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Review

Cardiac stem cell therapy to modulate inflammation upon myocardial infarction ☆

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ABSTRACT

Background: After myocardial infarction (MI) a local inflammatory reaction clears the damaged myocardium from dead cells and matrix debris at the onset of scar formation. The intensity and duration of this inflammatory reaction are intimately linked to post-infarct remodeling and cardiac dysfunction. Strikingly, treatment with standard anti-inflammatory drugs worsens clinical outcome, suggesting a dual role of inflammation in the cardiac response to injury. Cardiac stem cell therapy with different stem or progenitor cells, e.g. mesenchymal stem cells (MSC), was recently found to have beneficial effects, mostly related to paracrine actions. One of the suggested paracrine effects of cell therapy is modulation of the immune system.
Scope of review: MSC are reported to interact with several cells of the immune system and could therefore be an excellent means to reduce detrimental inflammatory reactions and promote the switch to the healing phase upon cardiac injury. This review focuses on the potential use of MSC therapy for post-MI inflammation. To understand the effects MSC might have on the post-MI heart the cellular and molecular changes in the myocardium after MI need to be understood.
Major conclusions: By studying the general pathways involved in immunomodulation, and examining the interactions with cell types important for post-MI inflammation, it becomes clear that MSC treatment might provide a new therapeutic opportunity to improve cardiac outcome after acute injury.
General significance: Using stem cells to target the post-MI inflammation is a novel therapy which could have considerable clinical implications. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

1. Introduction

Ischemic heart disease is the number one killer worldwide [1]. During ischemia there is a shortage of oxygen and nutrients in the heart leading to cellular apoptosis and necrosis. One of the key steps to prevent further cardiac deterioration is to restore blood flow into the affected myocardium. Upon reperfusion the restored blood flow reintroduces oxygen, leading to the generation of damaging reactive oxygen species [2]. In addition to the ischemia induced cell death, this reperfusion progresses cell death even further. As in all tissue damages an inflammatory response is stimulated to remove cell remnant and debris. The cardiac ischemic response also triggers a strong immune reaction in the heart [3–5]. This reaction includes the activation of local macrophages and the attraction of other immune cells from the blood, such as neutrophils, monocytes and lymphocytes [3,4,6]. This inflammatory reaction clears the wound of dead cells and debris, thereby simultaneously providing key signals to activate reparative pathways. The different immune cells produce a large number of pro-inflammatory cytokines. This leads to a cascade in which more immune cells are attracted, causing further damage and stress on the surviving cardiomyocytes and leading to even more cell death. Due to this strong response the inflammatory reaction has great influence on ventricular remodeling and cardiac function [7]. Resolution of the inflammatory response is currently thought to be an active process. It is mediated by factors produced by the cardiac cells, released from the matrix, and secreted by the infiltrated immune cells themselves [7].

These chemotactic and pro-inflammatory cytokines, which accumulate in high concentrations, attract and activate various components of the immune system. For over thirty years different ways of suppressing this immune reaction have been investigated to evaluate the effect on cardiac function. One of the most investigated approaches involves the administration of immunosuppressive drugs, usually corticosteroids [8]. Although the observed outcomes on cardiac performance differed strongly between studies, there was an overall decrease in leukocyte influx into the infarcted tissue. A recent meta-analysis on all clinical trials with corticosteroids shows that there is a non-significant trend towards decreased mortality with corticosteroid treatment [8]. At the same time, corticosteroids were also found to disrupt the healing process by delaying collagen deposition and scar formation. Smaller and weaker scars were formed, both in animal models and in humans, leading to an increased chance of LV rupture [8–10]. Non-steroidal anti-inflammatory treatments, such as ibuprofen, were also investigated. Although a reduction in neutrophils

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en leukocyte infiltrate was observed the broad suppression of the entire inflammation response resulted again in a thinner scar [11,12]. In addition, several NSAIDs were found to significantly increase the risk of recurrent myocardial infarction and death [13]. As a result, treatment with broad immunosuppressive drugs in the post-MI setting has largely been abandoned and no adequate therapy for the inflammatory response has yet emerged. An effective therapy that influences the immune response should reduce the length and damage of the inflammatory response and not interfere with or even augment the activation of reparatory pathways. This shift in balance between inflammation and repair might be achieved by using stem cell therapy in the heart.

2. Clinical stem cell therapy

During the last decades the use of stem cell transplantation therapy, to repair or regenerate damaged tissue, has become increasingly popular in clinical research. In the mid-fifties, researchers could cure mice with leukemia by near-lethal whole body irradiation, after which bone marrow from a healthy donor was transplanted [14]. Within a few years this treatment was also given to humans and despite initial disappointments, it quickly developed into a successful therapy [15].

