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Sensing the Cardiac Environment: Exploiting Cues for Regeneration

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Abstract

Recent pre-clinical and clinical studies indicate that certain exogenous stem cells and biomaterials can preserve cardiac tissue after myocardial infarction. Regarding stem cells, a growing body of data suggests that the short-term positive outcomes are mainly attributed to paracrine signaling mechanisms. The release of such factors is due to the cell's ability to sense cardiac environmentally derived cues, though the exact feedback loops are still poorly understood. However, given the limited engraftment and survival of transplanted cells in the ischemic environment, the long-term clinical benefits of these therapies have not yet been realized. To overcome this, the long-term controlled delivery of bioactive factors using biomaterials is a promising approach. A major challenge has been the ability to develop timely and spatially controlled gradients of different cues, pivotal for the development and regeneration of tissues. In addition, given the complexity of the remodeling process after myocardial infarction, multiple factors may be required at distinct disease stages to maximize therapeutic outcomes. Therefore, novel smart materials that can sense the surrounding environment and generate cues through on demand mechanisms will be of major importance in the translation of these promising advanced therapies. This article reviews how the cardiac environment can mediate the release profiles of bioactive cues from cells and biomaterials and how the controlled delivery impacts heart regeneration.

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Keywords

Cardiac regeneration; Stem cells; Paracrine factors; Biomaterial; On-demand release

Introduction

The heart has minimal capacity to heal after an ischemic insult such as myocardial infarction (MI). Although recent experimental data indicates that adult cardiomyocytes have the ability to enter the cell cycle during their lifetime, this process is insufficient to maintain the homeostasis of heart tissue after an insult [1]. In many cases, the contractile tissue is replaced by a non-contractile scar, leading to a degenerative process that often culminates in heart failure and death [2]. Currently available MI therapies have contributed to an increased survival of patients in the short term after the ischemic attack by decreasing the heart's oxygen demand through pharmacologic agents (e.g., β-blockers) and improving coronary blood perfusion [3]. However, current therapeutic approaches to treat MI are insufficient in the long term to restore heart function.

New therapies that have recently been proposed to treat damaged myocardium following infarction include (1) pharmacologic, (2) gene, (3) cellular, and (4) tissue engineering approaches (including biomaterials, biomolecules, and cells, either together or alone). Reports that present beneficial results typically show increased neo-vascularization, reduced inflammation and cardiomyocyte death, decreased fibrosis, and induction of cardiac progenitor cell proliferation. Excellent recent reviews have covered these therapeutic approaches and therefore they will not be discussed in this review [4–7].

To maximize or potentiate a specific biological effect, it is important to consider therapeutic approaches that may "sense" and respond to the insult induced by MI. For example, biomaterials can be used as scaffolds for cell transplantation; however, for enhanced therapeutic effect they should deliver the cells at an appropriate time to maximize cell engraftment, functional integration, and long-term survival. In addition, a recent body of studies has shown that in many cases, the therapeutic effect of stem cells is mediated by a paracrine effect. Therefore, it is important to understand the mechanisms underlying the cell's ability to sense the cardiac environment and secrete soluble factors. It is also of interest to consider how we may extend the life of these stimulus responsive "biosensors" to mediate the long-term regeneration of the heart.

The cardiac environment includes cross-talk between cells (cell–cell contacts, autocrine, and paracrine signaling), regulatory molecules (oxygen, nutrients, cytokines), extra-cellular matrix (structure, bioactivity, topology, stiffness), physical factors (tension and compression), and electrical signals. Normal tissue development, homeostasis, and regeneration requires orchestrated sequences of biophysical and biochemical signals [8]. In addition to the cardiac microenvironment, cardiac regeneration may be impacted by cells within the bone marrow niche and the bloodstream [9]. Therefore, a better understanding of the complex signaling pathways and feedback loops between and within these compartments is required for the design of effective therapeutics. In addition, the ability to develop delivery systems able to provide on demand regenerative cues will be pivotal to orchestrate the regenerative response.

This review focuses on advances in therapies that can sense the cardiac environment and respond accordingly. In the first section of the review, we will describe the cardiac environment following MI. We will highlight molecular cues released by the heart, which may interact with transplanted biomaterials and cells. In the second section, we will focus our attention on cellular mechanisms underlying the sensing and release of paracrine factors.

Finally, in the third section, we will describe smart biomaterials capable of sensing and releasing bioactive agents on demand.

Cardiac Microenvironment After MI

MI is characterized by a decrease in blood supply to the cardiac tissue with death of cardiomyocytes and loss of contractile function. The mechanical loading imposed on the non-functional tissue generates abnormal stresses at the infarct and peri-infarct zone with consequent expansion of the left ventricle (LV) [10]. The mechanical and biologic stresses developed generates continuous changes at the structural, mechanical, and molecular levels, known as postinfarct left ventricle remodeling [11]. This process is highly dynamic and time-dependent, comprising (1) an acute inflammatory phase, evolving to (2) a granulation stage, and then to (3) chronic fibrosis (Fig. 1). At all stages, different cytokines are upregulated contributing to the cascade of events that characterize cardiac remodeling (Table 1). The cardiac extracellular matrix (ECM) also serves a central function during this process, given its role in the maintenance of structural integrity, pumping capacity (based on its mechanical integrity), and in the support of cardiomyocyte and blood vessel viability and function [12, 13]. A balance between ECM synthesis and degradation is maintained by a tight control in the activity of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [14].

