Seminars in Cell & Developmental Biology 58 (2016) 26–33

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Macrophages and regeneration: Lessons from the heart

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ARTICLE INFO

Article history:
Received 25 November 2015
Received in revised form 18 March 2016
Accepted 17 April 2016
Available online 23 April 2016

Keywords:
Heart
Inflammation
Macrophage
Monocyte
Myocardial infarction
Regeneration

ABSTRACT

One of the most ambitious goals in modern cardiology is to regenerate the injured myocardium. The human myocardium has poor regenerative power. Thus, significant myocardial injury results in irreversible damage, scar formation, remodeling, and dysfunction. The search for therapies that will improve myocardial regeneration needs a better understanding of the mechanisms of repair and regeneration. While the role of macrophages in inflammation, scar formation, and fibrosis are well defined, their role in myocardial regeneration is less clear. Recent reports have suggested that cardiac macrophages regulate myocardial regeneration in neonatal mice. The present review aims to describe the latest discoveries about the possible role of macrophages in myocardial regeneration. We discuss the promises and difficulties to translate the latest findings into new therapies.

Contents

1. Introduction

Cardiomyocyte renewal in the adult heart is rare, and insufficient to cure significant myocardial damage [1–3]. The incompetence of endogenous pathways to regenerate the injured myocardium has led to stem cell–based therapies [4]. However, the results of clinical trials are inconsistent and benefits have been questioned and debated [4–7]. Thus, we need to explore other approaches for myocardial regeneration.

A promising therapeutic approach for myocardial regeneration is to stimulate endogenous mechanisms and to inspire growth of new myocardium from cardiac progenitors and cardiomyocytes

Abbreviations: bFG, basic fibroblast growth factor; IGF, insulin like growth factor; IL, interleukin; LIF, leukemia inhibitor factor; MCP, monocyte chemo attractant protein; MMPs, matrix metalloproteinase; MYDGF, myeloid derived growth factor; PDGF, platelet derived growth factor; TIMPs, tissue inhibitors of matrix metalloproteinase; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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http://dx.doi.org/10.1016/j.semcdb.2016.04.012
1084-9521/

that survived the injury [8]. The ability of macrophages to infiltrate every tissue, respond to local stimuli and transmit regenerative signals, positions them as potential regulators of tissue regeneration. Consistent with this view, we and others have shown that macrophages are essential for infarct healing and repair in the adult heart [9–13]. However, the role of different macrophage subsets in myocardial regeneration remains uncertain.

The finding that newborn mice can regenerate their injured myocardium [14] suggests that heart regeneration in mammals is possible. It raises the hope that we might be able to reactivate the intrinsic regenerative capacity in the adult heart. Furthermore, it provides an animal model to study the role of macrophages in myocardial regeneration [14–20].

The aim of the present review is to summarize the potential role of macrophages in myocardial regeneration and describe recent discoveries in the field. We will clarify the role of macrophages in response to myocardial damage, as well as outline potential therapeutic strategies to improve infarct healing and regeneration by modulating individual subsets of monocytes and macrophages. By understanding how macrophages support tissue regeneration, we may obtain insight into how regeneration can be boosted in injured human hearts.

2. Inflammation and regeneration

Depending on the organism and organ, tissue injury can result in either complete regeneration or scar formation (repair) [21,22]. Most tissues of mammals have a limited regenerative capacity, with injury leading to replacement of damaged tissue with scar formation. In contrast, lower organisms are capable of regenerating tissues and even entire organs [23,24]. The pathways that direct scar formation versus regeneration are unclear. Activation of the immune system is one of the earliest events that occur during tissue regeneration [24,25]. Indeed, recent studies have provided new insights into the regulatory role of the immune system in tissue regeneration vs. scar formation [21,23,26,27]. More specifically, recent publications on lower vertebra, zebra fish and neonatal heart of mouse, suggest that inflammation, particularly macrophages, is an essential component of tissue regeneration [24,27–29].

3. Monocyte and macrophage subsets

Macrophages are leukocytes belonging to the mononuclear phagocytic system [30] and are resident in all tissues where they participate in tissue homeostasis [31–33]. Macrophages were previously thought to originate from progenitor cells in bone marrow [34], but recent fate mapping studies have suggested that some macrophages in adult tissues are colonized during fetal development [19,35–39].

