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Exploring pericyte and cardiac stem cell secretome unveils new tactics for drug discovery☆

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ABSTRACT

Ischaemic diseases remain a major cause of morbidity and mortality despite continuous advancements in medical and interventional treatments. Moreover, available drugs reduce symptoms associated with tissue ischaemia, without providing a definitive repair. Cardiovascular regenerative medicine is an expanding field of research that aims to improve the treatment of ischaemic disorders through restorative methods, such as gene therapy, stem cell therapy, and tissue engineering. Stem cell transplantation has salutary effects through direct and indirect actions, the latter being attributable to growth factors and cytokines released by stem cells and influencing the endogenous mechanisms of repair. Autologous stem cell therapies offer less scope for intellectual property coverage and have limited scalability. On the other hand, off-the-shelf cell products and derivatives from the stem cell secretome have a greater potential for large-scale distribution, thus enticing commercial investors and reciprocally producing more significant medical and social benefits. This review focuses on the paracrine properties of cardiac stem cells and pericytes, two stem cell populations that are increasingly attracting the attention of regenerative medicine operators. It is likely that new cardiovascular drugs are introduced in the next future by applying different approaches based on the refinement of the stem cell secretome.

Contents

Abbreviations: Abi3bp, ABI Family Member 3 Binding Protein; Ang, Angiopoietin; CSCs, Cardiac stem cells; CDCs, Cardiosphere-derived cells; CM, Conditioned medium; CHD, Coronary heart disease; DPP-4, Dipeptidyl peptidase-4; ESCs, Embryonic stem cells; ECs, ECs; EPCs, Endothelial progenitor cells; bFGF, Fibroblast growth factor; FDA, Food and Drug Administration; GLP1, Glucagon-like peptide-1; EPCs, Endothelial progenitor cells; eNOS, Endothelial nitric oxide synthase; FAECs, Fetal aorta ECs; FOXO1, Forkhead box protein O1; G-CSF, Granulocyte-colony stimulating factor; HF, Heart failure; HGF, Hepatocyte growth factor; IGF-1, Insulin growth factor-1; IL, Interleukin; HGF, Hepatocyte growth factor; HUVECs, Human umbilical vascular ECs; MMPs, Metalloproteinases; MI, Myocardial infarction; MCP-1, Monocyte chemoattractant protein-1; MSCs, Mesenchymal stem cells; NHS, National Health System; NRG-1, Neuregulin 1; PDGFβ, Platelet-derived growth factor beta; sFRP1, Secreted frizzled-related protein 1; SCF, Stem cell factor; SDF-1, Stromal cell-derived factor-1; TGF-β1, Transforming growth factor beta1; TNF-α, Tumor necrosis factor; LC-MS/MS, Tandem Mass Spectrometry Detection; VEGF-A, Vascular growth factor A; VPCs, Vascular progenitor cells.

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1. Introduction

Coronary heart disease (CHD) caused by the narrowing of arteries that feed the heart is the UK's single biggest killer, being responsible for ~73,000 deaths each year, an average of 200 people each day. Acute myocardial infarctionl (MI) represents the most harmful form of CHD. Over the last decade, mortality due to CHD has declined in the UK, but more people live with secondary consequences. In fact, most of the current treatments are palliative, i.e. they reduce symptoms associated with heart dysfunction, without providing a definitive repair. Consequently, CHD patients undergo a progressive decline in the pumping function of the heart that ultimately leads to heart failure (HF). Today, post-infarct HF is the leading cause of invalidity, hospitalization and mortality in patients over 65. In 2012–13, the UK National Health System (NHS) expenditure for cardiovascular disease was £7.02billion, 63% of which devoted to secondary care (Bhatnagar, Wickramasinghe, Williams, Rayner, & Townsend, 2015) The NHS analysts have predicted a mismatch between total budget and patient needs of nearly £30 billion by 2020/21. Therefore, efficiency actions to increase quality and reduce expenditure growth are essential for all services, including those for treatment and care of CHD patients. However, efficiency alone may not suffice without the introduction of new technologies having a transformative impact on this unmet clinical field.

1.1. The urgent need for new therapies

Current care of CHD comprises pharmacotherapy and revascularisation. However, medical treatment can be ineffective as in the case of refractory angina (which has an estimated prevalence of 1.8 million in the USA and an incidence of 30–50,000/year in Europe). Additionally, a steadily increasing number of patients fall into the category in which revascularization cannot be applied or fails because of restenosis. This is especially true of patients with occlusive pathology extending to the microcirculation and diabetic or elderly patients who have had multiple bypasses and stenting operations. Also, the most important limitation of current treatments is that they do not replace cells irreversibly damaged by ischaemia.

Cardiovascular regenerative medicine is a fast-growing field of research that aims to improve the treatment of CHD through innovative restorative methods, such as gene therapy, stem cell therapy and tissue engineering (Assmus et al., 2002; Wollert et al., 2004). Clinical studies with skeletal myoblasts, bone marrow-derived cells, mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs) have shown feasibility and initial evidence of efficacy (Assmus et al., 2002; de Jong, Houtgraaf, Samiei, Boersma, & Duckers, 2014; Hare et al., 2009; Menasche et al., 2008; Sant'anna et al., 2010). After multiple systematic reviews and meta-analyses, the consensus is that transplantation of adult bone marrow cells modestly improves ventricular function, infarct size, and remodeling in patients with CHD compared with standard therapy, and these benefits persist during long-term follow-up (Martin-Rendon, 2016). Bone marrow cell transplantation also reduces the incidence of death, recurrent MI, and stent thrombosis in patients with CHD (Jeevanantham et al., 2012). Moreover, Steven Chamuleau, Andreas Zieher and collegaues have recently utilized interaction models in a multivariable fashion to identify subgroups of patients that are defined as potential treatment responders, while simultaneously correcting for relevant factors that affect general disease outcome. This kind of approach could be the next step towards optimal cell therapy in clinical care (Zwetsloot et al., 2016).

