Expert Opinion

Aiming for the heart: targeted delivery of drugs to diseased cardiac tissue

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Background: The development of a number of regenerative strategies in recent years for *curing* heart disease represents a paradigm shift away from conventional approaches which aim to *manage* heart disease. Effective administration of pharmaceutical agents targeted directly to the diseased tissue is the key to unlocking the potential of regenerative strategies, which could augment current conventional treatments. *Objective*: The authors review recent advances in targeted drug delivery to diseased cardiac tissue. *Methods*: Various therapeutic methodologies designed to selectively deliver pharmaceutical agents to diseased cardiac tissue are discussed in this review. *Conclusion*: Targeted delivery of survival and engraftment promoting factors to damaged cardiac tissue can be an important strategy, for example, in creating a suitable microenvironment encouraging the engraftment of stem cells. Further progress in this emerging field is contingent on the discovery of new biomarkers that are upregulated in damaged cardiac tissue and can be targeted for selective drug delivery. Once fully realized, breakthroughs in this field will have direct applications in the diagnosis and treatment of heart disease through more effective tissue-specific drug delivery and improved imaging modalities.

Keywords: adhesion molecules, antibody targeting, cardiac imaging, cardiac regeneration, heart disease, liposomes, microbubbles, microenvironment, myocardial infarction, stem cells, targeted drug delivery

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1. Introduction

Ischemic heart disease affects approximately 15.8 million Americans and of those 7.9 million suffer from a myocardial infarction (MI) [1]. Myocardial infarction often leads to congestive heart failure (CHF) and is a leading cause of death in the US and other industrialized countries.

A myocardial infarction refers to the process of cellular death and necrosis that occurs after the occlusion of a coronary vessel supplying blood to a specific area of the myocardium. A reduction in coronary flow (ischemia) may result in myocardial necrosis which in turn could lead to functional impairments in the compromised region. If large enough, significant myocardial necrosis can lead to severe contractile dysfunction with an inability of the heart to maintain perfusion to vital organs, with subsequent decompensation and death.

Cardiac remodelling refers to the process of healing and repair that occurs after various forms of injury to the left ventricle (LV), such as MI. The process includes adverse changes in LV geometry and increases in LV mass in response to altered hemodynamic conditions. Many investigators have correlated changes in LV geometry and hypertrophy with elevations in angiotensin II and other neurohormones post-MI. Several cardiac tissues, including cardiac myocytes,

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fibroblasts and endothelial cells, have been shown to produce angiotensin locally. This local production of angiotensin II is a key contributor to the global LV remodelling process [2]. Subsequent therapies that have correlated with a survival advantage after an MI have targeted regression of the LV remodelling process.

At the cellular level, the initial response of some affected myocytes to the diminished oxygen supply is the initiation of apoptosis, beginning 4 h after MI [3,4]. This is followed by a breakdown in the homeostasis of the cardiac cells and a deterioration of the microenvironment, which initiates mass necrosis starting 12 h after MI. Animal studies have shown that it is possible to attenuate the level of apoptosis and necrosis after MI through deletion of p53-upregulated modulator of apoptosis (Puma) [5]. Also, increased levels of circulating heat shock proteins (HSP) have been found to correlate with the level of cytokines in circulation, activation of monocytes and myocardial damage after MI [6]. However, pretreatment with hyperthermia, which causes an increase in the levels of circulating HSPs, played a cardioprotective role resulting in a significant reduction in infarct size [7].

The deterioration of the microenvironment as a result of this mass necrosis causes a significant inflammatory response in the infarct region [3,4]. This inflammatory response leads to the release of cytokines such as IL-6 and IL-8 which in turn results in the accumulation of and tissue infiltration by white blood cells (WBCs) such as neutrophils, lymphocytes and macrophages. In addition to cytokine release, myofibroblasts infiltrate the damaged tissue to assist in wound healing. Once the WBCs reach the site of injury, they are able to phagocytose the dead cells, hence beginning the remodelling process.

The loss of muscle mass in the left ventricle, caused by the phagocytosis of dead cells after the immune response, results in a weakening of the ventricle wall. Starting as early as 3 days after MI and continuing as late as 4 weeks after MI, granulation tissue replaces the lost cardiac tissue with strong fibrillar collagen types I and III to maintain structural integrity in the ventricular wall [8]. The remodelling process culminates in the formation of scar tissue which maintains the structural integrity of the infarcted heart wall but exhibits little contractile function [4,9]. At this stage, the cardiac tissue is unlikely to recover its normal function due to the difficulties associated with regenerating cardiac tissue in a densely packed fibrillar scar [10].

