Biomaterials for Treating Myocardial Infarctions

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Biomaterials are gaining attention in the development of biomedical therapies for treating patients after a myocardial infarction (i.e., heart attack). These materials may act as mechanical restraints, vehicles for the delivery of therapeutics, or as 3-dimensional scaffolds for tissue regeneration. This overview will focus on one particular class of materials, namely injectable hydrogels (water-swollen polymer networks). Injectable hydrogels, including both natural and synthetic, are a promising therapy to attenuate ventricular remodeling after myocardial infarction by acting as acellular bulking agents to mechanically stabilize the myocardium and as delivery vehicles for cells and/or therapeutic molecules. Various materials, cells, and therapeutic molecules have demonstrated positive outcomes in the repair of cardiac tissue after infarction and provide insight for future material development and optimization. Further development of injectable hydrogels for cardiac repair will have considerable clinical impact with respect to understanding their mechanisms of action and improving therapies to prevent progression to heart failure.

OVERVIEW OF HEART DISEASE

Heart failure is a major health issue that affects almost 23 million individuals worldwide (Bui et al. 2011). Of these cases of heart failure, nearly 70% are due to coronary artery disease (CAD), which causes myocardial infarction (MI) (Go et al. 2014). MI occurs following coronary artery occlusion, resulting in depletion of nutrients and oxygen to the cardiac tissue and subsequent cell death (Cleutjens and Creemers 2002). The death of cells (i.e., cardiomyocytes) leads to recruitment of inflammatory cells to remove the necrotic debris and activation of bioactive molecules, such as matrix metalloproteinases (MMPs) (Holmes et al. 2005; Dobaczewski et al. 2010). MMPs lead to degradation of the extracellular matrix (ECM) found in cardiac tissue, which weakens the myocardial wall and makes it susceptible to global geometric changes, including thinning and dilatation (Buckberg 2005; Nahrendorf 2011; Spinale 2007). Infarct expansion is a progressive pathologic process that causes abnormal stress distributions in the

borderzone (BZ) regions surrounding the infarct and occurs after these initial problems. This process and addition cell death and increases in BZ stress are generally termed left ventricular (LV) remodeling and can ultimately lead to altered contractile properties and heart failure (Jackson et al. 2003; Pilla et al. 2005; Epstein et al. 2002).

TREATMENT STRATEGIES

Given an understanding of the biological and mechanical processes following MI, there are many strategies that utilize biomaterials for the intention of patient treatment. Although several may focus on treating patients after significant tissue remodeling has occurred (such as with tissue engineering, where actual cardiac tissue is developed in the laboratory and subsequently implanted to replace the damaged tissue), an alternative, promising approach is to treat the tissue during the acute phase to try to attenuate the remodeling response before significant damage. One option is to limit the initial infarct expansion, which has been identified as being associated with the LV remodeling that leads to heart failure. Previous strategies to limit infarct expansion include surgical reconstruction of the dilated LV and physical restraint of the ventricle or infarct region using polymeric meshed materials to prevent dilation (Batista et al. 1997; Klodell et al. 2008; Starling et al. 2007). Despite some promising findings, these approaches are highly invasive and require an open surgery for repair.

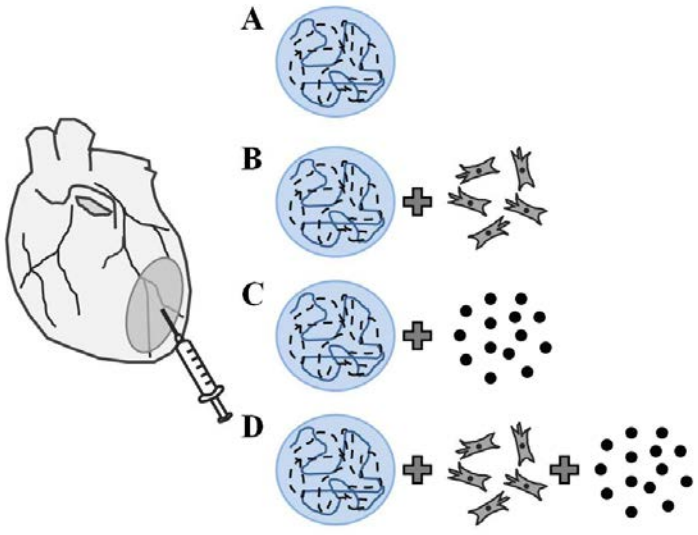

FIGURE 1 Injectable hydrogel approaches for the treatment of MI. Hydrogels can be used as acellular bulking agents (A) or as a vehicle for delivery of cells (B), therapeutic molecules (C), or a combination of cells and molecules (D).