Since then more research has focused on stem cell therapy. Over the years many more adult stem cells and progenitor cells have been investigated for potential regenerative therapies. One of the most investigated cells in recent years is the mesenchymal stem cells (MSC). MSC are present in the bone marrow, where they regulate the microenvironment. MSC secrete many paracrine factors, which can reduce cell death, fibrosis and even inflammation [6,16,17]. MSC are reputedly immuno-privileged, meaning that the host immune system will not attack them and allogeneic transplantation should be feasible [18,19]. The strength of the paracrine factors produced by MSC is demonstrated by experiments in which MSC-derived conditioned medium (CM) or components thereof are used. Such experiments demonstrated cytoprotective effects [20,21], reduced infarct size, improved cardiac function [10,22], stimulated human renal proximal tubule regeneration [23], and reduced autoimmune encephalitis [24]. Aside from numerous growth factors and cytokines produced by stem cells, exosomes have gained interest as one of the factors in the conditioned medium that serve an important role in these paracrine effects. Exosomes are small vesicles secreted by a large variety of cells containing a specific subset of proteins, mRNAs, and miRNAs, which can influence various biological processes [25]. For example, MSC-derived exosomes were found to reduce ischemia/reperfusion injury [26], while tumor-derived exosomes stimulated angiogenesis [27] and cardiac progenitor-derived exosomes stimulated endothelial cell migration [28]. Within the immune system exosomes offer an important means of cross-talk between the various subsets of immune cells, thereby regulating the immune response [29]. It is therefore not unlikely that exosomes produced by MSC can modulate the immune system as well.

The notion that MSC are active immune-suppressors appeared about ten years ago [30], when a suppressive effect of MSC on T-cell proliferation was observed. This immunomodulatory capacity was further investigated and quickly applied in therapy, as patients with therapy-resistant severe acute graft-versus-host-disease (GVHD) could be cured with repetitive MSC injections [31,32]. In fact, concomitant administration of MSC with the HSC transplantation enhanced engraftment of HSC and reduced the chances of acute GVHD [33]. These stunning results sparked an enormous interest to investigate their potential in other diseases. In the field of graft rejection, MSC were found to be able to prolong graft retention of skin grafts [34] as well as semi-allogeneic heart transplants [35]. MSC were also considered in auto-immune diseases. MSC applied in arthritis showed contrasting results, possibly related to the timing of administration [36–38], while research on inflammatory bowel disease (IBD) shows a positive response [37,39]. Interestingly, recently neural stem cells were also found to be immunosuppressive, raising the question whether immunomodulation is a general stem cell characteristic [40–43].

3. Current attempts in cardiac stem cell therapy

As cardiovascular disease is the most prevalent cause of death, still looking for new therapeutic modalities, it was quickly selected as a target population for stem cell therapy. In the past years, the focus of cardiac stem cell therapy has mainly been on the regeneration of damaged myocardium and angiogenesis, via paracrine signals or cellular differentiation. Results of these stem cell therapies include an increase in ejection fraction, a measure of cardiac function, and positive effects on cardiac remodeling [44,45]. After a week, however, only less than 5% of the injected stem cells are still present in the heart [45,46], none of which show true differentiation towards the cardiac phenotype. This clearly indicated that possible differentiation and direct functional contribution is only a minor factor in the observed effects, whereas supportive or paracrine factors are likely more important. These paracrine effects include a reduction in apoptosis and an increase in angiogenesis. However, a possible explanation, which has seen limited study, is the possible effect of MSC on post-MI inflammation. Since the immune response shortly after MI has a strong correlation with cardiac function and outcome [7], it is likely that these processes are affected by these paracrine factors of the transplanted MSC soon after injection as well. To gain more understanding of the transplanted stem cell effects on different cells in the immune system, and to investigate the possibilities of using cell therapy as a treatment for post-MI inflammation, it is important to know the temporal profile and location of inflammatory cells after MI. In this review, we provide an overview of post-MI inflammation, the protagonists from the immune system and known interactions between them and the MSC, one of the most abundantly studied cell types, in an effort to elucidate/predict the effects of immunomodulatory cardiac stem cell therapy.

4. Post-MI inflammation

During cardiac ischemia there is a shortage in supply of oxygen and nutrients to the cardiomyocytes. As the heart is extremely sensitive for ischemia, the first ultrastructural changes, such as myofibrillar relaxation, glycogen depletion and mitochondrial swelling, are visible within minutes of onset [47]. In humans, the effects of the oxygen-shortage are still largely reversible within the first twenty minutes. After that time permanent damage occurs [47]. During the following hours, oxygen-deprived cells can undergo necrosis, apoptosis or remain in a so-called hibernating state [47,48]. In response to, or during either of these processes, the stressed myocardial cells release cytokines, such as IL-1, express damage-associated proteins or loose proteins and lipids, thereby displaying their hydrophobic portions. After MI, these signals are all recognized as damage-associated molecular patterns (DAMPs) and are important for attraction and activation of various components of the immune system [49–51] (Fig. 1). Additionally, the complement system plays an important role in post-MI inflammation. The complement system becomes activated via natural IgM classes, targeting non-muscle myosin heavy chain type II A and C [52]. This IgM leads to the activation of the complement system, leading to a strong attraction of neutrophils and macrophages. Initially, the immune response is aimed at cleaning up the debris of dead cells and matrix. Later on, the actual repairs start with myofibroblast activation, collagen deposition and angiogenesis stimulation [2,7].

Toll like receptors (TLR) are of essential importance in the activation of the immune response after MI [7,53]. TLR are ubiquitously present receptors involved in perceiving danger signals. These danger signals were initially thought to be only pathogen-associated, yet recently it was found that DAMPs, released by stressed or damaged cells, can also activate TLR [49]. Although TLR were primarily found on

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