Immediately after MI, the ischemic tissue generates an acute stress response with mechanical stretching, complement activation, release of reactive oxygen species (ROS), and pro-inflammatory cytokines [15]. ROS are specially upregulated after reperfusion of the infarcted tissue and have been associated with cardiomyocytes apoptosis and necrosis, endothelial dysfunction, and promotion of the inflammatory process [16]. Nevertheless, studies have also shown that the release of ROS in non-lethal ischemic attacks has a cardioprotective effect to a subsequent ischemic episode by interfering with the mitochondrial adenosine triphospate-sensitive potassium channels [17–19]. The acute response following MI leads to the expression and activation of MMPs, in particular the subtypes MMP-2 and 9 [20–22]. At this stage, the low levels of TIMP are not able to compensate for the increased MMP activity, with consequent proteolysis of the ECM and modulation (activation or degradation) of cytokine activity. Furthermore, the increased expression of endothelial adhesion receptors and the formation of a leaky vasculature at the infarct site, promotes the migration of inflammatory cells, such as monocytes, lymphocytes, and granulocytes (e.g., neutrophils) to the infarcted area [15]. Exacerbated MMP activity has been associated with LV dilatation, dysfunction, and risk of cardiac rupture, given the damage caused on the ECM [23, 24]. However, it is important to consider that inflammation is essential for the healing process, namely, to remove necrotic tissue and to secrete cytokines and growth factors that signal the invasion of reparative cells. In addition to the events at the local level, the activation and release of chemo-attractant cytokines induces a systemic response responsible for the migration and homing of endogenous stem and progenitor cells, relevant to myocardial repair. Stromal-derived factor-1 (SDF-1), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) are key mediators released in the infarcted and peri-infarcted tissue compartments with chemoattraction capacity [9, 25–27]. Bone marrow is likely the main source of precursor cells, though the exact mechanism of cardiac repair is still unclear [5, 28].

With the removal of necrotic tissue and apoptosis of infiltrated granulocytes, the increased expression of inhibitory cytokines, such as interleukin (IL)-10 [29–32] or transforming growth factor-β (TGF-β) [33], leads to the suppression of the acute inflammatory response, inhibition of MMP activity, and induction of collagen deposition. TGF-β, a pro-fibrotic protein released by active macrophages [34], is thought to promote the proliferation and

phenotypic changes of cardiac fibroblast into contractile myofibroblasts [33, 35]. Myofibroblasts are a main source of collagen type I and III [36] and play an essential role in wound contraction, avoiding further thinning and dilation of the ventricular wall [37].

Maturation of the fibrotic tissue progresses with increased deposition of collagen type I and the establishment of crosslinks between collagen chains, giving resilience and tensile strength to the damaged tissue [38]. The dense scar formed is critical to avoid cardiac rupture, given the limited capacity of the heart to generate functional tissue at an adequate rate. However, its non-contractile properties compromise cardiac function in the long-term. Strategies that can shift this balance in favor of cardiac regeneration are of great interest.

Cells as Sensors and Effectors at the Cardiac Environment

Several studies in animal models of cardiac injury have indicated that part of the therapeutic effect of stem cells is mediated by their ability to secrete soluble factors (paracrine effect). These factors influence (1) myocardial protection, (2) neovascularization, (3) cardiac metabolism, (4) contractility, (5) cardiac regeneration, and (6) cardiac remodeling [39]. Some of the cytokines, chemokines, and growth factors that show beneficial effects on MI have been identified (Fig. 2). It is likely that some of these factors are more important in terms of regeneration than others. Comprehensive reviews focused on the effect of these molecules have been recently reported [9, 39, 40].

In addition to proteins, other cell-secreted molecules have been identified as potential therapeutic agents in MI. miRNAs are a class of highly conserved, small non-coding RNAs, which interfere with translation [41]. Each miRNA can target several genes and therefore represents a very promising strategy for heart repair. It has been shown that human mesenchymal stem cells (MSCs) secrete exosomes rich in phosphatidylcoline, sphingomyelin, cholesterol, and miRNA predominantly on its precursor form [42, 43]. The injection of exosomes isolated from MSCs culture in a mouse model of ischemia/reperfusion injury has been associated with cardioprotective effects translated in the reduction of the infarcted area [42]. Other recent study has shown that the injection of miRNA 210 in a murine model of MI improved cardiac function at week 8 post-infarction [44].

Yet, it is unclear how these biomolecules are orchestrated in time and concentration to contribute to the regeneration of the heart. The profile of secreted factors is likely quite different according to the type of exogenous cells that are delivered. A recent comparative analysis of the efficacy of different cell candidates delivered through intramyocardial injection, including bone marrow mononuclear cells, MSCs, skeletal myoblasts and fibroblasts, indicated that mononuclear cells exhibited a more favorable survival pattern which translated into a more robust preservation of cardiac function [45]. However, this is an issue under intense scrutiny since the final therapeutic effect is likely dependent in the initial number of cells injected, animal model, timing of cell delivery, and origin of the stem cell population [46]. Furthermore, although most in vivo studies have used acute MI models, it is likely that donor cells behave differently in chronically falling myocardium. Main differences between acute and chronic MI animal models include the profile of pro-inflammatory cytokines, cellular density, and matrix fibrosis.

