International Journal of Pharmaceutics 523 (2017) 454–475

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Hydrogel based approaches for cardiac tissue engineering

Laura Saludas[a,b,1], Simon Pascual-Gil[a,b,1], Felipe Prósper[b,c], Elisa Garbayo[a,b,2,*], María Blanco-Prieto[a,b,2,*]

[a] Pharmacy and Pharmaceutical Technology Department, School of Pharmacy, Universidad de Navarra, Pamplona, C/Irunlarrea 1, E-31080, Spain
[b] Instituto de Investigación Sanitaria de Navarra, IdiSNA, Pamplona, C/Irunlarrea 3, E-31008 Pamplona, Spain
[c] Hematology Service and Area of Cell Therapy, Clínica Universidad de Navarra, Foundation for Applied Medical Research, Universidad de Navarra, Pamplona, C/Irunlarrea 1, E-31080, Spain

ARTICLE INFO

Article history:
Received 31 August 2016
Received in revised form 24 October 2016
Accepted 26 October 2016
Available online 29 October 2016

Keywords:
Myocardial infarction
Cell therapy
Protein therapy
Hydrogel
Biomaterial
Tissue engineering

ABSTRACT

Heart failure still represents the leading cause of death worldwide. Novel strategies using stem cells and growth factors have been investigated for effective cardiac tissue regeneration and heart function recovery. However, some major challenges limit their translation to the clinic. Recently, biomaterials have emerged as a promising approach to improve delivery and viability of therapeutic cells and proteins for the regeneration of the damaged heart. In particular, hydrogels are considered one of the most promising vehicles. They can be administered through minimally invasive techniques while maintaining all the desirable characteristics of drug delivery systems. This review discusses recent advances made in the field of hydrogels for cardiac tissue regeneration in detail, focusing on the type of hydrogel (conventional, injectable, smart or nano- and micro-gel), the biomaterials used for its manufacture (natural, synthetic or hybrid) and the therapeutic agent encapsulated (stem cells or proteins). We expect that these novel hydrogel-based approaches will open up new possibilities in drug delivery and cell therapies.

1. Introduction

1.1. Myocardial infarction and current treatments

In the history of myocardial infarction (MI), the limited regenerative capacity of the heart has been understood as a key restrictive factor when treating the damage caused after an ischemic event, which ultimately results in heart failure and death (Leor et al., 2016; Rubin et al., 2016; Zhang et al., 2016a). In fact, if we take a look at the incidence of this disease in the global death rate, MI is responsible for almost 8 million deaths each year (Mendis et al., 2011), making it the most deadly cardiovascular disease and the principal cause of death worldwide.

Going deeper into the physiopathology of the disease, MI is initiated when a coronary artery is blocked by a blood clot. As a consequence, the heart region irrigated by this artery loses blood supply and the affected cardiomyocytes (CMs) start dying within minutes to hours of the onset of ischemia, generating an infarcted area. At this stage, progressive morphological and functional changes in the heart muscle are triggered due to the replacement of lost cardiac muscle by a fibrous scar. This scar is unable to contract rhythmically and is not as efficient conductor of electrical signals as CMs (Ongstad and Gourdie, 2016; Pascual-Gil et al., 2015a). As a result, an increase in left ventricular (LV) volume and a thinning of the LV wall take place, which finally leads to relevant deterioration of LV performance, cardiac global function and a high risk of heart failure and death (Kurrelmeyer et al., 1998; Ongstad and Gourdie, 2016).

Considering that the lack of functional heart muscle recovery seems to be the most important drawback after a MI, the ideal treatment should address both palliative and regenerative strategies. Thus, MI treatment must first avoid scar and infarct area progression. In addition, it should be able to induce the renewal of CMs and other cardiac cells in order to restore normal organ function. Concerning current treatments for MI such as bypass, balloon angioplasty, stents and pharmacological approaches (Toyoda et al., 2013), these are only focused on the palliative aspect, failing to address the fundamental issue of myocyte loss and replacement that underlies incipient cardiomyopathy. Therefore, although current strategies have helped to decrease the

* Corresponding authors at: Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, Universidad de Navarra, C/Irunlarrea 1, E-31008 Pamplona, Spain.
E-mail addresses: egarbayo@unav.es (E. Garbayo), mjblanco@unav.es, maria.blanco@nanomedicinas.es (M. Blanco-Prieto).
[1] Laura Saludas and Simon Pascual-Gil contribute equally to this work.
[2] Elisa Garbayo and M.J. Blanco-Prieto are equal senior authors

http://dx.doi.org/10.1016/j.ijpharm.2016.10.061
0378-5173/

mortality rate over recent decades, MI unfortunately still constitutes a major clinical problem that every year causes the death of too many people.

Encouraged by the relevance of MI, a large number of scientists have focused their efforts on developing new therapies for treating this pathology, paying special attention to the regenerative requirements of the heart. Thus, in recent years, there has been an increasing number of data regarding potential new treatments, as will be discussed in the following section.

1.2. New treatments for myocardial infarction

Recent findings in the field of cardiac regeneration have changed previous assumptions and have demonstrated that mammalian hearts, including humans, have the ability to trigger cardiomyogenesis (Bergmann et al., 2015; Heusch, 2011), opening new therapeutic doors in the treatment of MI. However, it is important to note that the heart's capacity to induce proliferation of contractile cells is very low and is severely reduced over time (Zacchigna et al., 2014), making it insufficient to rescue cardiac function after a MI. Enhancing CM proliferation and recovery in the infarcted area constitutes a promising approach and one of the most important strategies in new therapies for adequate post-ischemic repair (Pascual-Gil et al., 2015a). Along similar lines, angiogenesis (Formiga et al., 2012) and recruitment of stem cells (Grimaldi et al., 2013; Matar and Chong, 2014) are crucial points that may help to address total heart regeneration.