In addition to the lost muscle mass, a transmural MI also involves the deterioration of the microenvironment through the proteolysis of extracellular matrix, vasculature and nerves. Subsequent tissue repair does not involve a significant regeneration of the microenvironment. For example, some angiogenesis/vasculogenesis occurs naturally starting 3 days after MI, but, due to the extent of the injury, this is ineffective in completely restoring the lost vasculature, which is an essential component of the microenvironment [8,11,12].

2. Mending the broken heart

The central function of the heart, that is pumping blood, can be compromised by disease and/or injury, particularly ischemia. To restore adequate circulation, a number of pharmacological and/or invasive therapies are currently used to treat heart disease. Clinical trials have provided a rationale for medical and interventional treatment of ischemic heart disease and its complications. These treatments include the use of diuretics and vasodilators, such as Lasix™ and Isosordil™, which reduce left ventricular filling pressure and volume. Angiotensin converting enzyme (ACE) inhibitors have been successful in lowering blood pressure and attenuating the effects of angiotensin II, and thus the cardiac remodelling process. Beta-blockers, such as Metoprolol™, block the receptor sites of noradrenaline, with positive actions on LV remodelling, adrenergic activity and oxidative stress. Newer adjunctive therapies allowing further improvements to survival include the use of an angiotensin receptor antagonist, post-MI. While aspirin remains a current therapeutic agent for this disorder, recent advances in antiplatelet therapy have allowed for the development of newer antiplatelet regimens such as clopidogrel and 2b3a glycoprotein inhibitors which improve the short-term and long-term outcomes among patients who have received a coronary intervention with a stent [13]. Invasive therapies to restore vital coronary perfusion, including coronary bypass surgery and percutaneous catheter interventions, rescue only the at risk myocardium, not the severely damaged tissues, and have the risk of restenosis. While these interventions have been efficacious, they do not restore myocardial function in the long term and only moderately recover LV function post-MI [14]. Many experimental drugs and new invasive treatments are currently under development which have the potential to prevent aberrant cardiac remodelling and repair the lost microenvironment post-MI. Implementing these therapies through targeted or systemic pharmacological interventions may represent important strategies for treating heart disease.

There is potential for a number of these emerging treatments to slow the progression of heart failure and widen the time frame where other treatments can be effectively administered, resulting in restoration of LV function after an MI. For example, during the second week after MI, a small percentage of cardiac cells naturally undergo some cell division, however, this level of proliferation is insufficient to repair the widespread damage after a myocardial infarction [15]. These myocytes can be encouraged to dedifferentiate and undergo mitosis, for example, when treated with a p38 MAP kinase inhibitor [16]. Slowing the pathological remodelling process using long-acting Ca^{2+}-channel blockers injected directly into the heart has also been shown to significantly improve the ejection fraction by as much as 42% [17].

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Over the past few years there has been much excitement and interest in developing regenerative approaches for curing heart disease, by restoring the contractile function of the heart through engineering replacement myocardium and its supporting microenvironment, using approaches such as cell-based therapy. Stem cells are self-renewing undifferentiated cells that in the proper environment can develop into specialized cells. Stem cells, therefore, have the potential to regenerate cardiac tissue lost after an MI. A variety of stem cells, including embryonic, bone marrow-derived stem/progenitor cells and skeletal myoblasts have been used to repair impaired myocardial tissue [18].

Embryonic stem cells are totipotent and therefore have the highest potential for differentiation into cardiac muscles. However, research into the implementation of this type of therapy is currently pending the development of an ethical consensus regarding their use. Bone marrow-derived adult stem/progenitor cells can differentiate into cardiomyocytes and endothelial cells and have been shown to improve damaged heart function in several animal studies by induction of myocardial angiogenesis and/or regeneration in the infarcted scar [19-21]. Therefore, bone marrow-derived stem/progenitor cells have been the focus of many recent investigations in animal studies and clinical trials [18,22-24]. In clinical applications, transplantation of bone marrow-derived cells has resulted in small (2.9 – 5.5%) but significant improvements in ejection fraction [24,25]. Hematopoietic/endothelial progenitor stem cells are derived from bone marrow cells and are very rare. These are still the most promising type of stem cells for use in treating ischemic diseases due to their ability to produce vasculature [18]. Skeletal myoblasts are another plentiful source of cells that have the potential to regenerate infarcted myocardium and are extremely resistant to ischemia [18]. In addition, endothelial cells, which have traditionally been assumed to be terminally differentiated, may also have the potential to be dedifferentiated to cardiac cells under appropriate conditions [26].

