Innate Immunity in Heart Failure

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With 2 Figures

Abstract

The immune system of higher vertebrates consists of two components: the innate and adaptive immunity. While the adaptive immune system relies on somatically generated and clonally selected antigen receptors, the innate immune system detects the presence of pathogens by their evolutionarily highly conserved, relatively invariant structural motifs. Various components of the innate immune system are activated in cardiac diseases without direct involvement of infectious pathogens. For example, a number of inflammatory cytokines, including TNF (tumor necrosis factor), IL (interleukin)-1β, IL-6 and IL-8, as well as iNOS (inducible nitric oxide synthase), all components of innate immunity, are increased after cardiac injury. Moreover, they are all functionally implicated in ischemia/reperfusion injury, and in the abnormal myocardial remodeling characteristic of advanced congestive heart failure. Additionally, downstream targets of these proteins, the transcription factors nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), are activated in cardiac injury. Thus, an understanding of the regulation and activation of the innate immune system in diseases not obviously related to an immune response to specific pathogens could provide new therapeutic targets for cardiovascular diseases.

Zusammenfassung


1. Introduction

Recent data implicate a number of inflammatory stimuli, including cytokines like tumor necrosis factor (TNF) and interleukin (IL)-1β in myocardial depression and the abnormal myocardial remodeling characteristic of congestive heart failure. Since there is no evidence for an infectious pathogen in most pathophysiologic states associated with heart failure except infectious myocarditis, the proximal events triggering cytokine expression are not well understood. However, all of these proinflammatory proteins are part of the “innate immune” response.
2. Innate Immunity

Immunity to infections is mediated by two distinct pathways: the innate and the acquired immune response. Whereas acquired immunity recognizes specific antigens by distinct antigen receptors based on clonal selection of B and T cells, innate immunity recognizes specific invariant patterns shared by groups of microorganisms, but not by the host. For example all different lipopolysaccharides (LPS), components of the outer bacterial wall, can be recognized by a single innate immune receptor, toll like receptor 4 (TLR). By consecutive production of costimulatory molecules (e.g. B7.1, B7.2) as well as effector cytokines, the innate immune system can then activate the adaptive immune response (Frantz et al. 2005).

We have hypothesized that the innate immune system in cardiac diseases is activated analogous to the immune system (see Fig. 1). Upon a cardiac injury, ligands are generated, like collagen, uric acid, heat shock proteins, etc. Those ligands can bind to the specific innate immune receptors and then activate innate immune specific transcription factors, like NF-κB or AP-1. This leads then to the production of cytokines, matrix-metalloproteinases, etc., all factors implicated in cardiac remodeling.

Toll like receptors (TLRs) have recently been recognized as the most important innate immune receptors (Medzhitov and Janeway 1997). TLR 2 and 4 are critical components of the bacterial lipoprotein and lipopolysaccharide signaling pathway, respectively. TLRs induce

Fig. 1  Parallel activation of the innate immune system in the heart and in the immune system. Reprinted from Current Pharmaceutical Design (Frantz et al. 2005); Copyright 2005, with permission from Bentham Science Publishers Ltd.
NF-κB, IL-1β, IL-6, IL-8, and the costimulatory molecule B7.1 (Medzhitov et al. 1997). Indeed, these important immune receptors are expressed in the heart (Frantz et al. 1999). TLR4 KO mice have reduced ischemia reperfusion injury (Oyama et al. 2002), indicating that TLRs could play an important role in the response to cardiac injury.

The signal transduction cascade of TLRs is similar to that employed by IL-1 and IL-18 with a final activation of NF-κB. Thus, should IL and TLR signaling be important in myocardial ischemia, also the transcription factor NF-κB should be activated. Indeed, we could demonstrate an activation of NF-κB in rats with chronic myocardial infarction (Frantz et al. 2003, Tillmanns et al. 2006) (see Fig. 2.). This has also functional importance, since prevention of NF-κB activation in mice with targeted deletion of the NF-κB subunit p50, was

Fig. 2  Myocardial infarction induces NF-κB dependent luminescence in the heart of transgenic mice when compared to sham-operated mice. Maximal NF-κB activity was observed 3 days after myocardial infarction by serial molecular imaging. Reprinted from Biochemical and Biophysical Research Communications (Tillmanns et al. 2006); Copyright 2006, with permission from Elsevier.
associated with significantly improved left ventricular remodeling after myocardial infarction (Frantz et al. 2006).

In conclusion, cardiac injury activates pro-inflammatory proteins that are part of the innate immune response. The components of the innate immune system are expressed in the heart and have functional importance. Thus, a better understanding of the regulation and activation of the innate immune system in the heart could provide new therapeutic targets for cardiovascular diseases.

References