Certain macrophage activities are contradictory, with either a pro- or an anti-inflammatory effect. Macrophages respond to local signals by a unique activation program called “polarization” [40–42]. Initially, macrophages were classified as M1 (classic) and M2 (alternative), based on *in vitro* activation by T-helper cell-type 1 (Th1) or Th2 cytokines. However, the M1–M2 concept is an oversimplified classification that only characterizes two extreme, opposing activation states. The various classifications of monocyte and macrophage subsets are behind the scope of our review and have been described by others (for example, see references [30,31,43–46]). The classification of macrophages *in vivo* is more complicated than those *in vitro,* and includes a spectrum of functionally overlapping phenotypes [40–42]. Macrophages at the site of injury may exist at any one point in the range of macrophage polarization states [42,47]. Still, the M1 and M2 classification remains a widespread terminology to define the functional status of macrophages during myocardial injury, repair and regeneration.

4. Reparative properties of macrophages

Modulation of the inflammatory response is an important supportive approach to increase the efficiency of regenerative medicine. Given their plasticity and paracrine properties, macrophages can coordinate and influence tissue repair and regeneration [33,43,48–52] (Fig. 1). Macrophages secrete a variety of cytokines, pro-inflammatory and trophic mediators [53,54]. For example, the release of interleukin (IL)-10, fibroblast growth factor (FGF)-1, insulin-like growth factor (IGF)-1, and leukemia inhibitory factor by activated macrophages have been suggested to inhibit apoptosis of hypoxic cardiomyocytes *in vitro* [55].

Additionally, macrophages clear apoptotic polymorphonuclear leukocytes, and promote efferocytosis (phagocytosis of apoptotic cells), which is essential for the resolution of inflammation [43,56]. Upon ingestion of apoptotic cells, macrophages secrete anti-inflammatory cytokines that may restrict inflammatory injury, thereby attenuating progressive and collateral tissue damage [57,58]. A dysregulation of efferocytosis leads to chronic inflammation which in turn impairs the healing process [43]. Macrophages also mediate ECM deposition by promoting fibroblast activation, ECM degradation, and altering MMP activity [9,24].

Macrophage-derived factors dictate cell fate decisions, and are implicated in the regeneration of neurons, [59] nerves, [60] skeletal myocytes, [48,51] [61], kidney, [62] pancreas [63,64] and liver [65]. Particularly, macrophages are implicated in skeletal muscle regeneration [48,51,66,67]. The mechanism is complex and includes clearance of dead cells [61], secretion of reparative cytokines such as IGF-1 [68], and interaction with skeletal stem cells [29,69]. Thus, macrophages play critical roles in tissue regeneration.

Deficiency of macrophages impairs tissue regeneration in zebra fish and salamanders [70,71], and ablation of macrophages disrupts heart regeneration in neonatal mice [17,18]. However, molecular links between injury response and the induction of regeneration are poorly understood.

Macrophages are also important regulators of angiogenesis. Both M1 and M2 macrophages are pro-angiogenic [72,73]. Restoration of damaged blood vessels, angiogenesis, and revascularization are major components of tissue regeneration. One of the mechanisms by which macrophages regulate angiogenesis includes a broad range of secretory factors produced by macrophages, such as trophic factors, cytokines and proteases (Fig. 1) [74–76]. Another relevant mechanism by which macrophages regulate angiogenesis is their production of Wnt ligands. Macrophage Wnts were shown to regulate vascular remodeling and angiogenesis during development [77] [78], and tumor progression by increasing its vascular density and facilitating macrophage angiogenic switch [79].

Apart from their paracrine induction of angiogenesis, macrophages have also been reported to be able to transdifferentiate towards endothelial-like cells [80] or endothelial progenitor cells [81], which is another possible mechanism behind their pro-angiogenic properties. After MI in the adult heart, pro-angiogenic macrophages have a protective effect on cardiac repair and function [12,82]. Thus, the pro-angiogenic properties of macrophages can ameliorate myocardial repair and regeneration.

Finally, macrophages interact with implanted mesenchymal and cardiac stromal/stem cells, and by secretion of angiogenic, reparative cytokines, mediate the therapeutic effects of stem cell therapy [10,11,50,83,84]. For example, macrophage polarization by mesenchymal stem cells is associated with change in function, increased secretion of reparative cytokines, such as IL-10 and VEGFs, and decreased secretion of pro-inflammatory cytokines,