In contrast to surgical or restraint techniques, injectable biomaterials are being developed as a more minimally invasive alternative to decrease damage to surrounding tissues. Although there are numerous potentially injectable biomaterials (e.g., microparticles), injectable hydrogels are quite promising and have been shown to mechanically stabilize the myocardial wall and modulate LV remodeling alone or through delivery of therapies, such as cells and growth factors (Figure 1) (Nelson et al. 2011; Tous et al. 2011). Hydrogels are water-swollen networks of polymer chains with a high degree of tunability that can be formed through numerous crosslinking mechanisms (Ruel-Gariepy and Leroux 2004).

Acellular Approaches

Many investigators believe that the regional mechanical changes and stresses in the myocardium after MI should be addressed when designing biomaterial-based approaches for cardiac repair (Nelson et al. 2011; Holmes et al. 2005; Gupta et al. 1994). As described by the Law of Laplace (Equation 1), stress (T) is directly proportional to pressure (P) and the radius of curvature (R) and inversely proportional to the myocardial thickness (h). Therefore, the increase in ventricular radius (R) and decrease in wall thickness (h) that occur after MI leads to an increase in myocardial stress.

$$T = \frac{P*R}{h} \quad (1)$$

Injectable biomaterials can limit infarct expansion by bulking the damaged myocardial wall through mechanical stabilization (Tous et al. 2011). Infarcts naturally stiffen over time as wound healing progresses and collagen is deposited; by modifying the tissue properties of the infarct region before the body compensates for the remodeling process, infarct expansion and remodeling post-MI can be limited (Tous et al. 2011). Thus, injectable hydrogels act as bulking agents by increasing the myocardial wall thickness (h) to decrease LV dilatation (R) and in turn, decrease wall stress (T). Theoretical finite element models have confirmed this mechanism of treatment by demonstrating that hydrogels decrease LV dilatation and reduce elevated myofiber stresses (Wall et al. 2006).

Towards these goals, injectable hydrogels can be grouped into either natural or synthetic materials. Natural materials offer advantages such as inherent biological properties, including receptor-binding ligands and susceptibility to proteolytic degradation (Karam et al. 2012; Lutolf and Hubbell 2005). For

cardiac applications where the goal is to replace or repair the damaged ECM, natural biomaterials more closely mimic features of the native ECM and can also be therapeutic in their degradation products through the recruitment of cells (Sui et al. 2011). Commonly used natural, injectable materials for cardiac repair include fibrin, alginate, collagen, Matrigel, chitosan, hyaluronic acid, keratin, and decellularized matrices (Tous et al. 2011).

Despite several advantages, natural materials have limited tunability in properties. In contrast, synthetic materials have defined material properties, including molecular weight, gelation, hydrophilic/hydrophobic properties, degradation, and mechanics, without batch-to-batch variations (Lutolf and Hubbell 2005). Synthetic materials can also be modified with cell binding sites or adhesive ligands to encourage cell interaction (Davis et al. 2005). Various synthetic materials have been explored for cardiac repair therapy, including poly(N-isopropylacrylamide) (PNIPAAm) and poly(ethylene glycol) (PEG) based hydrogels (Tous et al. 2011). An example of an injected hydrogel is shown in Figure 2.

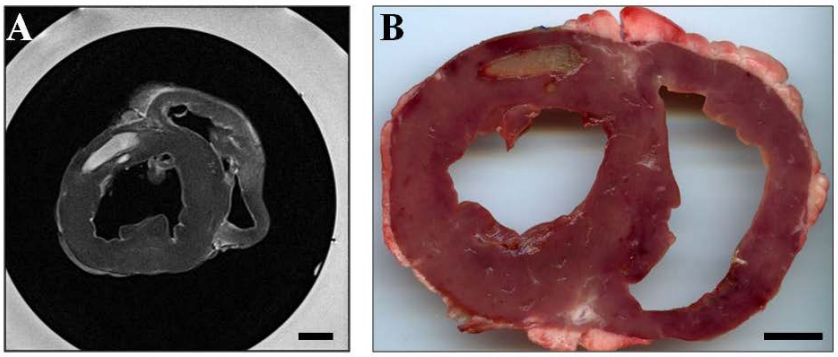

FIGURE 2 Acellular hydrogels as bulking agents for MI repair. Injectable hydrogel distribution in cardiac tissue explant as shown by magnetic resonance imaging (A) and ex vivo sectioning (B). Scale bar = 1 cm.

