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Alginate biomaterial for the treatment of myocardial infarction: Progress, translational strategies, and clinical outlook☆
From ocean algae to patient bedside

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ABSTRACT

Alginate biomaterial is widely utilized for tissue engineering and regeneration due to its biocompatibility, non-thrombogenic nature, mild and physical gelation process, and the resemblance of its hydrogel matrix texture and stiffness to that of the extracellular matrix. In this review, we describe the versatile biomedical applications of alginate, from its use as a supporting cardiac implant in patients after acute myocardial infarction (MI) to its employment as a vehicle for stem cell delivery and for the controlled delivery and presentation of multiple combinations of bioactive molecules and regenerative factors into the heart. Preclinical and first-in-man clinical trials are described in details, showing the therapeutic potential of injectable acellular alginate implants to inhibit the damaging processes after MI, leading to myocardial repair and tissue reconstruction.

Contents

Abbreviations: MI, myocardial infarction; ECM, extracellular matrix; MW, molecular weight; ROS, reactive oxygen species; FDA, Food and Drug Administration; MSC, mesenchymal stem cells; PEG, poly-(ethyleneglycol); RGD, arginine-glycine-aspartate; HBP, heparin-binding peptide; Cx-43, connexin-43; NW, nano-wire; SEM, scanning electron microscopy; MNP, magnetically responsive nanoparticles; LAD, left anterior descending; LV, left ventricle/ventricular; AHI, alginate hydrogel implant; BCM, bioabsorbable cardiac matrix; HF, heart failure; EF, ejection fraction; PCI, percutaneous coronary intervention; SMA, smooth muscle actin; CABG, coronary artery bypass graft surgery; MRI, magnetic resonance imaging; GAG, glycosaminoglycan; IGF-1, insulin-like growth factor-1; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; SDF-1, stromal cell-derived growth factor-1; PDGF-BB, platelet-derived growth factor-BB; TGF-β1, transforming growth factor-β1; FGF-2, fibroblast growth factor-2.

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1. Introduction

Tissue engineering and regenerative medicine solutions are of particular interest for the treatment of heart diseases such as myocardial infarction (MI), where large portions of functional tissue are lost with very limited intrinsic regeneration ability. MI, which results from temporary or permanent occlusion of the main coronary arteries, causes a significant blood supply reduction to the beating heart muscle of the left ventricle (LV). Because of its high metabolic rate, the myocardium begins to undergo irreversible injury within 20 min of ischemia. Five partially overlapping phases can be distinguished in the progression from healthy to infarcted myocardium: 1) cardiomyocyte loss due to an initial ischemic event, 2) acute inflammatory response, 3) extracellular matrix (ECM) remodeling, 4) granulation tissue formation, and 5) scar formation and LV remodeling. The structural remodeling of the heart (i.e. infarct wall thinning, scar formation and noninfarcted myocardium hypertrophy) leads to LV functional remodeling; a progressive deterioration in the heart muscle function that eventually leads to congestive heart failure (CHF) [1].

In order to compensate for the low and insufficient intrinsic regeneration ability of the adult heart, novel strategies for therapeutic regeneration are being developed, aimed to induce myocardial regeneration, improve tissue salvage, facilitate self-repair, reverse or attenuate adverse remodeling, and ultimately achieve long-term functional stabilization and improvement in the heart function [2,3]. Five major processes associated with MI are targeted at present by various experimental regeneration strategies: 1) cardioprotection — the prevention of progressive cardiomyocyte loss following MI by applying various apoptosis-inhibiting reagents or by inducing pro-survival signaling; 2) inflammation — time-adjusted modulation of the post-MI pro/anti-inflammatory cytokine/chemokine profile or cellular responses (e.g. granulation tissue formation and macrophage infiltration) in an attempt to induce effective tissue healing and repair and to avoid negative inflammatory effects (e.g. cell death, fibrosis); 3) ECM remodeling and fibrosis — time-adjusted positive modulation of the fibrotic response (i.e. ECM remodeling and scar formation), utilizing recent knowledge on pro-fibrotic signaling, such as modification of the ratio between metalloproteinases and their inhibitors, which may lead to successful anti-fibrotic therapy; 4) angiogenesis — increasing the blood supply to ischemic regions is an extensively used approach for effective tissue healing, by application of a variety of proteins, genes or cells, aimed at inducing the formation of new vasculature at the infarct site; and 5) cardiomyogenesis — myocyte regeneration by activation and/or migration of distinct cell populations with stem- or progenitor-like properties in the adult myocardium, or by the induction of cardiomyocyte cell cycle re-entry by reprogramming of differentiated cardiomyocytes toward proliferation.