Effect of Time in the Secretion of Paracrine Factors

Few studies have characterized the temporal secretion of soluble factors by stem cells when delivered into the infarcted heart. In case of bone marrow-derived mononuclear cells, cardiac mRNA levels of basic fibroblast growth factor (bFGF) and angiopoietin-1 (Ang-1) were upregulated for 14 days after cell injection, whereas VEGF was most abundant after 1 day and reverted to the baseline level after 7 days [47]. In case of human embryonic stem

cell-derived vascular cells, VEGF, epidermal growth factor (EGF), and HGF were significantly secreted at day 1 after cell injection into the heart; however, were not detectable at day 3 after injection, except HGF [48]. Human survivin, an apoptosis inhibitor was strongly upregulated at day 1 and even more at day 3 but not at day 42. In the case of human cardiac progenitor cells (cardiosphere-derived cells), secretion of human VEGF peaked at day 1, decreased significantly at week 1, and faded at week 3; human IGF-1 peaked at week 1 and reverted to baseline levels at week 3; and finally human HGF was highly secreted over 1 week and then decreased to baseline levels at week 3 [49]. Overall, these studies suggest that the nature and temporal expression of soluble factors may change according to the stem cell type. Furthermore, VEGF seems to be one of the first soluble factors secreted by the stem cells while HGF and IGF-1 are secreted at late stages. Studies have indicated that the in vitro concentration of these factors can be between 50 and 2,000 pg/mL [49].

Unfortunately, the survival of transplanted cells in ischemic and inflammatory environments such as post-MI is normally low, with few cells persisting beyond 1–3 weeks. Host pro-inflammatory molecules such as IL-1β play an important role in the death of transplanted cells [50]. According to some studies in acute animal models, mononuclear cells (bone marrow-derived cells characterized by a single prominent and round nucleus, including lymphocytes, monocytes, and dendritic cells) show the most favorable survival pattern after injection into the infarcted heart compared to MSCs and skeletal myoblasts. Yet, the survival of the mononuclear population at week 6 was only 0.4% of the initial number of cells injected at the heart [45]. This number is significantly low when mono-nuclear cells are injected in a chronic MI animal model (injection 21 days after coronary artery ligation). In this case, no more than 5% of the cells injected by intra-myocardial or intracoronary injection were detected within the heart on day 7 [51]. Therefore, the enhancement of stem cell engraftment and paracrine potency are important strategies to increase their therapeutic effect.

One of the strategies being pursued to improve survival and paracrine potency of stem cells is by genetic manipulation. Some studies have reported that cell survival/grafting can be improved by the upregulation of Akt (retroviral transfection of MSCs) [52], IL-18-binding protein (using transgenic mouse models) [53], Bcl-2 (polyethylenimine transfection of MSCs) [54], Hsp-20 (adenoviral transfection of MSCs) [55], chemokine receptor CCR1 (retroviral transfection of MSCs) [56], among others. In some cases, the improved survival/grafting of the cells is due to an upregulation in the secretion of certain biomolecules, while in other cases is due to the secretion of new paracrine factors (i.e., factors not typically secreted by the non-manipulated stem cells) [52]. For example, MSCs genetically modified to overexpress Akt gene contribute to myocardial survival and repair after ischemic injury through the secretion of frizzled related protein. Yet, a topic that deserves further investigation is to evaluate the temporal expression of paracrine factors generated by genetically modified cells following transplantation into infarcted heart tissue.

Effect of Hypoxia on the Secretion of Paracrine Factors

Stem cells and their progenies sense and respond to hypoxia by secreting high levels of pro-angiogenic factors. The response to hypoxic stress generates a transcriptional response mediated by hypoxia-induced factor 1 (HIF-1), whose α subunit is stabilized in the absence of oxygen [57]. MSCs-conditioned medium obtained under hypoxic or normoxic conditions have more than 15 different cytokines, including EGF, keratinocyte growth factor, IGF-1, glial cell line-derived neurotrophic factor, platelet-derived growth factor-BB (PDGF-BB), VEGF-α, Ang-1, erythropoietin (EPO), thrombopoietin (TPO), macrophage inflammatory protein-1 (MIP-1), MIP-2, monocyte chemotactic protein-5 (MCP-5), and soluble tumor necrosis factor receptor-1 (sTNF-R1). Importantly, compared to normoxic conditions,

hypoxic treatments dramatically increased the release of several cytokines including VEGF-α, Ang-1, and EPO by bone marrow MSCs [58].

Effect of Inflammation on the Secretion of Paracrine Factors

Stem cells sense the inflammatory environment and express soluble factors that have important signaling and immuno-suppressive functions. TNF-α receptors (TNFR1 and TNFR2) mediate the response to TNF-α. MSCs exposed to TNF-α increase the release of VEGF, IGF-1, and HGF paracrine factors by a p38 mitogen-activated protein kinase pathway [59]. Interestingly, the prevalence of one TNF receptor over the other might have a strong influence on the cellular response [60]. For example, TNFR1 has been associated with the activation of apoptotic pathways and decreased secretion of VEGF while TNFR2 has been shown to induce VEGF expression and correlated with the beneficial effects of MSCs in MI models [61].

