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Polysaccharide-based strategies for heart tissue engineering

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ABSTRACT

Polysaccharides are abundant biomolecules in nature presenting important roles in a wide variety of living systems processes. Considering the structural and biological functions of polysaccharides, their properties have raised interest for tissue engineering. Herein, we described the latest advances in cardiac tissue engineering mediated by polysaccharides. We reviewed the data already obtained *in vitro* and *in vivo* in this field with several types of polysaccharides. Cardiac injection, intramyocardial *in situ* polymerization strategies, and scaffold-based approaches involving polysaccharides for heart tissue engineering are thus discussed.

1. Introduction

Polysaccharides are long carbohydrate molecules which contain repeated monosaccharide units joined together by means of glycosidic bonds. Polysaccharides constitute the most abundant biomolecules in nature and they present essential roles in a wide variety of living systems processes (Muthana, Campbell, & Gildersleeve, 2012; Nitta & Numata, 2013; Oh, Lee, & Park, 2009). Polysaccharides are molecules that display high biocompatibility and biodegradability. They can be classified according to their origin: vegetal origin (*e.g.* pectin), algal origin (*e.g.* alginate), microbial origin (*e.g.* dextran, xanthan gum), and animal origin (chitosan, heparin) (Sinha & Kumria, 2001). Polysaccharides may also be classified as a function of their charge: cationic (chitosan), anionic (hyaluronic acid, heparin) and nonionic (dextran). Most natural polysaccharides present groups such as hydroxyl, carboxyl and amino groups (Quignard, Di Renzo, & Guibal, 2010), which easily enable their chemical modifications.

Considering the structural and biological functions of polysaccharides, it is reasonable to consider the interest in exploiting them for cardiac tissue engineering. In fact, biomaterials exhibiting both mechanical and biochemical functions may contribute to tissue engineering and are worthy of development (Chi, Yang, Chung, Chou, & Wang, 2013). Additionally, polysaccharides meet several criteria for an eligible biomaterial for tissue engineering, which include biocompatibility, biodegradation, and the ability to deliver and foster cells (Silvestri, Boffito, Sartori, & Ciardelli, 2013). It is important to highlight that the concept of the ideal biomaterial relies not only on its chemical constitution but also on macroscopic structural features. The biomaterial scaffold should present a porous structure to enable mass transport (permeability and diffusion) (Hollister, 2005). Besides, the biomaterial design should attempt to reproduce the organizational, mechanical, and elastic properties of native tissues, which is even more important for vital and highly specialized tissues, such as the cardiac one (De Mulder, Buma, & Hannink, 2009; Engelmayr et al., 2008; McDevitt, Woodhouse, Hauschka, Murry, & Stayton, 2003). Therefore, the ideal biomaterial should consist of a structure that support

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cells' attachment and growth while facilitating their organization and possibly differentiation toward a highly ordered biomimetic construct (Sokolsky-Papkov, Agashi, Olaye, Shakesheff, & Domb, 2007). The biomaterial should be also a resistant structure prone to withstand the high and permanent mechanical stresses related to cardiac contraction and relaxation. Another major role concerns the integration within the host tissue and eventual progressive replacement by the host extracellular matrix (Giraud, Guex, & Tevaearai, 2012). Additionally, biomaterials should ideally present biological properties that enhance tissue repair. Functions such as angiogenesis, cell recruitment and cardiomyocyte protection may be promising assets to contribute to the treatment of heart disease (Nelson, Ma, Fujimoto, Hashizume, & Wagner, 2011). Last but not least, tissue engineering products must be both efficient and cost-effective by combining functionality and ease of production (Place, Evans, & Stevens, 2009).

Polysaccharides are promising materials for meeting many of the above mentioned criteria for eligible biomaterials for cardiac tissue engineering. In combination with appropriate cells and bioactive molecules, polysaccharides may represent an important asset to promote heart tissue regeneration. In this regard, it is important to mention that regeneration capacity varies between different cell types and also depends on the nature of the tissue as well as the extent of injury or insult. Tissues that are in constant renewing as the skin are capable of regrowth in an important extent. In comparison, the cardiac tissue lacks mechanisms of regeneration in adults (Sokolsky-Papkov et al., 2007). The aim of this paper is to provide an overview of polysaccharide-based approaches for heart tissue engineering. Initially, the general context of tissue engineering is disclosed. It is followed by heart tissue engineering strategies related to xylan, alginate, pullulan and dextran, chitosan and hyaluronan. Finally, challenges in the field are discussed and concluding remarks are presented.