Although stem cells herald the possibility of repairing the damaged heart, recent attempts at rebuilding the myocardium using stem cells have yielded disappointing results [27,28]. Short-term studies have shown small gains in cardiac function, while long-term improvements as a result of stem cell treatments are uncertain [28]. The lack of a supporting microenvironment, which ensures the survival and engraftment of transplanted cells, may in part explain these disappointing findings. Concurrent delivery of survival and differentiation promoting factors into the damaged heart is an important strategy for enhancing the regenerative potential of transplanted stem cells in the heart. For example, rebuilt myocardium must include a vascular network able to nourish it under diverse metabolic demands. During natural healing of injured tissue, endothelial cells, which are the building blocks of these vascular networks, may be partially formed by circulating bone-marrow-derived stem cells migrating to the site of injury [29,30]. However, this process is unable to regenerate a sufficient microvascular network for the healing heart [8,11,12].

The high affinity of mesenchymal stem cell (MSC) migration to the site of injury and an absence of T-cell response to MSCs [31] makes them attractive not only as potential donor cells for myocardial regeneration, but also as a vehicle for gene transfer to the target cardiac tissue. For example, mesenchymal stem cells taken from bone marrow and genetically engineered to produce VEGF were found to provide a cardioprotective effect, as well as to induce angiogenesis in diseased cardiac tissue [32]. In addition, other findings suggest that heme-oxygenase-1 may increase cell survival in ischemic myocardium through anti-apoptotic and antioxidant activities. Expression of heme-oxygenase-1 by engineered MSCs resulted in protection of transplanted MSCs from apoptosis and led to the enhanced survival of transplanted cells in the hypoxic environment of the ischemic myocardium [33]. Delivery of genes into the infarcted heart using cells other than MSCs, such as VEGF transfected skeletal myoblasts, has demonstrated increased angiogenesis in ischemic recipient myocardium compared to animals treated with non-transfected cells [34]. Stem cells combined with other methods, such as gene therapy, can provide a powerful therapy for salvaging damaged myocardium. The timely delivery of survival and engraftment promoting factors may have significant implications on the viability of implanted stem cells for regenerating lost cardiac tissue.

Administration of pro-angiogenic compounds, such as VEGF, to the ischemic heart may represent a significant strategy for encouraging new blood vessel formation before or in combination with stem cell therapy [35-38]. However, our experimental and mathematical modelling studies indicate that systemic administration of VEGF may not be able to regenerate cardiac vasculature to a level capable of supporting stem cells [39,40]. In addition, concerns over possible side effects have hampered attempts at revascularizing the infarcted myocardium using systemic delivery of pro-angiogenic compounds such as VEGF and basic fibroblast growth factor (bFGF) [41-44]. Therefore, targeted drug delivery may be able to play a key role in our attempts to provide an appropriate microenvironment that can support the regeneration of cardiac tissue lost to MI.

3. Aiming for the heart

Developments in targeted drug delivery to tumors have provided the groundwork for the burgeoning field of targeted drug delivery to cardiac tissue. Anti-cancer drugs often have undesirable side effects which limit the maximum tolerated dose of the drug and often contribute to the quality of life reduction in many patients undergoing cancer treatment.

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Therefore, selective targeting of drugs, genes, or contrast agents to tumors has been an active area of research and development for many years [45,46]. An important development has been the recognition of drastically different endothelial surfaces in tumors which has lead to the concept of endothelial cell adhesion molecule mediated targeted drug delivery to tumors. For example, we have shown that the anti-vascular drug Combretastatin selectively targeted to irradiated tumors using immunoliposomes bearing an arginine–glycine–aspartate tripeptide (RGD) tripeptide sequence, which binds to the $\alpha_v\beta_3$ integrin in the tumor vasculature, results in significant tumor growth delay [47].

During the past few years, and in part due to the discovery of several biomarkers that are differentially upregulated in diseased cardiac tissue [48,49], various experimental therapies for targeting drugs, genes, or contrast agents to the heart have also been developed [50]. These experimental therapies have been selectively delivered via either intravascular administration or direct injection into the cardiac tissue. Ultrasound energy has also been used to enhance the delivery of the drugs and image echogenic microbubbles [51-53].

3.1 Particulate drug carriers

Nano-particulate drug carriers often passively accumulate in regions of high vascular permeability such as those present in many types of solid tumors [54]. For example, polyethyleneglycol propyl ether (PEG-PE) (7 – 20 nm in diameter) polymeric micelles have been shown to passively accumulate in the infarct tissue at a rate eight times higher than that observed in the adjacent normal myocardium in a rabbit model of MI [55]. IL-1 antagonist encapsulated liposomes injected directly into the coronary artery, passively accumulate in the infarct region of diseased cardiac tissue, attenuating the inflammatory response [56].

