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Minireview

Innate immunity and cardiomyocytes in ischemic heart disease

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ABSTRACT

Myocardial ischemia/reperfusion (I/R) is the most common cause of myocardial inflammation, which is primarily a manifestation of the innate immune responses. Innate immunity is activated when pattern recognition receptors (PRRs) respond to molecular patterns common to microbes and to danger signals expressed by injured or infected cells, so called pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The expression of various PRRs in cardiomyocytes and the release of DAMPs from cardiomyocytes subjected to I/R injury, through active mechanisms as well as passive processes, enable cardiomyocytes to generate innate immune responses. Studies in isolated heart and cardiomyocytes have confirmed the inflammatory and functional effects of cardiac PRRs especially Toll-like receptors in response to I/R-derived DAMPs, such as heat shock proteins. This review addresses the active role of cardiomyocytes in mediating innate inflammatory responses to myocardial I/R. We propose that cardiomyocytes act as innate immune cells in myocardial I/R injury.

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Abbreviations: AIM, absent-in-melanoma; CARD, caspase recruitment domain; CLR, C-type lectin receptor; DAMP, damage-associated molecular pattern; HMGB1, high-mobility group box 1 protein; HSC, heat shock cognate protein; HSP, heat shock protein; ICAM, intercellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; I/R, ischemia/reperfusion; IRF, interferon regulatory factor; KC, keratinocyte-derived chemokine; LPS, lipopolysaccharide; LRR, leucine-rich repeat; Mal, MyD88 adaptor-like protein; MIP, macrophage inflammatory protein; MR, mannose receptor; MyD88, myeloid differentiation primary-response gene 88; NF-κB, nuclear factor-kappa B; NLR, NOD-like receptor; NLRC, CARD-containing NLR; NLRP, PYD-containing NLR; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen-associated molecular pattern; PI3K, phosphatidylinositol 3-kinase; PRR, pattern recognition receptor; PYD, pyrin domain; RLR, retinoic acid-inducible gene (RIG)-I-like receptor; RT-PCR, reverse transcription-polymerase chain reaction; TIR, Toll/IL-1 receptor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adaptor protein inducing interferon-β.

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Introduction

Ischemic heart disease is the leading cause of heart failure. Growing evidence supports that innate immunity plays a critical role in myocardial ischemia and the development of heart failure. A mild to moderate innate immune response may limit the extent of cardiac injury and facilitate tissue repair, whereas an excessive response is likely to be deleterious (Mann, 2011). The persistent activation of innate immune responses, as characterized by progressive increases in serum inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6, is associated with the development of heart failure.

The innate immunity, which manifests as inflammation, is typically generated by innate immune cells, including neutrophils, monocytes, macrophages and dendritic cells. It is activated when pattern recognition receptors (PRRs) in immune cells respond to conserved motifs of invading pathogens and nonself elements, namely pathogen-associated molecular patterns (PAMPs). PPRs may also respond to endogenous molecular patterns released during cellular injury or death, namely damage-associated molecular patterns (DAMPs), and subsequently induce sterile inflammation (Rock et al., 2010).

Recently, several lines of data have suggested that cardiomyocytes can be a significant source of innate immune responses. First, the release of multiple DAMPs from stressed cardiomyocytes through active pathways has been found. Second, the expression of a variety of PRRs has been identified in both basal and stressed cardiomyocytes. Third, activation of cardiomyocyte PRRs by either PAMPs or DAMPs leads to inflammatory signaling and cytokine expression, similar to the case for immune cells. The current review focuses on the active role of the heart in inducing and coordinating innate responses to myocardial ischemia/reperfusion (I/R) (Fig. 1).