Another molecule that stem cells can sense is TGF-β. This molecule is associated with the fibrotic response after MI. MSCs exposed to TGF-β secrete pro-angiogenic bFGF and VEGF factors and are primed to express cardiac markers [62]. In response to pro-inflammatory cytokines, MSCs also secrete immunomodulatory factors, such as IL-4, IL-10, prostangladin E2 (PGE2), TNF-stimulated gene 6 protein (TSG-6), and interact with immune cells (lymphocytes B an T) through cell–cell contact and paracrine secretion mechanisms, thereby modulating the inflammatory status of the infarcted tissue [63–65].

Endogenous stem cells located within the bone marrow can also sense inflammatory molecules released into the circulation from the myocardium after infarction. Bone marrow is the major reservoir of endogenous stem cells able to respond to gradients of inflammatory mediators. TNF-α, IL-8, MCP-1, and VEGF have been described to enhance the migration and/or engraftment of stem cells towards the injured myocardium [66–68]. In addition, inflammation and hypoxia stimulate the expression of the chemokine SDF-1 shortly after the onset of MI [25, 26, 69]. This is an important molecule able to mediate the trafficking and homing of CXCR4 presenting cells, such as endothelial progenitor, bone marrow, and cardiac stem cells.

Biomaterials as Sensors and Effectors at the Cardiac Environment

External delivery of regenerative cues to the infarcted myocardium presents considerable challenges. Studies on the efficacy of local (intracoronary or intramyocardial) or systemic (intravenous) infusion of stem cells have observed that, in all scenarios, the majority of cells are lost within 2–3 days after infusion [70, 71]. The inefficient homing of stem cells is described as a main reason for the limited success of the systemic delivery route [72]. Cells able to reach the myocardium are exposed to hypoxia, inflammation, and a disrupted ECM matrix that is likely unable to support and maintain cell survival as healthy tissue. For cytokine delivery, major challenges result from fast diffusion and short half-life caused by proteolytic or oxidative degradation [73].

A strategy to improve the efficiency of these therapies includes the use of biomaterials that are able to modulate cell behavior and spatial organization, and to control the release of biomolecules. The establishment of a favorable microenvironment for tissue regeneration requires the synergistic action between precursor cells, multiple growth factors, and a scaffolding matrix (biomaterial) able to regulate the spatial and temporal presentation of soluble factors and promote cell survival [74, 75]. In the case of therapeutic proteins, the release profile (dose and kinetics) can be engineered using different immobilization strategies on carrier biomaterials (Fig. 3). Such strategies include non-covalent immobilization (through electrostatic, hydrophobic, and hydrogen-bonding interactions),

covalent linkage to the polymer backbone or physical encapsulation. The strategic immobilization of growth factors on the carrier, or the differential affinity forces between protein-polymer [76], allows the establishment of complex multi-release kinetics (Fig. 3a) [77].

Biomaterials for cardiac applications should meet several design criteria. They should (1) have compliant mechanical properties with native tissue, (2) be biodegradable, (3) have a pore size and interconnectivity favorable to the establishment of vascular networks, colonization by cardiomyocytes or progenitors, and facilitate oxygen and nutrients diffusion, (4) promote cellular adhesion (e.g., peptide sequence RGD in hydrogels), and (5) allow the incorporation of bioactive molecules to be released with specific kinetics. Examples of materials already tested in MI therapy include natural (e.g., collagen, fibrin, hyaluronan, alginate) or synthetic (e.g., polyethylene glycol (PEG) hydrogels; poly (glycerol sebacate), polyester urethane urea elastomers) materials [78]. These biomaterials can be envisioned as the first generation biomaterials for cardiac tissue engineering (Fig. 3a).

Within a physiologic environment, growth factors interact with the ECM through specific binding domains (e.g., proteoglycans) [79] and are released after enzymatic cleavage or dissociation, creating gradients favorable to localized biologic functions. Therefore, the inexistence of a feedback loop between microenvironment and material, with inefficient control over the signaling sequences and release doses, likely limits therapeutic outcomes. A new generation of biomaterials has recently been developed to interact dynamically with the tissue environment (Fig. 3b). These smart biomaterials have the ability to sense and respond dynamically to the cardiac tissue environment. This self-regulating process, which responds to disease progression, may help to overcome inter-patient differences in a step towards personalized medicine.

Biomaterials as Sensors of the Cardiac Environment

Protease-Sensitive Biomaterials—The importance of MMP expression and activity during cardiac remodeling [21], its spatial confinement to the diseased area and its specificity for certain peptide linkages present in the ECM [21], makes MMPs a relevant trigger for smart materials. The use of enzyme cleavable sites enables one to mimic the on-demand release provided by the ECM [80]. Recently, Kraehenbuehl et al. evaluated the therapeutic effect of an MMP-responsive bioactive hydro-gel incorporating vascular cells (endothelial and smooth muscle-like cells derived from embryonic stem cells [81, 82]) and a pro-survival peptide, thymosin β4 (Tβ4), in a MI model [48]. In vitro results showed that gel degradation and Tβ4 release was influenced by the concentration of MMPs (Fig. 3b) [83]. The degradation of the gels was also confirmed in an MI animal model and correlated with the tissue levels of MMP-2. At 24-h post-injection, rat cells could be observed within the gel. Over time, the gel degraded leaving around 25% of the injected gel at 28 days. By day 42 post-injection, the gel could not be detected. The on-demand release of cells and Tβ4 preserved cardiac tissue after MI, with an improvement in the LV ejection fraction at 6 weeks of 12% when comparing with PBS-treated group. The positive results observed were attributed to the action of pro-angiogenic factors released by the transplanted cells, whose survival is supported by Tβ4.