2. The context of heart tissue engineering

Cardiac infarct is followed by a sequence of wound repair processes associated with cell death, inflammation, the formation of granulation tissue (constituted by myofibroblast, macrophage, and collagen), and finally fibrosis. In response to the loss of cardiomyocytes, there is a reorganization of the extracellular matrix for compensation. This remodeling will result in cardiac wall thinning, ventricle dilatation and heart failure (Ertl & Frantz, 2005; Gajarsa & Kloner, 2011; Stefanon et al., 2013; Vilahur et al., 2011). Cardiac cell death, depending on its extent, renders the heart enable to deliver sufficient blood to meet the body's metabolic requirements leading to cardiac failure. After myocardial injury such as following important myocardial infarction, the heart regenerative capacity is overwhelmed (Giraud et al., 2012). Cardiac cell loss requires strategies to repair and regenerate the infarcted area of the myocardium (Jawad et al., 2007). Treatment options may concern approaches ranging from medication to surgical interventions. Most surgical options mainly rely on heart transplants. However, there is a chronic shortage of sources for human donors (Lam & Wu, 2012). In fact, the complex series of events involved in myocardial cell loss, and the subsequent post-myocardial infarction remodeling that result in heart failure are inefficiently addressed by current clinical strategies (Martinez & Kofidis, 2011). Current cardiac tissue engineering research aims to design tissue constructs to support, repair, replace, or enhance the function of injured or diseased myocardial tissue (Venugopal et al., 2013). Initial studies focused on the direct injection of viable cells into the infarcted myocardium tissue, a technique which is termed cellular cardiomyoplasty (Christman & Lee, 2006). The aim was to replace necrotic cardiomyocytes *via* the direct administration of cells from an aqueous cell suspension. It can be performed via intravenous, intracoronary or direct injection into the myocardium. Some improvement in cardiac performance has been observed by using cellular cardiomyoplasty. However, there are several hurdles associated with this technique. Indeed, the technique suffers from limited cell retention and poor cell survival. The results are quite disappointing considering an acute cell retention (within 24 h of delivery) in the heart that is generally <10%, irrespectively to the cell type or the administration route. In this regard, it would be important to gain deeper insight into the mechanisms underlying cell retention following coronary delivery as a function of the time (Dib et al., 2010). A main reason for that relies on the poor cell attachment ability due to the lack of extracellular matrix attached to them (Wang et al., 2008). Therefore, cells are soon washed out *via* the coronary venous system and mechanically ejected, as attested by retention rates in beating hearts markedly lower than in non-beating hearts (Malliaras & Marbán, 2011). It has been reported that cells injected into injured myocardium often relocate to the lungs, spleen, liver, kidneys and non-infarcted cardiac muscle (Hale, Dai, Dow, & Kloner, 2008; Zhang et al., 2007). The long-term engraftment of the remaining fraction of cells is also low. This raises the question concerning the real mechanisms at play. It seems difficult to state that the injected cells effectively contribute to the contractility capacity of the infarct zone. Alternatively, they seem to act mostly as a short-term reservoir of growth factors and cytokines that support the survival of host cells *via* a paracrine effect (Giraud et al., 2012; Nelson et al., 2011). In large panel of actions may be potentially induced *via* paracrine effect, such as angiogenesis (Zhou et al., 2011), pro-survival effect on cardiomyocytes (Kawaguchi et al., 2010), antifibrotic effects (Li et al., 2009), mobilization of endogenous stem cells (Bollini, Smart, & Riley, 2011) and cardioprotective action mediated by an anti-inflammatory effect (Premaratne et al., 2011).

Beyond the paracrine effect, some strategies have been developed in order to improve cell engraftment and enhance cell survival. They rely on the preconditioning of the cells prior to graft *via* heat shock, hypoxia approaches as well as exposition to pro-survival factors and enhancement of the expression of survival factors (Gerczuk & Kloner, 2012; Giraud et al., 2012).

Still concerning cell suspension injection approach, a main limitation is that such strategy relies mainly on the cells to improve cardiac function, without considering biomechanical factor that could be provided from a biomaterial (Wang & Guan, 2010). An alternative strategy involving the use of biomaterials seems to be very promising. This will be further discussed as follows.

Concerning the biomaterial approach, many of the investigated strategies for cardiac repair focused on the application of the biomaterial externally anchored to the myocardium in order to provide support. This is the case of cardiac restraint devices such as the CorCap (Acorn Cardiovascular Inc) and Heart Net (Paracor Medical Inc) that are based on Dacron and nitinol wraps, respectively, in order to mechanically support ventricular wall (Mann et al., 2007; Starling et al., 2007; Topkara, Kondareddy, & Mann, 2009). Additionally, devices such as CardioClasp (CardioClasp Inc) and Myosplint (Myocor Inc) reduce heart wall stress by constraining the dilated ventricle and decreasing intraventricular radius (Fukamachi & McCarthy, 2005; Kashem et al., 2003; Sabbah, 2003).

An alternative strategy to the cardiac restraint devices is the incorporation of the biomaterial within the heart wall in direct contact with cardiac cells. These approaches rely on natural or synthetic materials in an injectable form in combination or not with cells (Fig. 1, first, second and third panels), which are then directly injected *in vivo* (Christman et al., 2004; Zhang et al., 2010). By this way, the emerging field of tissue engineering has begun to provide promising alternatives to cellular cardiomyoplasty. The advantages of such an approach include providing a cell-friendly microenvironment to engrafted cells (Habib et al., 2011).