Upregulated expression of biomarkers, such as myosin, after MI has long been recognized as an effective target for selective delivery of drugs to the infarcted myocardium [57,58]. Recently, in a rabbit model of MI, radiolabelling was used to show that anti-myosin PEGylated liposomes injected into the myocardium preferentially bind to the compromised infarcted heart vasculature [59,60]. Interestingly, cytoskeletal antigen-specific immunoliposomes targeted to myosin post-MI have been shown to prevent oncotic cell death by fusing with the cell membranes using a 'plug and seal' approach to augment the membrane repair process [61]. Treatment with cytoskeletal antigen-specific immunoliposomes in a rabbit animal model of MI, using this 'plug and seal' effect, resulted in a fivefold reduction in average infarct size [61].

Several recent studies have shown that the inflammatory response that often accompanies ischemic cardiac episodes may result in the upregulation of a number of endothelial cell adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and platelet selectin (P-selectin) [62-64], within the diseased tissue. These adhesion molecules can in turn be used as targets for treatment or selective delivery of therapeutic agents to the infarct region [41]. Direct injection of anti-P-selectin [65-67] and anti-ICAM-1 [67] antibodies into ischemic myocardium was found to attenuate early remodelling by prevention of leukocyte infiltration in the diseased tissue, resulting in an overall 20 – 25% reduction in infarct size. Also, a marked reduction in infarct size (59%), improved myocardial blood flow and regional function, and reduced myocardial inflammation has been reported with simultaneous inhibition of glycoprotein IIb/IIIa and $\alpha_v\beta_3$ integrin [68].

Upregulated expression of adhesion molecules in the vasculature of the diseased cardiac tissue represents the most promising target for drug delivery. Competitive binding of liposomes conjugated to the carbohydrate sialyl Lewis^x, which is a ligand for the selectin class of adhesion molecules, with polymorphonuclear leukocytes, was found to reduce cardiac necrosis by 70% in a feline model of ischemia/reperfusion injury [69]. Using antibody-coated model drug carriers and immunohistochemical staining in a rat model of MI, we have shown that P-selectin expression by endothelial cells reaches a peak of upregulation at 4 h after MI and its level returns to normal by 48 h after MI, while ICAM-1 expression reaches a peak at 24 h and returns to normal 48 h after MI [64]. Furthermore, anti-P-selectin conjugated radiolabelled PEGylated immunoliposomes injected immediately or 4 h after MI and allowed to circulate for 24 h preferentially accumulated in the infarcted myocardium [64]. In preliminary experiments, we have found that anti-P-selectin conjugated immunoliposomes containing VEGF, when injected immediately post-MI, result in significant improvements in fractional shortening and end-diastolic diameter (**Figure 1**), which persists up to 4 weeks after treatment (**Figure 2**).

3.2 High frequency ultrasound

An external high frequency beam of ultrasound aimed at the infarcted heart can disrupt drug/gene carrying vesicles, thereby locally delivering their payload [51-53]. In general, these vesicles are in the range of 1 – 2 microns in diameter and their optimum release is dependent on several parameters [70], including a critical pressure amplitude larger than 1.2 MPa [71]. Vesicles carrying a recombinant adenovirus containing the β-galactosidase gene, injected into the jugular vein of rats, and disrupted with high frequency ultrasound targeted to the myocardium resulted in a 10-fold increase in the level of gene expression in the myocardium compared to control [72]. Using this technique, the disruption in the endothelial barrier as a result of vesicle destruction may be the key to successful viral transduction in targeted tissue [72]. Rats that underwent ultrasonic microbubble destruction prior to injection with microbubbles containing the β-galactosidase gene showed a twofold increase in gene expression [72]. High frequency ultrasound vesicle disruption

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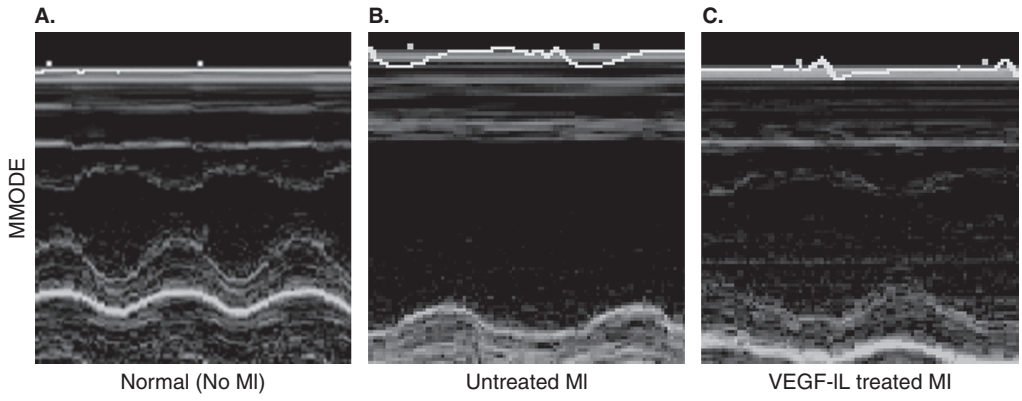