pH-, ROS-, Biomolecule-, and Mechanically Sensitive Biomaterials—Cardiac tissue suffers pH changes during an ischemic attack as a result of lactic acid production during anaerobic metabolism [84]. The acidic pH at MI has been used to trigger the release of an anti-inflammatory agent from acid-sensitive microparticles [85]. The microparticles were formulated from the polymer poly(cyclohexane-1,4-diyla-cetone dimethylene ketal). Upon degradation, the micro-particles originate neutral excretable, FDA-regulated

compounds 1,4-cyclohexanedimethanol and acetone. The anti-inflammatory containing-microparticles sustain the release of the drug for at least 7 days, and its administration was correlated with a 10% improvement in fractional shortening following MI. Other technologies based on pH-responsive biomaterials can be used for cardiac applications and further research is needed to fully explore this potential [86]. For example, polyelectrolytes hydrogels can be designed to be stable at a physiologic pH and swell in an acidic environment releasing its payload (Fig. 3b). The increase in swelling is due to their ability to accept protons from the environment since they incorporate pH-sensitive pendant groups such as carboxylic or sulfonic acids [87]. Polymer design allows one to define the specific stimuli pH to achieve the desired response. One relevant example is the application of these materials in the oral delivery of insulin [88]. Related systems include biomolecule-triggered drug-delivery materials [89] able to undergo conformational changes in the polymeric network in the presence of specific stimuli, such as antigens [90] or glucose concentration [91].

Recently, materials able to specifically degrade in response to the oxidative stress were described [92, 93]. Their ability to deliver sensitive molecules, such as proteins and RNA, on its active form, allows them to join the pipeline of stimuli-responsive materials for biomolecule release. Given the cardiac upregulation of ROS in an early phase after the ischemic attack, it will be interesting to evaluate the use of these materials as delivery systems of molecules with therapeutic effect in the initial phases of MI (e.g., anti-apoptotic factors).

Interestingly, the stretching of cardiac tissue and the different stress patterns developed after MI may provide a mechanical stimulus to tailor the bioactive material. Lee and colleagues have established a first proof of concept of this approach, by developing a material able to release VEGF when subject to mechanical forces, with positive functional outcomes in a hind-limb ischemia model [94]. However, it is not clear if such an approach would be relevant in a cardiac setting.

Non-Disease-Related Stimuli-Sensitive Biomaterials—The use of biomaterials that are sensitive to external stimuli, such as light, ultrasound, small molecules, and magnetic or electric fields, provides an easy to control on–off release behavior of pharmacologic agents [43]. This approach has been previously explored on the epicardial delivery of anti-arrhythmic drugs using iontophoresis [95]. In this case, the anti-arrhythmic agent was contained within an epicardial reservoir implant and its release was controlled by an electrically conductive barrier. Therefore, the transport across the barrier could be controlled by an external constant current source. When this approach is used, electrical current passes through only the electrical conductive barrier and not the myocardium. The translation of these strategies to the regenerative field will bring important control over the pharmacokinetics of therapeutic molecules and/or cell release [96]. They also present the possibility of exploring novel therapeutic schemes that are not feasible with current delivery technologies.

Biomaterials as Biologic Effectors

Based on the paracrine mechanism and secretome analysis of stem and progenitor cells with regenerative capacity, it is easy to surmise that cardiac regeneration involves a complex interaction between multiple soluble factors [39]. Therefore, fundamental knowledge on the function, synergies, and kinetics of bioactive elements is required to design efficient and safe therapies. To this end, besides providing a promising clinical tool for regenerative therapies, biomaterials have been pivotal to define the biologic role and therapeutic potential of different proteins, cells, and combinations of both, by allowing the controlled presentation

of regenerative cues to the ischemic site. This has been demonstrated by positive pre-clinical trials with factors able to promote cytoprotection (e.g., anti-apoptotic mechanism) [97–99], angiogenesis [100–104], or the mobilization, homing, and differentiation of endogenous stem or progenitor cells populations [105]. It is important to consider that most proteins are pleiotropic, generating different biological outcomes depending on concentration, the targeted receptor and/or cell type, and it is not clear how these outcomes differ between species (e.g., rodents versus humans).

