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Self-assembling peptide-based delivery of therapeutics for myocardial infarction☆

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ABSTRACT

Cardiovascular disease, including myocardial infarction, is the number one cause of death. Current treatments are palliative and slow the progression toward heart failure, but to not regenerate healthy tissue. Self-assembling peptides are biomimetic, readily produced, non-immunogenic and non-cytotoxic. They do not assemble into hydrogels until triggered, allowing them to be injected into the myocardium and providing opportunities for minimally invasive therapies. The ability to tune the mechanical and bioactive properties of self-assembling peptides will continue to make them readily adaptable for mimicking natural microenvironments. To date, a variety of growth factors and signaling moieties have been incorporated into self-assembling peptide hydrogels, enhancing cell behavior and tissue function. Furthermore, the hydrogels serve as delivery vehicles for cells in vivo and platforms for improved cell culture. In addition to a brief review of self-assembling peptides, we will discuss a variety of their approaches for myocardial infarction therapy. Moreover, we will assess approaches taken in other tissue and discuss how these could benefit therapies for myocardial infarction.

Contents

Abbreviations: MI, myocardial infarction; PDGF, platelet-derived growth factor; FGF-1, fibroblast growth factor 1; VEGF, vascular endothelial growth factor; SDF-1, stromal cell-derived growth factor 1; IGF-1, insulin-like growth factor 1; CPC, cardiac progenitor cell; GFP, green fluorescent protein; Sca, stem cell antigen; MMP, matrix-metalloproteinase; NO, nitric oxide.

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1. Introduction

Myocardial infarction (MI) is triggered by the occlusion of a coronary artery which prevents blood flow to a region of the myocardium (Fig. 1). This results in a low oxygen (ischemic) environment in the tissue, leading to the quick death of myocytes due to their high metabolic demands. The injured cells then secrete cytokines triggering an inflammatory response, leading to the recruitment of neutrophils and macrophages, as well as fibroblasts. During the adaptive remodeling phase, a non-contractile collagen scar is deposited to prevent ventricular rupture, cellular debris is removed and fibroblasts differentiate into the less-contractile myofibroblasts. In a clinical setting, removal of the occlusion restores blood flow, but leads to the production of reactive oxygen species, causing further tissue damage. The myocardium ultimately enters a chronic remodeling phase as it adjusts to the altered mechanical properties. If left unchecked, this process will proceed to heart failure.

Annually there are 515,000 new incidences of MI and an additional 205,000 recurrent incidences [1]. This accounts for $300 billion in direct and indirect costs yearly, with an expectation for this cost to triple in the next decade [1]. Thanks to a better understanding of disease progression, changes in lifestyle, and the recognition of the need for rapid reperfusion therapy, more people survive their first cardiac event than ever before. However due to the limited regenerative potential of the myocardium the incidence of heart failure following MI remains high, producing patients facing a reduction in lifespan and quality of life. There is a need in the field to prevent adverse cardiac remodeling, while promoting cardiomyocyte regeneration and vascularization.

Currently gold-standard therapies for MI rely on pharmacological agents and surgical intervention [2–4]. Interventional therapies, such as coronary angioplasty and the placement of a stent, restore blood flow to the damaged myocardium. Pharamcological agents (e.g. angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers and statins) provide symptomatic relief, while slowing the progression to heart failure. With the progression of disease, invasive surgical therapy such as implantation of a left ventricular assist device, becomes necessary. Ultimately, the only cure for heart failure is transplantation. Thus, there is a great need to develop novel strategies to repair or regenerate the injured heart. Controlled delivery of therapeutics remains one of the fundamental hurdles to regenerative cardiology [5].

The emerging field of tissue engineering holds the promise of the rational design of biomaterials to facilitate regeneration. Current bioengineering approaches include injectable acellular scaffolds, cellular therapies and scaffolds combining any number of cells, growth factors, nucleic acids/genes, and drugs. This review will focus on self-assembling peptide based approaches for myocardial infarction. We also explore the recent developments of this technology in other relevant models and consider the implications for the future of cardiac tissue engineering with smart self-assembling materials.

2. Self-assembling peptides

Self-assembly is the non-covalent, weak interactions of components to form ordered structures from an unordered state, determined by the nature and positioning of the component [6,7]. Although the process of self-assembly is best understood for molecules, biological systems are replete with self-assembling supramolecular structures such as molecular crystals [8], viral particles, membranes bilayers, nucleic acid complexes and detergent surfactant molecules [9]. The increasing interfacing of chemistry and material engineering with biology has enabled concepts of self-assembly from these biological systems to be applied to micro- and nano-fabrication of useful molecular materials for applications in nanotechnology, microelectronics, photonics as well as drug delivery systems and tissue engineering scaffolds for regenerative medicine [7,9]. Peptides are especially versatile building blocks as their ability to assume secondary structures dictated by the primary amino acid sequence provides a unique platform for the design of self-assembling biomaterials with complex three-dimensional architectures, nanoscale features and tunable physical properties [10]. Furthermore, peptide self-assembly is highly specific—the intermolecular interactions such as hydrogen bonding, ionic, electrostatic, hydrophobic and van der Waals interactions are mediated by molecular recognition [9] and therefore highly programmable.

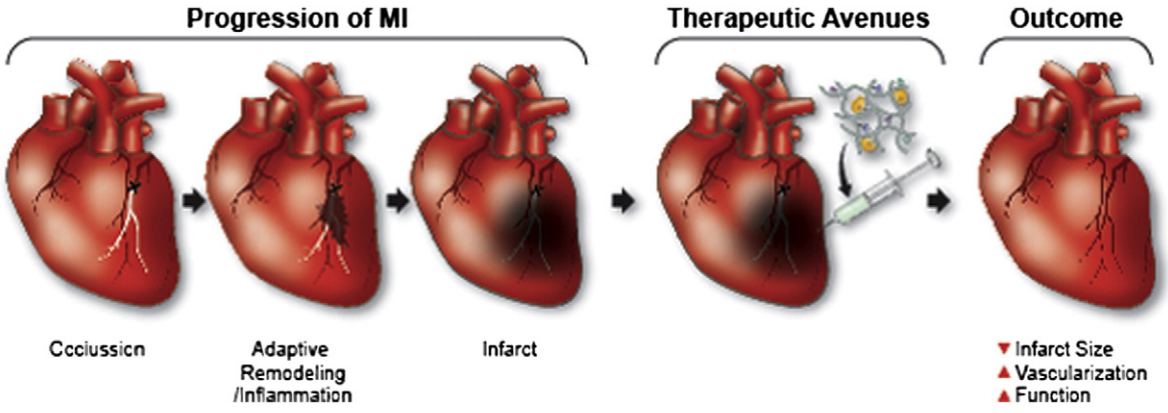

Fig. 1. Progression of myocardial infarction. From left to right, the occlusion of a coronary artery blocks blood flow to the myocardium, triggering a cascade of tissue remodeling events. The injection of self-assembling peptides alone or with proteins and/or cells is a possible therapeutic option to reduce infarct size, improve vascularization and tissue function.