To achieve the goals of therapeutic myocardial regeneration, the actively pursued tissue engineering strategies include development of functional cardiovascular tissue substitutes, biomaterial-assisted cell transplantation to improve retention and function, acellular strategies to confer mechanical support and extracellular matrix (ECM) replacement for the failing heart muscle, and drug delivery platforms to enhance self-repair and induce endogenous regeneration [2,4,5].

Biomaterials represent a cornerstone of the tissue engineering paradigm, as a standalone strategy, or in combination with cells and/or bioactive molecules. Passion, creativity, and hard work of multidisciplinary teams of researchers have led to engineering of multiple biomaterial-based strategies and platforms, significantly advancing these approaches toward state-of-the-art clinical care of patients.

Alginate, an algae-derived polysaccharide, has become a biomaterial of choice in tissue engineering and regeneration due to its biocompatibility, relatively low cost, non-thrombogenic nature, mild and ionotropic gelation process, and its structural resemblance to the ECM. Alginate hydrogels have been used for bioengineering of cardiac grafts, stem cell delivery, in acellular injectable form for tissue support and reconstruction, and as a platform for sustained delivery and presentation of multiple growth factors in nature-inspired ways. Two injectable alginate implants (one of them developed by our group for intracoronary delivery) have already reached clinical investigation phase, further confirming the promising potential of alginate-based approaches for myocardial repair and regeneration.

In this review, we present an up-to-date view of alginate-based approaches for cardiac tissue engineering and myocardial regeneration, with emphasis on functional studies, translational status, and clinical advancements.

2. Alginate biomaterial

2.1. Composition and hydrogel formation

Alginate is a naturally-occurring polysaccharide found in certain species of brown algae (*Macrocystis pyrifera*, *Ascophyllum nodosum*, *Laminaria hyperborea*, and several others) in a proportion of 18–40% of the total biomass [6–9]. The process of isolating alginate from algal biomass is simple. It includes several stages of pre-extraction with hydrochloric acid, which are followed by washing, filtration, and neutralization with alkaline buffer. Sodium alginate is precipitated from the solution using alcohol, and to achieve higher purity can be re-precipitated in the same way [7,8]. Alginates isolated from algae are polydispersed, and are generally of high molecular weight (MW), typically in the range of 100,000 and 1,000,000 Da, corresponding to about 500–5000 residues per chain.

Alginate is an anionic polymer composed of two types of uronic acid monomers distributed as blocks of 1→4 linked α-L-guluronic acid (G) or β-D-mannuronic acid (M), as well as heteropolymeric mixed sequences (G–M, usually alternating) (Fig. 1). Thus, very often, commercial alginate is characterized by its "G:M" ratio. At pH >6, divalent cations, such as Ca^{2+}, Ba^{2+}, or Zn^{2+}, interact with high affinity with the G monomer blocks to form ionic bridges between different alginate chains (referred to as the "egg box" model), leading to physical hydrogel formation (ionotropic gelation) (Fig. 1).

The concentration of the cross-linking cation is a critical determinant of the resultant hydrogel's mechanical properties. Higher cation concentrations will result in stronger gels, thus matching cross-linker concentration to the required hydrogel function is important. For instance, variations in cation (e.g., calcium) concentration in the target tissue with time could affect in situ gelation properties of cross-linked alginate