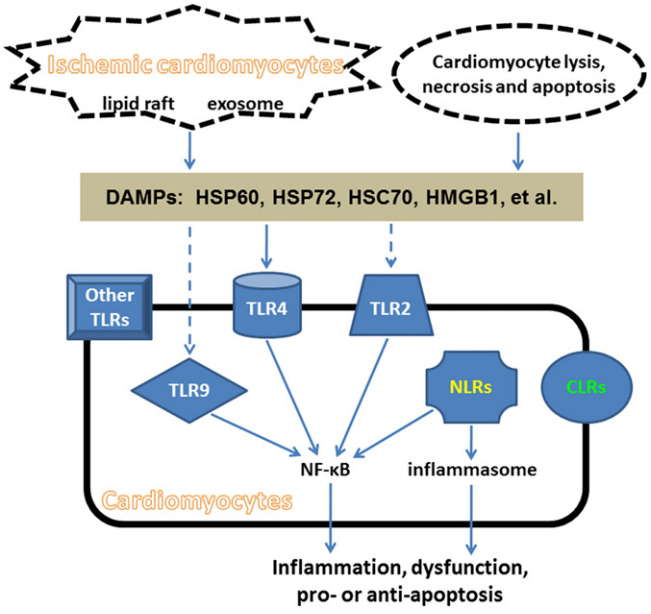

Fig. 1. Activation of PPRs in cardiomyocytes by DAMPs during myocardial I/R injury. Cardiomyocytes express a variety of PRRs including transmembrane receptors such as TLRs and CLRs, and cytoplasmic receptors such as NLRs. During myocardial I/R, DAMP molecules including HSP60, HSP72, HSC70 and HMGB1 can be released from ischemic cardiomyocytes, as well as cardiomyocytes undergoing lysis, necrosis and apoptosis. The release of HSP60, HSP72 and HSC70 is dependent on exosomes and/or lipid rafts, but not the classical secretory pathway. All the above DAMPs have been demonstrated to be able to activate TLR4 in cardiomyocytes. HSP72, but not HSP60, were shown to be able to activate TLR2 in cardiomyocytes. The activation of TLR2 and TLR9 by HMGB1 was demonstrated by studies in immune cells, but remains to be examined in cardiomyocytes. Endogenous DAMPs for other TLR subtypes, NLRs and CLRs remain unclear, though their expression has been recognized. The activation of cardiomyocyte TLR4, TLR2 and TLR9 results in NF-kB activation, which subsequently leads to inflammation, cardiac dysfunction and apoptotic effects. The activation of NLRs majorly results in the formation of inflammasome, which activates caspase-1 and trigger inflammation.

Overview of innate immunity and the heart

The immune system was originally described to function by making a distinction between self and nonself. In the relatively recent 'danger model' of immunity, the system is believed to react to 'danger signals', either self or nonself (Matzinger, 2002). The exogenous 'danger signals', so called PAMPs, are highly conserved motifs in microbial pathogens, such as lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid and flagellin of bacteria, mannan of yeast, chitin and ergosterol of fungi, and single- and double-stranded RNA of viruses. The endogenous 'danger signals', so called DAMPs, may come from distressed or injured cells, such as ischemic cardiac myocytes (Seong and Matzinger, 2004). Both PAMPs and DAMPs can activate the immune system through PRRs, a class of germline-encoded receptors, and lead to innate and adaptive immune responses (Akira et al., 2006). Innate immunity is a rapid response serving as the first line of host defense against danger signals. It is actually not nonspecific, as was originally thought, due to the specificity of PRRs for PAMPs and DAMPs. Furthermore, innate immunity is the major contributor to acute inflammation induced by PAMPs and DAMPs, and important for the activation of acquired immunity (Takeuchi and Akira, 2010). The processes of innate and adaptive immune responses following PRR activation have been addressed in several excellent reviews (Akira et al., 2006; Medzhitov, 2007; Kawai and Akira, 2010). Notably, the activation of PRRs, with the exception of some nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), leads to the production of inflammatory mediators including cytokines and chemokines (Takeuchi and Akira, 2010). Although PRRs are essential for protective immunity against danger signals, inappropriate PRR responses contribute to acute and chronic inflammation, and autoimmune diseases.

From an immunological perspective, the heart is not as active as other organs like the skin, gut, lung and liver, which undergo constant surveillance of pathogens from the external environment. The normal heart does not constitutively express inflammatory cytokines (Kapadia et al., 1995, 1997). However, a variety of physical and chemical stresses, including pathogen infection, ischemia and mechanical stretch, can cause innate and adaptive immune responses in the heart. Most commonly, the heart becomes involved by innate immunity and acute inflammation as a result of I/R injury (Taqueti et al., 2006). Based on the fact that PRRs are expressed in virtually all cell types, the cardiomyocytes themselves, as well as immune cells that migrate into the myocardium, can respond to DAMPs generated by I/R. Thus, the heart acts as an immune organ in initiating cardiac immunity and inflammation, not just as a target organ affected by immunity.

The capacity of the heart to tolerate inflammatory processes is limited by the anatomy, function and limited regenerative capacity of the myocardium (Taqueti et al., 2006). As reviewed before (Mann, 2011), short-term innate immune activation confers adaptive and protective effects in the heart, whereas a long-lasting activation likely leads to maladaptive and detrimental effects. It has been well-documented that a brief episode of ischemia confers protection against subsequent sustained ischemia, a phenomenon termed as preconditioning, which was first described in the heart (Murry et al., 1986) and later extended to other organs. In contrast, prolonged ischemia leads to significant loss of cardiomyocytes and irreversible damage to the structure and function of the heart. In addition, deleterious remodeling occurs in both the infarcted and non-infarcted myocardium, which can impair cardiac function and increase the incidence of arrhythmias.

PRRs in cardiomyocytes

The discovery of PRRs has greatly advanced our understanding of how the body recognizes pathogens and starts immune responses. PRRs are a large family, including transmembrane receptors such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), as well as cytoplasmic receptors such as the retinoic acid-inducible gene