Figure 1. Administration of VEGF-immunoliposomes (VEGF-IL) targeted to P-selectin immediately after ligation of left anterior descending coronary artery to induce a myocardial infarction (MI) resulted in significant improvements in left ventricular wall motion 4 weeks after MI. Panels **A**, **B**, and **C** are representative ultrasound MMODE traces of left ventricular wall motion of a normal (No MI) heart, an untreated infarcted heart 4 weeks after MI and an infarcted heart treated with VEGF-IL 4 weeks after MI, respectively.

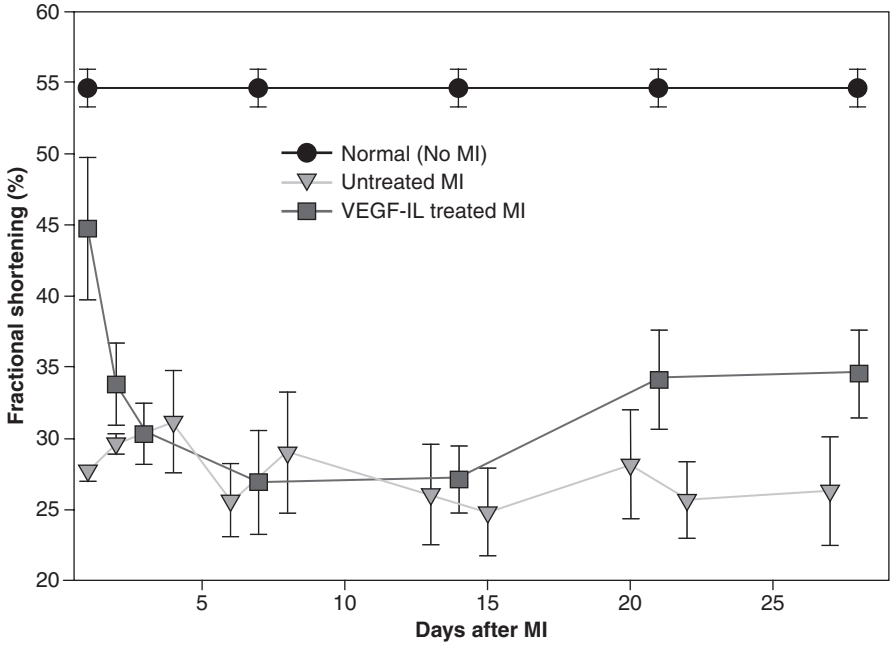

Figure 2. Improvements in fractional shortening in rats treated with immunoliposomes containing vascular endothelial growth factor (VEGF-IL) targeted to P-selectin injected immediately post-MI.
MI: Myocardial infarction.

has also been utilized to deliver a gene for VEGF to the infarct site of rat myocardium [73,74] resulting in a significant increase in VEGF expression as well as a significant increase in vascular density [73].

3.3 Peri-infarct injections

The direct injection of drugs/genes into the peri-infarct myocardium or vasculature has also been used to target therapeutic agents directly to the diseased tissue. Direct injection of adeno-cyclin A2, which has previously been shown to initiate cardiomyocyte mitosis, into the peri-infarct region of rat hearts, resulted in a 26% increase in ejection fraction [75]. Animals pretreated with an injection of an adenoviral vector coding for heat shock protein 70 (HSP70) into the wall of the left ventricle showed a decrease in infarct size (24.5 versus 41.9%) after a 30 min episode of ischemia [76]. In another study, direct injection of an adenovirus encoding for human growth hormone, which has been shown to induce myocardial hypertrophy and reverse ventricular remodelling, was shown to improve cardiac

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function in a rat MI model [77]. Gene therapy, administered directly into the heart vasculature, was shown to promote the expression of the therapeutic transgene S100A1 in a rat MI model, resulting in a ≈ 30% improvement in global cardiac function after 8 weeks of treatment [78].