The SCIPIO clinical trial, the first in man to investigate c-kit+ CSCs, reported that 16 patients with ischemic cardiomyopathy received intracoronary infusions of 0.5-1 $\times$ 10^6 c-kit+, autologous CSCs and compared to controls these patients benefited from an 8 and 12 unit increase in left ventricular ejection fraction, 4 and 12 months after infusion, respectively (Bolli et al., 2011). A subset of 7 patients was subject to cMRI analysis, which showed that the infarct region had significantly decreased in size by ~10 g up to 12 months following c-kit+ CSC transplantation (Bolli et al., 2011).

However, there is a persisting dispute regarding the mechanisms underpinning the benefit of cell therapy. The direct contribution of transplanted cells in vascular and cardiac reconstitution has been questioned (Balsam et al., 2004; Murry et al., 2004), and presently the concept of paracrine promotion of spontaneous healing processes prevails (Gnecchi et al., 2005; Tang et al., 2016a,b). Indeed, the general consensus is that cell therapy and resultant improvements in cardiac function and decreased infarct size in human trials is due to a 'paracrine' effect (Tang et al., 2016a,b). However, the lack of cardiomyocyte differentiation capability of bone marrow cells or CSCs could be due to lack of characterisation of the transplanted cell type, poor cell survival and retention, hostile host environment and subsequent restriction of cell proliferation, integration and differentiation in this damage-regeneration infarct model.

Despite the adult mammalian heart being composed of terminally differentiated cardiomyocytes that are permanently withdrawn from the cell cycle (Chien & Olson, 2002; Nadal-Ginard, 1978), it is now apparent that the adult heart has the capacity, albeit low, to self-renew cardiomyocytes over the human lifespan (Bergmann et al., 2012, 2015). This is supported by the detection of small, newly-formed, immature cardiomyocytes, which incorporate BrdU/EdU and/or stain positive for Ki67, Aurora B, and embryonic/neonatal myosin heavy chain, as well as cardiomyocytes undergoing mitosis, under normal conditions and in response to diverse pathological and physiological stimuli (Bergmann et al., 2015; Bostrom et al., 2010; Ellison et al., 2013; Urbanek et al., 2003, 2005; Waring et al., 2014). The source of these newly formed cardiomyocytes is a matter of debate (Laflamme & Murry, 2011). Three main sources of origin of the new cardiomyocytes have been claimed: (a) circulating progenitors, which through the bloodstream home to the myocardium and differentiate into cardiomyocytes (Quaini et al., 2002); (b) mitotic division of the pre-existing cardiomyocytes (Bersell, Arab, Haring, & Kuhn, 2009; Bostrom et al., 2010; Engel, Hsieh, Lee, & Keating, 2006; Senyo et al., 2013); and (c) a small population of resident multipotent stem cells able to differentiate into the main cell types of the heart (i.e., cardiomyocytes, smooth and endothelial vascular and connective tissue cells) (Rasmussen et al., 2014; Torella, Ellison, Karakikes, & Nadal-Ginard, 2007).

Blood-borne precursors, although well documented for having a role in inflammation and healing, and when adult mouse bone marrow cells were injected into the chick embryo they converted to a myocardial phenotype (Eisenberg, Burch, & Eisenberg, 2006), their cardiomyogenic potential in the damaged adult heart is very limited, if any (Ellison et al., 2013; Loffredo, Steinhauser, Gannon, & Lee, 2011). The evidence so far presented in support of re-entry of terminally differentiated cardiomyocytes into the cell cycle has been limited to show division of cells that express proteins of the contractile apparatus in their cytoplasm (Bersell et al., 2009; Bostrom et al., 2010; Kuhn et al., 2007; Senyo et al., 2013). This evidence is equally compatible with new myocyte formation from the pool of multipotent cardiac stem/progenitor cells, which as precursor cells express contractile proteins and because newly born myocytes are not yet terminally differentiated they are capable of a few rounds of division before irreversibly withdrawing from the cell cycle (Nadal-Ginard, 1978; Nadal-Ginard, Kajstura, Anversa, & Leri, 2003). However, the mechanisms underlying a strict postmitotic state in the heart during pathological remodeling have yet to be fully elucidated (Zebrowski, Becker, & Engel, 2016).

The best documented source of the small, immature, newly formed cardiomyocytes in the adult mammalian heart, including the human (Torella, Ellison, Mendez-Ferrer, Ibanez, & Nadal-Ginard, 2006), is a small population of endogenous cardiac stem and progenitor cells (eCSCs) distributed throughout the atria and ventricles, which are clonogenic, self-renewing and can give rise to functional cardiomyocytes and vasculature in vitro and in vivo. Importantly, owing to genetic