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Role of inflammatory cells in fibroblast activation ☆

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ABSTRACT

Although fibrosis is an essential response to acute cardiac tissue injury, prolonged myofibroblast activation and progressive fibrosis lead to further distortion of tissue architecture and worsened cardiac function. Thus, optimal tissue repair following injury requires tight control over myofibroblast activation. It is now recognized that inflammation plays a critical role in regulating fibrosis. In this review we will highlight how advances in the field of innate immunity have led to a better understanding of the role of inflammation in cardiovascular disease and, in particular, in the regulation of fibrosis. Specifically, we will discuss how the innate immune system recognizes tissue damage in settings of acute injury and chronic cardiovascular disease. We will also review the role of different cell populations in this response, particularly the unique role of different macrophage subsets and mast cells.

Contents

1. Introduction

Recovery from tissue injury requires the coordinated activation of a variety of different reparative pathways. In the context of healing of damaged tissue, the term "repair" refers to the restoration of tissue architecture and function resulting either from tissue regeneration and/or tissue replacement. Regeneration refers to the type of wound healing wherein new tissue growth completely restores portions of damaged tissue to their normal state, whereas replacement refers to a type of wound healing in which severely damaged non-regenerable tissues are replaced by the creation of new connective tissue (i.e. tissue scarring), that is essential for maintaining the structural integrity of the injured tissue. Given that the adult mammalian heart has negligible regenerative capacity, the repair process following tissue injury requires a coordinated process that allows for the removal of the dead cells, followed by the replacement of the dead cells with new connective tissue. Here we will review the literature which suggests that the inflammation that occurs following tissue injury is required for proper tissue repair, as well as review the literature which suggests that if the inflammatory response becomes hyperactive following tissue injury, that this homeostatic repair process can lead to unwanted collateral damage and pathological tissue fibrosis. Finally, we will highlight the central role of fibroblast activation in tissue injury-induced inflammation and myocardial fibrosis.

2. Recognition of acute tissue injury by the immune system

Work over the last two decades has led to a greater understanding of the molecular mechanisms by which the innate and adaptive immune systems recognize infection and tissue injury. A wide variety of immune

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and non-immune cell types residing in the myocardium express germ line encoded pattern recognition receptors (PRR) that are capable of recognizing conserved molecular motifs shared by pathogenic bacteria and/or viruses, referred to as pathogen-associated molecular patterns (PAMPs). PAMPs are structures conserved among microbial species such as lipopolysaccharide of Gram negative bacteria, teichoic acids of Gram positive organisms, and double-stranded RNAs of viruses. The PRRs that have been implicated in sensing PAMPs include the canonical PRRs such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors and retinoic acid-inducible gene I (RIG-I) receptors, or atypical PRRs such as the RAGE receptor [1]. Germane to this discussion, activation of PRRs leads to activation of a variety of inflammatory mediators in the heart (reviewed in [2]). More recently it has become apparent that PRRs not only recognize PAMPs, but are also capable of recognizing molecular motifs residing on endogenous molecules that are released from damaged tissues, which have been referred to as damage associated molecular patterns (DAMPs) [1, 3]. When cells die by accidental necrosis, regulated necrosis (necroptosis), and/or secondary necrosis (late apoptosis), they release their cytosolic contents into the extracellular space, thereby initiating a brisk inflammatory response that mimics the inflammatory response triggered by pathogenic bacteria and/or viruses [4] [3]. Because the inflammatory response that ensues following tissue injury occurs in the absence of a known pathogenic infection, it is referred to as "sterile inflammation."

Ischemic injury is one of the best characterized models of acute cardiac injury [5,6]. Infarction leads to necrotic cell death, with the subsequent release of DAMPs (Fig. 1). The biological activity of DAMPs depends upon the overall extent of tissue injury, the type of cell death (necrosis vs apoptosis) and the type of cells dying (epithelial vs mesenchymal). DAMPs have been subdivided into 3 major categories, although some molecules can be included in multiple groups depending on the situation: leaderless proteins secreted by professional immune cells, also referred to as "alarmins" (e.g. high mobility box group 1 protein (HMGB1), interleukin IL-1β, galectin-3, uric acid); intracellular molecules released by dying cells (S100 proteins, HMGB1, IL-1α, galectin-3, heat shock protein (HSP) 60, HSP 70, HSP 72 [7]) and/or molecules that are expressed on the cell surface membranes of stressed of dying cells (e.g. phosphatidylserine); and components of the extracellular matrix (hyaluronan, heparan sulfate, fibronectin and degraded matrix constituents). The precise biochemical moieties that distinguish whether an intracellular protein is immunogenic or non-immunogenic are unclear; however, it has been proposed that many known DAMPs contain hydrophobic regions that are ordinarily hidden in healthy living cells, that then become immunogenic when released into the extracellular space [8]. Importantly, DAMPs are capable of triggering the activation of NF-κB, AP1, CREB, c/EBP, and IRF transcription factors, which activate genes encoding chemokines, cytokines, and adhesion molecules that promote the recruitment and activation of leukocytes [9].