Growth factors such as IGF-1, HGF, VEGF, granulocyte-colony stimulating factor (G-CSF) or the hormone EPO have shown cardioprotective effects mediated by the phosphoinositide-3/Akt pathway, promoting improvements in cardiac function [97]. Despite EPO's anti-apoptotic and anti-fibrotic effect [106], the requirement for high doses during systemic infusion with risk of polycythaemia and thrombo-embolic complications, have been limiting factors for its clinical use. To overcome this, it was recently described the effect of EPO local delivery through gelatin patches [98] and injectable hydrogels [107]. This route of administration allowed a targeted effect with activation of survival pathways and a decrease in infarct size without systemic side effects. In one other study, the combinatorial delivery of IGF and HGF from affinity-binding hydrogels has shown longer-term (4 weeks) positive outcomes (reduced fibrotic area) in an MI model when comparing with a bolus infusion of factors, possibly resulting from the slow release of the bioactive molecules [108]. The positive outcomes were attributed not only to anti-apoptotic and pro-angiogenic mechanisms, but also to the stimulation of endogenous regenerative pathways. However, the functional impact of activation of these endogenous pathways is still unclear. In addition to their effect on end-organ cardiomyocytes, pro-survival factors are also important for improving the efficiency of stem cell-based therapies. Davis and colleagues described the use of self-assembling peptide nanofibers with tethered IGF-1, a highly diffusible protein [109], as a carrier for neonatal cardiomyocytes [99]. The slow release of IGF-1 promoted a favorable microenvironment with longer-term survival of transplanted cells and significant functional outcomes, when comparing with freely diffusing IGF-1. Protein engineering through fusion with ECM-binding domains is another interesting strategy to promote the long-term residence of growth factors within the cardiac tissue [110, 111]. For example, IGF-1 modified with a heparin-binding domain is retained on proteoglycan-rich tissues [110]. The main challenge of this approach is the correct design of the fusion protein to assure its bioactivity.

Therapeutic neovascularization is a complex and highly controlled processes involving attraction and spatial organization of endothelial cells (angiogenesis), followed by the attraction of vascular mural cells (arteriogenesis) and the establishment of a functional and stable network [112]. Despite its attractiveness for myocardial regeneration, simple infusion of factors that promote neovascularization (e.g., VEGF, FGF, Ang-1, PDGF) have shown limited therapeutic benefits [113]. Challenges such as (1) rapid factor clearance [114] with subsequent regression of newly formed vessels [115, 116], (2) increased vascular permeability with the establishment of tissue edema [117, 118], and (3) aberrant vessel formation caused by bolus doses [119, 120] have been suggested as reasons for therapeutic failure when an infusion delivery method was attempted. To overcome this, controlled or cell-mediated delivery of angiogenic factors has been shown to provide beneficial therapeutic outcomes in pre-clinical and clinical studies [102, 121–124]. For example, VEGF delivered from poly (glycolic acid) microparticles in an MI model resulted in the establishment of a functional and mature vasculature associated with favorable LV remodeling, though cardiac function improvements have not been reported [101]. In addition to the correct dose and spatio-temporal presentation of growth factors, targeting the release of agents at different stages of neovascularization has potential to significantly improve the response [125]. The development of carrier polymers with multi-release capacity permitted

testing some of these potential synergies with tight control over the concentration at the bioactive site. A rational approach, involves the sequential delivery of factors primarily acting on endothelial cells (e.g., VEGF, bFGF), followed by factors targeting vascular mural cells and promoting vascular stabilization (e.g., angiopoetin-1, PDGF) [54, 100]. Other interesting strategies make use of combinations of growth factors and endothelial progenitor cells that, in addition to contributing to the angiogenic process, are able to modulate cardiomyocyte organization, contractile properties, and survival [126]. Silva et al. developed a material that has potential to mediate cell migration and survival through VEGF gradients [103]. The goal of this cell-deployable strategy is to promote the functional integration of transplanted cells with the native tissue. Alternatively, the physical immobilization of angiogenic factors on the biomaterial promotes the establishment of a vascular network within the scaffold [104], improving the survival of co-transplanted cells [127] and/or the ingrowth capacity of native tissue. The approaches provide advantages including the slower degradation, diffusion, and cellular uptake of the bioactive factor, with consequent prolonged therapeutic effect.

The release of cytokines, with the capacity to mobilize endogenous stem and progenitor cell populations, is another interesting approach to provide continuous migration of cells during the remodeling process. To this end, SDF-1 is one of the most explored molecules. However, SDF-1 is quickly degraded by MMPs and dipeptidylpeptidases [128, 129]. The fast clearance leads to a short action time, unable to guarantee therapeutic effects [69, 130]. To overcome this, Segers et al. designed a protease-resistant SDF-1 derivative and incorporated the bioengineered molecule in a local drug-delivery system [105]. The slow release of SDF-1 maintains a chemotactic gradient for extended periods, favoring its regenerative capacity. The functional improvements by day 28 were significant, with an increase in the LV ejection fraction from 34% (MI only) to 50.7% (MI followed by local release of protease-resistant SDF-1). Complementary approaches to potentiate SDF-1 effect include its combinatorial delivery with G-CSF and/or protease inhibitors [129]. G-CSF acts on the bone marrow compartment, stimulating cell mobilization and expression of the CXCR4 receptor, promoting cells to be more responsive to SDF-1 gradients [131].

Most of the studies available are limited to short-term (1 month) endpoints. Given the dynamics of the post-MI environment, it will be important to evaluate the long-term effects of these novel therapies and the capacity to prevent the progression to a heart failure stage—the major challenge with currently available therapies. While interpreting these studies, it is also important to consider the effect of mechanical support provided by the biomaterials used, as these have been shown to improve, without addition of exogenous factors, ventricle function, and wall thickness [132]. The positive effects on cardiac remodeling, resulting from the decreased wall stress and cardiac stretching, are reviewed elsewhere [133, 134].