Cellular Approaches

Since MI results in the loss of over one billion cardiomyocytes in the infarct region, one strategy is to use cell delivery for tissue repair (Beltrami et al. 1994). A variety of cell types have been delivered, including fetal or neonatal cardiomyocytes, embryonic stem cells (ESCs), skeletal myoblasts, bone marrow-derived stem cells (BSCs), adipose-derived stem cells, and cardiac stem cells

(Menasche 2005; Segers and Lee 2008). Each of these cells has advantages and disadvantages for use in therapies. For example, ESCs offer the advantage of differentiating into both cardiomyocyte and vascular lineages but are limited due to their immunogenicity, risk of tumor development, and ethical concerns (Zimmermann 2011). BSCs are an autologous option that can be readily isolated and delivered to cardiac tissue, but their fate is not necessarily clear (Le Blanc and Pittenger 2005).

Even though both animal models (Segers and Lee 2008) and clinical studies (Menasche 2005) have demonstrated some enhancement in cardiac function with cell delivery, these improvements are often insufficient and transient, which is believed to be due to unsatisfactory cell retention, survival, and engraftment (D'Alessandro and Michler 2010). For example, it has been observed that less than 10% of BSCs delivered are detected even two hours after injection (Hofmann et al. 2005; Hou et al. 2005) and of those that stay at the injury, approximately 90% die within the first week due to physical stress, ischemia due to microvasculature obstruction, inflammation, and release of cytokines and reactive oxygen species (Robey et al. 2008). Due to these challenges, injectable hydrogels have been explored to enhance cell retention and engraftment for cardiac repair by improving cell attachment, migration, and survival upon delivery (Huang et al. 2005).

Hydrogels permit high encapsulation efficiency since cells are entrapped during gelation and precise control over the biophysical and biochemical microenvironment surrounding cells after delivery (Bian et al. 2009). As with acellular hydrogels, both synthetic and natural polymers have been investigated. Natural materials, such as fibrin, alginate, collagen, and Matrigel, are a popular choice for cell delivery due to their inherent biological activity that initiates cell-biomaterial interactions (Tous et al. 2011). Synthetic hydrogels can also be used to deliver cells for cardiac repair. Due to their tunability, synthetic materials can be modified to control both adhesion for cell retention and degradation for desired timing of cell release into the tissue environment. Similar to acellular hydrogels, the primary synthetic materials used for cell delivery are PNIPAAm and PEG (Tous et al. 2011).

Injectable Hydrogels for Molecule Delivery

In addition to the approaches described above to alter the local mechanical stabilization as well as to act as a cell-delivery vehicle, injectable hydrogels can also deliver therapeutics molecules to address the LV remodeling process that occurs after MI. Tissue repair is a complex process controlled in part by

numerous molecules (e.g., growth factors and cytokines). Therefore, delivery of exogenous molecules, such as growth factors, cytokines, and stem-cell mobilizing factors, can modulate endogenous biological responses post-MI (Segers and Lee 2010). Delivery of therapeutic molecules alone, either by direct myocardial injection or systemic intravenous circulation, has helped restore cardiac function in some animal models; however, the short half-life of the molecules and off-target complications limits clinical application (Urbanek et al. 2005).

Due to these limitations in molecule delivery alone, injectable hydrogels have been used as delivery vehicles to localize molecules and tailor release kinetics through changes in polymer-molecule interactions, polymer hydrophobicity, and hydrogel degradation (Kretlow et al. 2007; Chen and Mooney 2003). Hydrogels can both sustain local molecule release and prolong molecule bioactivity (Langer and Folkman 1976). For cardiac applications, injectable hydrogels are useful to deliver anti-apoptotic molecules that limit cell death after injury, angiogoenic factors to promote vessel formation, or chemoatttractants to recruit cells for repair and attenuation of remodeling post-MI (Tous et al. 2011).

LOOKING FORWARD

As discussed here, a range of injectable hydrogels, cell types, and molecules have been delivered with the intent of attenuating LV remodeling post-MI. Although many hydrogels have shown positive outcomes in animal models, only one (e.g., alginate) has progressed to clinical trials (BioLineRX Ltd 2007; Ikara Holdings Inc. 2010). From a translational perspective, it is important to elucidate the effects of hydrogel properties, mode of delivery (e.g. direction injection vs. catheter delivery), and timing of delivery (e.g. acute vs. chronic MI) on LV remodeling. Future studies should further investigate the mechanisms by which hydrogels act on the heart, including both biological and mechanical effects, and focus on clinically relevant parameters to optimize repair outcomes.

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