Although a variety of different DAMPs have been implicated in initiating inflammation following myocardial infarction, the relative importance of individual molecules in the heart is unknown. While it is intuitively obvious that DAMPs play an important role in the setting of myocardial infarction, it is less clear what role DAMPs play, if any, in more chronic forms of tissue injury, such as sustained hemodynamic overloading, wherein the burden of ongoing cell death is much lower. Further, assessing the importance of DAMPs in vivo has been complicated by the redundancy of the system and the essential role that many DAMPs play in normal biology. A recent paper was able to dissect an important role for HMGB1 (a non-histone nuclear protein) in various forms of liver injury [10]. Mice with hepatocyte specific deficiency of HMGB1 survived doses of acetaminophen that are normally lethal. However, HMGB1 deficiency did not have an effect on inflammation or lethality in response to tumor necrosis factor (TNF), Fas-mediated apoptosis or LPS induced shock, suggesting that HMGB1 was not required for mediating classical inflammatory signaling pathways. As will be discussed below, following myocyte death that results from any form of tissue injury, DAMPs released by the dying cells are responsible for initiating myocardial inflammation and myocardial fibrosis.

3. Myofibroblasts

Myofibroblasts are mesenchymal cells that reside within the connective tissue of the heart, and are responsible for laying down extracellular matrix and generating scar tissue following tissue injury [11,12]. These cells express α-smooth muscle actin (α-SMA), and share characteristics of both fibroblasts and smooth muscle cells. Fibroblast activation is determined by the increased α-SMA expression on fibroblasts, increased fibroblast proliferation, and increased fibroblast production of extracellular matrix components [13]. Although fibroblasts are abundant in the healthy heart, few if any myofibroblasts are present in the naïve heart. The ultimate source of myofibroblasts in the heart has been studied extensively, and is reviewed elsewhere in this series (see review by Davis). Myofibroblast activation and accumulation are

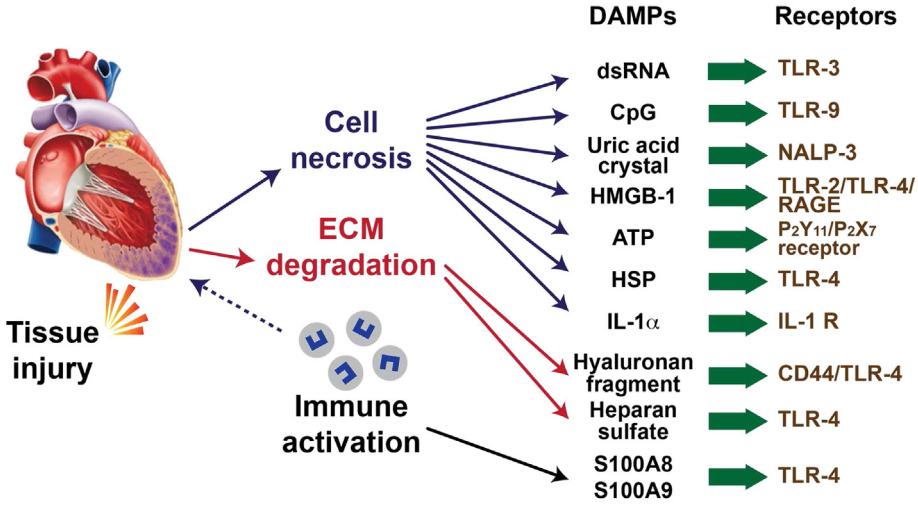

Fig. 1. Damage associated molecular patterns (DAMPs) are derived from dying cells that release their cytosolic content following myocardial injury, or from degradation of the extracellular matrix, as well as by immune cells that become activated following tissue injury. (Key: ATP = adenosine triphosphate, HSP = heat shock protein; HMGB1 = high mobility box group 1 protein, IL-1α — interleukin-1α; IL-1R —interleukin receptor, NALP = NACHT, LRR and PYD domains-containing protein 3 (cryopyrin); RAGE = receptor for advanced glycation end products, TLR = Toll-like receptor).
(Reproduced with permission Mann DL. In Blankesteijn WM and Altara R, eds. Inflammation in Heart Failure, Elsevier/Associated Press; 2015. p. 191–201).

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