Future Perspectives

The characterization of paracrine factors secreted by stem cells and identification of specific factors that mediate the observed response may lead to the replacement of exogenous stem cell-based therapies by soluble factor-based therapies. However, based on the likely requirement for use of multiple factors that act synergistically, the strategy will require the orchestration of these factors to regulate the acute and chronic phases of cardiac disease. This will likely be enabled by the development of biomaterials capable of sensing and releasing biomolecules on demand. Further elucidation of critical biology that mediates cardiac repair is also important to tailor design relevant therapeutics. Although several stem-cell paracrine factors have been identified in vitro [135], including proteins, phospholipids, antioxidants, hormones, miRNAs among others, the in vivo temporal expression and how that translated in therapeutic outcome is unknown.

If cell-based approaches are able to prove beneficial therapeutic effects beyond the paracrine mechanism, namely by functionally integrating in the myocardium and providing direct contractile support, on demand materials may act as protective carriers able to guide cell delivery and spatial organization to maximize long-term outcomes. Such guidance might be achieved by the parallel release of bioactive mediators able to modulate the environment and transplanted cell fate.

A critical factor for the success of these therapies will be the temporal orchestration and direct correlation between the disease stage, kinetics, and therapeutic effect of the factor(s) to be released. The physiopathologic differences between the acute and chronic stages, namely in what relates to blood supply, cellular density, cytokine patterns, and fibrosis, will require the delivery of different bioactive agents to improve cardiac function. With this end in mind, a better understanding of specific stimuli derived from the diseased environment at all stages and the design of compliant biomaterials able to integrate the corresponding sensing elements will be essential.

Differences in the localization (MI, border or non-MI zone) of the delivery system might also introduce variability in the release kinetics. This can be a result not only from changes in the stimuli that defines the kinetics, but also from the ability of the released biomolecule to reach the bioactive site, as this will have to diffuse in a environment prone to protein degradation. Therefore, to maximize the clinical potential of such strategies, the delivery route is a critical point to consider. Though less-invasive procedures, such as intravenous injection, are normally preferred in a clinical setting, they offer considerable challenges in the ability to achieve targeted delivery to maximize the bioavailability in the MI site and minimize its systemic toxicity. The development of local drug-delivery systems, namely cardiac patches and injectable biomaterials, is now an intensive area of research with the promising capability of providing targeted delivery of the bioactive agents. Furthermore, minimally invasive surgical procedures, namely thoracotomies, are now starting to be explored to deliver such biomaterials with precision and without requiring open-chest procedures. The safety and efficacy of these techniques will be critical in the translation of smart biomaterials as cardiac drug-delivery systems into the clinics.

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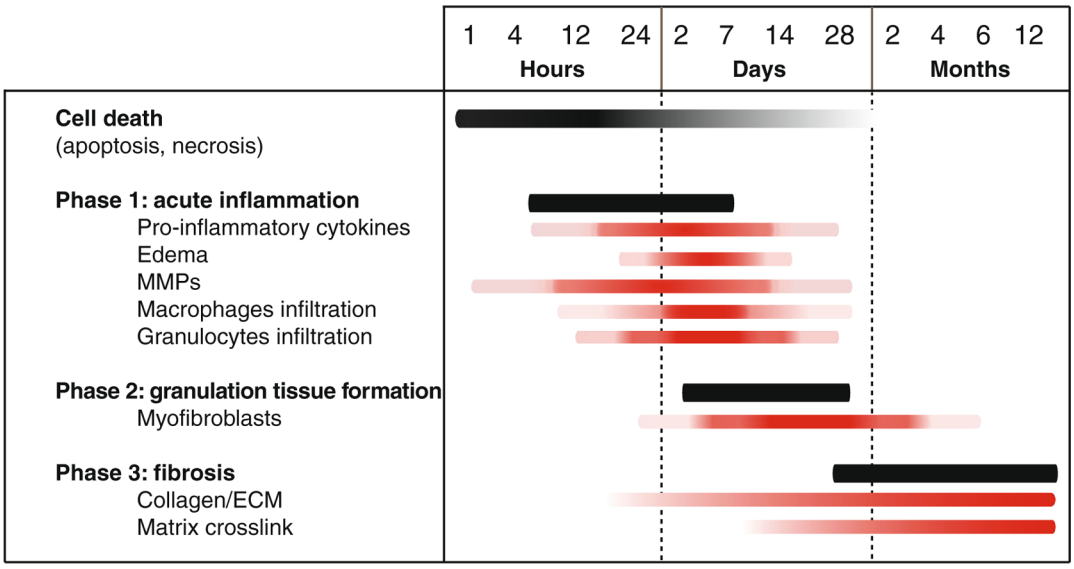