Clinically, gene transfer through direct injection of plasmid DNA encoding for VEGF into ischemic myocardium has been shown to promote angiogenesis [37]. In addition to stimulating angiogenesis, direct intramyocardial injection of a plasmid encoding human VEGF has been shown to promote cardiomyocyte entrance into mitosis [79]. While adult cardiomyocytes have receptors for VEGF, it is unclear if VEGF acts on them directly to promote division or through an indirect pathway [79]. In addition to its angiogenic properties, the cardioprotective properties of VEGF and bFGF make them ideal candidates for targeted delivery to post-MI tissue [32,80,81]. However, VEGF therapy alone can lead to the possible development of functionally abnormal blood vessels [44]. Therefore, targeted delivery of VEGF along with complementary angiogenic compounds such as angiopoietin-1, RhoA and Rac1 should result in the establishment of a functional vasculature post-MI.

Administering these direct injections in a controlled release formulation may effectively increase the plasma half-life of many cardiac drugs. Biodegradable hydrogel microspheres containing bFGF injected into the peri-infarct region in a pig MI model resulted in improvements in left ventricular function, reductions in left ventricular remodelling and an increase in vessel density [82]. Nanofibers combined with platelet-derived growth factor, which is thought to have cardioprotective properties, were locally injected into the myocardium of infarcted rats resulting in significant improvements in fractional shortening (38.3 versus 28.2% for controls) and end-systolic dimension 3 months after MI [83]. In a similar study, direct injection of insulin-like growth factor (IGF-1) biotinylated with nanofibers into the infarct region of rat myocardium provided a targeted and sustained release of IGF-1 for 28 days after MI [84]. When combined with an injection of transplanted cardiomyocytes, this treatment resulted in a reduction in infarct size, a 25% increase in myocyte cross-sectional area, and a significant improvement in systolic function [84].

3.4 Targeted contrast agents

Several commercially available echogenic microbubbles have been used clinically for contrast enhanced echocardiography [71,85]. These microbubbles are gas-filled lipid shells which reflect more ultrasound than the surrounding tissue, thus providing a clear image of myocardial perfusion [71]. Inherently echogenic, acoustically reflective liposomes can also be generated by adjusting the lipid composition using a dehydration/rehydration procedure [86].

The upregulation of the inflammatory response post-MI provides an opportunity for targeting contrast enhancing particulate and/or molecular probes to site-specific biomarkers on diseased cardiac tissue. The development of microbubbles for targeted therapy and imaging has been reviewed recently [87] and will be discussed here only briefly.

Small (1 – 2 microns) acoustically reflective ligand-targeted microbubbles have been used for *in vivo* cardiac contrast imaging [88-90]. Clinically, large microbubbles targeted to areas of inflammation, which express ICAM-1, have been used in myocardial contrast echocardiography (MCE) to detect regions of acute cardiac transplant rejection [91]. Quantifying the degree of intramyocardial infiltration of macrophages and T lymphocytes by leukocyte-targeted microbubbles may have the potential to noninvasively assess the degree of rejection of transplanted hearts [92,93]. Leukocytes, which attach to the walls of inflamed endothelial cells after a period of ischemia/reperfusion, can also be targeted using echogenic albumin and lipid microbubbles [94].

In animal models, intravascular and transvascular ultrasound has been successful in detecting plaques using inherently echogenic ligand-coated liposomes [95,96]. P-selectin, which is generally upregulated within minutes to hours of inflammatory/ischemic episodes [64,97-100], has been used as a prime target for the delivery of echogenic vesicles. Strong enhancement of ultrasound images in inflamed tissue, resulting from microvascular retention of microbubbles targeted to P-selectin, can be used to assess the extent of inflammation and tissue injury [101]. Gas-filled microbubbles targeted to P-selectin have also been used to identify recently ischemic myocardium [63].

Other imaging modalities that have been used to provide contrast in cardiac tissue, including MRI, CT and SPECT, have been reviewed elsewhere [102-105] and are outside the scope of this review. These and other advances in targeted imaging techniques have direct applications to targeted drug delivery [87]. Further progress in the field of targeted drug/contrast agent delivery is in part contingent on the discovery of new biomarkers that are differentially upregulated in inflamed/ischemic cardiac tissue.

3.5 Vehicles for drug delivery

The development of new and novel drug/contrast agent delivery vehicles, including liposomes, polymeric micelles, biodegradable nanoparticles and dendrimers, has been the focus of many studies [106]. An ideal drug delivery vehicle must be non-toxic, biocompatible, non-immunogenic and biodegradable.

The most common vehicle currently used for targeted drug delivery is the liposome [107]. Liposomes are non-toxic, non-hemolytic and non-immunogenic even upon repeated injections; they are biocompatible and biodegradable and can be designed to avoid clearance mechanisms (reticulo-endothelial system (RES), renal clearance, chemical or enzymatic inactivation, etc.) [108,109]. Lipid-based, ligand-coated nanocarriers can store their payload in the hydrophobic shell or the hydrophilic interior depending on the nature of the drug/contrast agent being carried.