To date, a number of preclinical and clinical studies have been carried out around the world to try to find the best way to regenerate the infarcted heart. Several strategies have been followed using different therapeutic agents, from siRNA to stem cells including growth factors (GFs) and inflammatory mediators (Awada et al., 2016; Feyen et al., 2016; Meng and Hoang, 2012; Monaghan et al., 2012). Among them, cell and protein therapies are the ones that have reached most success so far (Pascual-Gil et al., 2015a). It is important to note that the latest research trend strongly suggests that controlling the inflammatory response of the heart tissue after a MI may be the critical step to modulate in order to achieve full organ regeneration (Frangogiannis, 2014; Lavine et al., 2014; Uygur and Lee, 2016). Nevertheless, although this strategy may be the most promising one, it is still a relatively fresh field of research, and further investigations are needed before obtaining conclusive results.

1.2.1. Cell therapy

Cell therapy is based on the administration of living cells into a damaged organ or tissue to reverse or prevent a disease or condition. In the heart, stem cells are known to improve tissue repair through regeneration of vessels and cardiac muscle cells (Grimaldi et al., 2013). A number of different cell sources have already been tested in preclinical and/or clinical studies so far, including bone-marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived stem cells (ADSCs), induced pluripotent stem cells (iPSs), cardiac progenitor cells (CPCs), endothelial progenitor cells (EPCs) and induced CMs, among others (reviewed in (Pascual-Gil et al., 2015a)). Importantly, benefits derived from stem cells seem to be mainly due to a paracrine effect rather than differentiation towards cardiac lineages (Gnecchi et al., 2008). Consequently, GFs and exosomes released by stem cells are the major factors responsible for the therapeutic effects observed (Singla, 2016; Smits et al., 2005). Controversial results have been published in this field. Current findings vary from studies where injection of stem cells was related to improvements in cardiac function and angiogenesis, reduction of fibrosis and generally positive remodeling of the heart (reviewed in (Sanganalmath and Bolli, 2013)), to other reports proving no relation between stem cell administration and recovery of cardiac function or differences with respect to conventional pharmacological treatments (Hirsch et al., 2011; Menasché et al., 2008; Traverse et al., 2011; Vu et al., 2012). Concerning the clinical application of stem cells, a limited level of success was obtained when cell therapy was translated into the clinical arena (revised in Emmert et al., 2014; Pascual-Gil et al., 2015a).

1.2.2. Protein therapy

This strategy consists of administering proteins, GFs or cytokines with specific therapeutic actions that can modulate determined biological processes and therefore, control the development of a disease or malignant event. Protein therapy in the heart has been mainly focused on promoting proangiogenic effects, since *de novo* formation of microvessels has the potential to salvage ischemic myocardium at early stages after MI (Cochain et al., 2013). To date, several GFs have been studied, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), neuregulin (NRG), hepatocyte growth factor (HGF), and stromal cell-derived factor-1 (SDF-1), among others (Jay and Lee, 2013). Similar to cell therapy, a wide variety of studies have been published examining protein therapy and its applications to treat MI, showing both favorable and unsuccessful results. In preclinical studies, injection of GFs promoted myocardial repair through reducing infarct size, enhancing angiogenesis and cardiac function and recruiting endogenous stem cells into the infarcted area (Awada et al., 2014; Tang et al., 2011). On the other hand, other researchers could not confirm such promising outcomes, and reported no improvements in cardiac function or infarct size (Engelmann et al., 2010; Ott et al., 2010). In addition, some authors associated protein administration with a higher risk of suffering adverse cardiac events (Kovacic et al., 2008). Remarkably, protein therapy was observed to be ineffective when this strategy was transferred to clinical trials (reviewed in (Jay and Lee, 2013; Pascual-Gil et al., 2015a)). However, in general, together with cell therapy, protein therapy is one of the most promising new approaches to treat MI. Although there are still areas for improvement, a great effort is being put into making this strategy a clinical reality in the near future.

1.3. Drug delivery systems

As mentioned above, the results available so far offer contradictory findings regarding the efficacy of cell and protein therapies for MI. Nowadays, it is widely known that the lack of success when using these therapies is due to the harsh microenvironment of the ischemic tissue and the intrinsic characteristics of the therapeutic agents. Regarding cell therapy, poor cell engraftment, fast dissemination from the cardiac tissue, inadequate cell sources and difficulties in the establishment of the optimal timing for cell administration are responsible for the inefficacy of this therapy (Hastings et al., 2015; Schulman and Hare, 2012; Sheng et al., 2013) (Fig. 1). On the other hand, proteins are labile molecules with half-lives of a few hours in the extracellular environment. This degradable nature means that proteins are eliminated rapidly after administration in any biological tissue, which results in low efficacy for this treatment (Hastings et al., 2015; Jain et al., 2013) (Fig. 1). Increasing the quantity of cells or proteins is not the solution, as important side effects could set in when large amounts of therapeutic agents are administered (Tayalia and Mooney, 2009). Therefore, it is of utmost importance to develop vehicles able to enhance cell and protein bioavailability, which act as suitable microenvironments for stem cell growth, survival and differentiation once they are administered (Naderi et al., 2011), and which overcome hurdles related to protein instability (Awada et al., 2016; Jay and Lee, 2013).