Fig. 1.
Temporal overview of the cardiac remodeling phases after MI

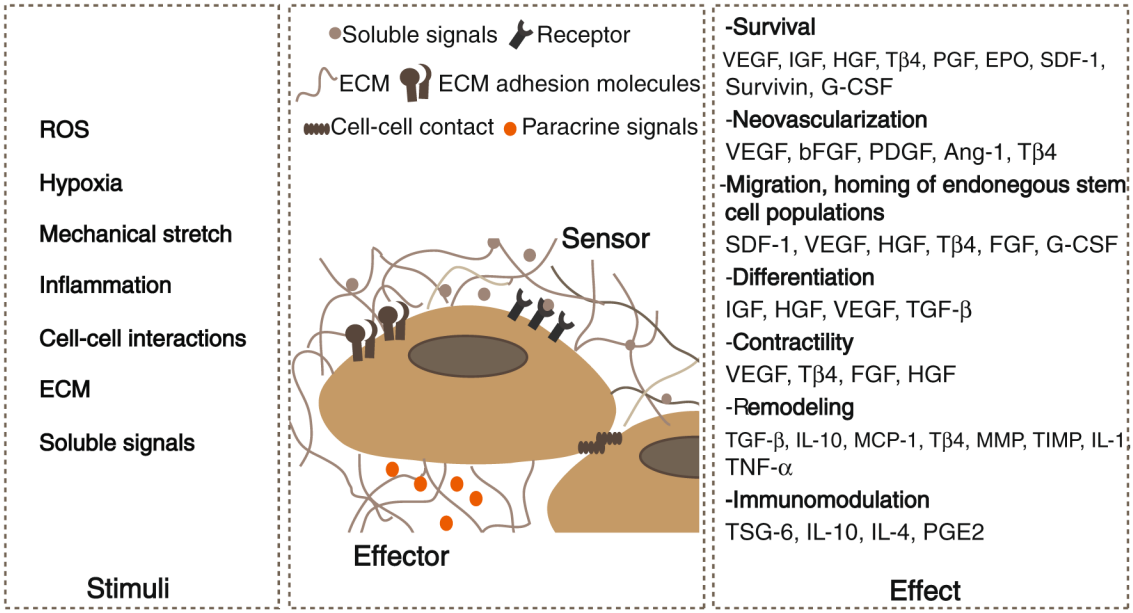

Fig. 2.

Environmental modulation of the cellular response and main paracrine factors responsible for improved function and cardiac regeneration after MI

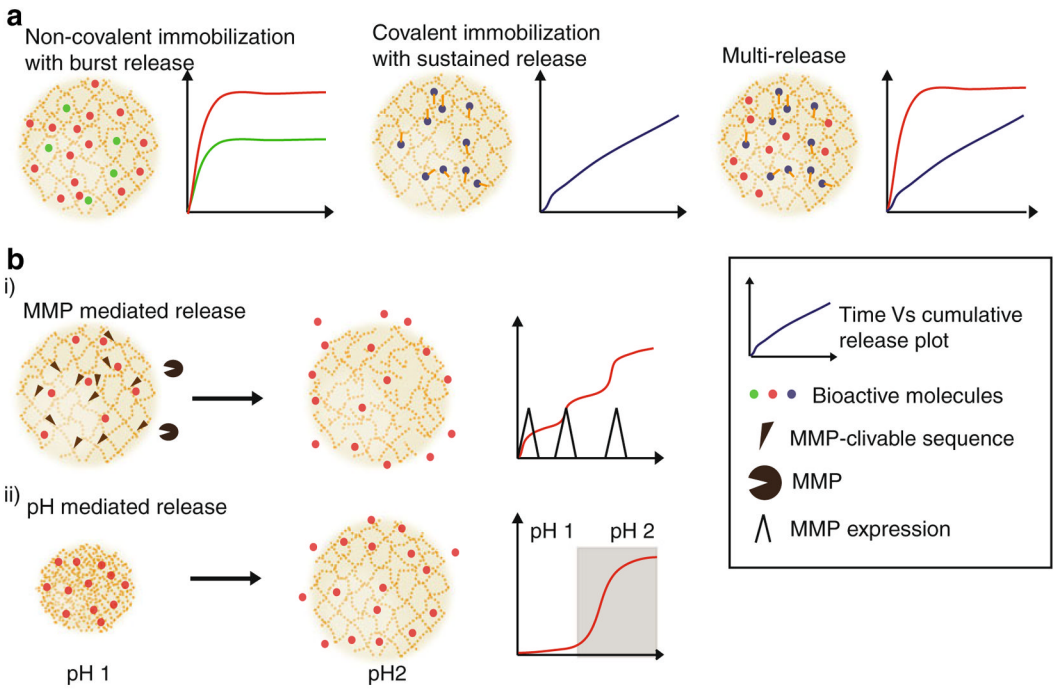

Fig. 3.

Engineered biomaterials for controlled release: *a* controlled release through physical encapsulation or covalent tethering of bioactive molecules on polymer network; *b* smart materials able to provide environmentally triggered delivery after specific stimuli such as MMP activity (*i*) or pH (*ii*)

Table 1

Cytokines involved in myocardial infarction

Cytokine	Major function	Ref.
IL-1	Stimulates MMPs transcription; collagen synthesis inhibitor, upregulation of cellular adhesion molecules	[136]
IL-6	Upregulation of cellular adhesion molecules; negative inotropic effect	[137, 138]
IL-10	Suppresses inflammation; collagen deposition	[139, 140]
MCP-1	Macrophage chemoattraction and activation, myofibroblasts infiltration	[34]
TGF-β	Suppresses inflammation; promote phenotypic changes from fibroblasts to myofibroblasts; promote collagen deposition	[33, 35, 136]
TNF-α	Upregulation of other inflammatory mediators; negative inotropic effect; upregulation of cellular adhesion molecules, neutrophil chemoattraction; stimulate MMPs transcription; collagen synthesis inhibitor	[136, 141–143]

TNF tumor necrosis factor, *IL* interleukin, *IP* interferon-γ inducible protein, *TGF* tumor growth factor, *MCP* monocyte chemoattractant protein