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Depending on the formulation and design, liposomes can effectively control the pharmacokinetics and biodistribution of the drug, and specific tissues can be avoided or targeted, and thus therapeutic index enhancement can be achieved in principle both via toxicity reduction and efficacy enhancement. A major drawback to liposome usage *in vivo* is their immediate uptake and clearance by the RES system and their relatively low stability *in vivo*. To combat this, polyetheleneglycol (PEG) can be added to the surface of the liposomes. Increasing the mole percent of PEG on the surface of the liposomes by 4 – 10% significantly increased circulation time *in vivo* from 200 to 1000 min [59].

Polymeric micelles are another type of drug delivery vehicle used for drug delivery [54]. Polymeric micelles are made from self-assembling co-polymers which, once formed, have a hydrophobic core that can be used to carry poorly soluble drugs [54,110]. Dendrimers are polymer-based delivery vehicles which have a core that branches out in regular intervals to form a small, spherical and very dense nanocarrier [111]. The extravasation rate of dendrimers across the microvasculature can be controlled by their size, molecular weight and physiochemical properties [112]. Biodegradable particles have the potential to not only target the diseased myocardium, but also deliver their payload as a controlled release therapy [113]. Biodegradable particles bearing ligands to P-selectin, endothelial selectin (E-selectin) and ICAM-1 have been found to adhere to inflamed endothelium [100] and their use can be easily extended for use in inflamed cardiac tissue.

4. Conclusion

The limited advances in the field of targeted drug delivery to diseased cardiac tissue have their roots in targeted drug delivery to tumors or have resulted from developments of novel targeted contrast agents for imaging. Many of the processes that underlie the progression of heart disease (e.g., upregulation of the inflammatory response) are similar to those observed in other pathologies (e.g., cancer). Therefore, advances in targeted drug delivery to tumors, for example, could have a direct influence on our attempts to selectively deliver therapeutics to cardiac tissue.

Ligand-targeted liposomes and microbubbles have been the most widely used vehicles for preferential delivery of contrast agents to cardiac tissue. However, these lipid-based nano-carriers have a low signal-to-noise ratio during sonography. Therefore, identification of more suitable biological targets in the cardiac tissue is required before these techniques can become widely used in a clinical setting [89]. Improved targeted imaging modalities are critical to our efforts in developing truly individualized treatments for heart disease, including better detection and demarcation of the extent of the MI as well as the determination of the optimum conditions for administration of stem cells and other therapeutics [114]. Success in the field of targeted contrast agent delivery to cardiac tissue will be highly dependent on advances in bioimaging technology and carrier optimization [115].

While the design of new drug carrying vehicles has been the focus of intense research and development during the past decade, the efforts to identify biomarkers that are differentially upregulated in diseased (cardiac) tissue has received less attention. The search for appropriate biomarkers that are significantly and differentially upregulated in diseased cardiac tissue is a prerequisite in our efforts to develop targeted drug delivery technologies that could have clinical applications. Many biological targets currently used for preferential delivery of imaging and therapeutic agents to cardiac tissue exhibit a low differential of upregulation between normal and diseased tissue. While advances in imaging technologies (such as software/hardware developments) can potentially compensate for the low selectivity of targeted contrast agents, ligand-based targeted drug delivery is more dependent on the availability of optimal biomarkers that can be preferentially targeted. This lack of optimal biomarkers is not unique to cardiac pathologies and is in part why targeting drugs to tumor endothelium that has been 'sensitized' with ionizing radiation, for example, has been more successful [47]. Currently, it is not clear whether existing clinical interventions can 'sensitize' cardiac tissue in a manner that further upregulates biomarkers which can then be targeted using ligand-based drug delivery vehicles.

The development of a number of novel therapies for curing heart disease represents a paradigm shift away from conventional approaches which aim to manage heart disease. Many of these emerging novel treatments, for example stem cell therapies, require the formation of an appropriate microenvironment that can only be generated through administration of pharmaceutical agents whose side effects can be circumvented with targeted drug delivery. Advances in the field of targeted drug delivery to cardiac tissue will be an integral component of our efforts to regenerate cardiac tissue.

5. Expert opinion

Current treatments for heart disease, such as bypass surgery, stenting, β-blockers and diuretics are either highly invasive or rely on continuous administration of various pharmaceuticals. In the past few years there has been much excitement and interest in developing regenerative approaches for curing heart disease using stem cells, pro-angiogenic drugs and treatments that prevent cardiac remodelling. However, these regenerative strategies have, at best, resulted in marginal improvements in cardiac function and at this time, clinical management of heart disease still relies primarily on traditional treatment methodologies.

Once fully realized, rebuilding lost myocardium using novel approaches such as stem cell therapy may prevent the appearance of chronic cardiac failure following MI. However, cardiomyocytes are highly dependent on their microenvironment for survival and currently it is not clear

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if treatments such as stem therapy alone can produce the robust microenvironment capable of supporting the survival and engraftment of transplanted cells. For example, recent evidence indicates that the limited improvements in cardiac function observed after current stem cell treatments may be in part due to angiogenesis [32]. Furthermore, the lack of a supporting vasculature for the highly oxygen-dependent cardiomyocytes may in part explain why recent attempts at rebuilding the myocardium using only stem cell therapies have yielded disappointing results [27,28]. The presence of an appropriate microenvironment in the infarct region may also be an important factor in enhancing the integration of transplanted cells into the surrounding tissue.

Regenerating the appropriate microenvironment in post-MI tissue may require the administration of a number of pharmaceuticals which unfortunately often have undesirable side effects [41-44]. For example, concerns over possible side effects have hampered attempts at revascularizing the infarcted myocardium using systemic delivery of pro-angiogenic compounds such as VEGF and/or bFGF. Therapies combining stem cell administration with novel approaches for preferentially delivering various drugs to infarct tissue may offer our best hope for regenerating myocardium lost during an infarction.

Many of the limited advances in the field of targeted drug delivery to cardiac tissue have been adapted from targeted cancer therapies or have been variations of techniques used in the development of targeted contrast agents. At present, targeted delivery of drugs to cardiac tissue relies on either the application of an external source of energy to initiate the drug release (e.g., ultrasonic disruption of microbubbles) [72] or the active accumulation of ligand-coated drug carriers which preferentially adhere to altered endothelium in diseased cardiac tissue [59,64,69].

The use of external energy sources to initiate drug release may be limited by the accessibility and location of the tissue being targeted, which is often deep inside the chest cavity. This could result in drug release to non-targeted tissue, which effectively lowers the maximum tolerated dose of the drug being administered. In addition, the precision of delivery using this method is directly dependent on how well the location and extent of the targeted tissue can be identified with other imaging modalities.

Ligand-coated drug carriers are ideally not as dependent on pinpointing the location and extent of the diseased tissue. Once injected into the bloodstream, for example, ligand-coated particles circulate until they encounter altered endothelium to which they bind and release their payload. However, the effectiveness of ligand-coated drug carriers is highly dependent on target identification/selection. A key requirement in this approach is that certain molecules, which are at a low basal level in normal tissue, be dramatically upregulated in diseased tissue. Antibody-based targeting schemes for drug delivery and imaging applications have had limited success, in major part due to the fact that molecule expression differential between normal and targeted tissues is often not high. While in recent times developing novel drug delivery vehicles has been the focus of many studies, progress in identifying more appropriate biomarkers that are significantly upregulated in diseased tissue has been limited. In our opinion, future advances in the fields of ligand-based targeted drug delivery/imaging will be highly dependent on identifying more appropriate biological targets in cardiac tissue.

At present it is not known whether, and to what degree, stem cells benefit the cardiac tissue, either by directly regenerating cardiomyocytes or by indirectly releasing factors that prevent cardiac remodelling. For example, if bone marrow mononuclear cells reduce the infarct size primarily by releasing VEGF into the surrounding tissue [116], then targeted drug delivery may be a more effective means for delivering VEGF to diseased myocardium. The underlying mechanisms of how stem cells may benefit diseased cardiac tissue have yet to be systematically studied. Given our current state of knowledge, at this time it is difficult to judge which targeted delivery technologies will be most effective in revitalizing the microenvironment for regenerating cardiac tissue.

Over the next 10 years, advances in the field of targeted drug delivery should play a more central role in our efforts to make the transition from treating heart disease to curing it. Regenerative strategies such as stem cell treatments are likely to play a key role in this transition. However, it is unlikely that stem cell therapies alone will be able to regenerate lost cardiac tissue. Combining stem cells with other (targeted) therapies to regenerate the appropriate microenvironment will provide the required framework to ensure that newly generated cardiac tissue can function normally and can integrate into and work in unison with the existing tissue. Given the central role of the vasculature, it is likely that regenerating the vascular framework through targeted delivery of pro-angiogenic drugs will be a central feature of these therapies. Future therapies will combine stem cells with appropriate signaling molecules that will ensure stem cell proliferation towards cardiac lineage and enhance their integration into the surrounding tissue.

Scientific advances are not the only obstacle in the path to the development of these therapies. The scientific community must also make a concerted effort to educate the public on the benefits and risks associated with these novel therapies.

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