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Mechanisms of cardioprotection via modulation of the immune response

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Both morbidity and mortality as a result of cardiovascular disease remain significant worldwide and account for approximately 31% of annual deaths in the US. Current research is focused on novel therapeutic strategies to protect the heart during and after ischemic events and from subsequent adverse myocardial remodeling. After cardiac insult, the immune system is activated and plays an essential role in the beginning, development, and resolution of the healing cascade. Uncontrolled inflammatory responses can cause chronic disease and exacerbate progression to heart failure and therefore, constitute a major area of focus of cardiac therapies. In the present overview, we share novel insights and promising therapeutic cardioprotective strategies that target the immune response.

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Introduction

Cardiovascular disease (CVD) still accounts for 31% of all annual deaths in the US, of which ~20% are patients <65 years of age [1]. These statistics comprise patients with hypertension and chronic heart failure (HF), including myocardial infarction (MI), angina pectoris, and stroke. Cardiac injury induces cell death and/or tissue damage that stimulates an inflammatory response to remove cell/tissue debris [2]. This inflammatory response includes activation of toll-like receptor (TLR)-mediated pathways, complement system cascade, and generation of reactive oxygen species [3]. These, in turn, induce nuclear factor kappa B (NFκB) activation and upregulate the synthesis of chemokines and cytokines, which respectively stimulate recruitment of inflammatory leukocytes into the myocardium and promote adhesive interactions between leukocytes and endothelial cells, resulting in the infiltration of inflammatory cells into the site of injury [2–4].

Numerous reports show that the immune response elicited by cardiac ischemia and injury has an important role in CVD and progression to HF. For the last 20 years, research and ensuing clinical trials addressing modulation of the inflammatory response have focused mainly on immune-cells, such as leukocytes [2,3], decrease/inhibition of oxidative stress [5], and the use of anti-inflammatories [6]. Nevertheless, patient mortality and morbidity remain significant. For example, the use of immunosuppressive drugs, such as corticosteroids, has no effect on MI risk ratio or reduction of patient mortality [7]. Therefore, treatment with broad spectrum immunosuppressive drugs is not an adequate therapy for all CVD patients and innovative (personalized) immune-targeted therapeutics have not yet emerged in the clinical setting. In this short review, we will outline cardioprotective mechanisms that target the immune system (innate and adaptive) and are currently promising novel therapeutic strategies.

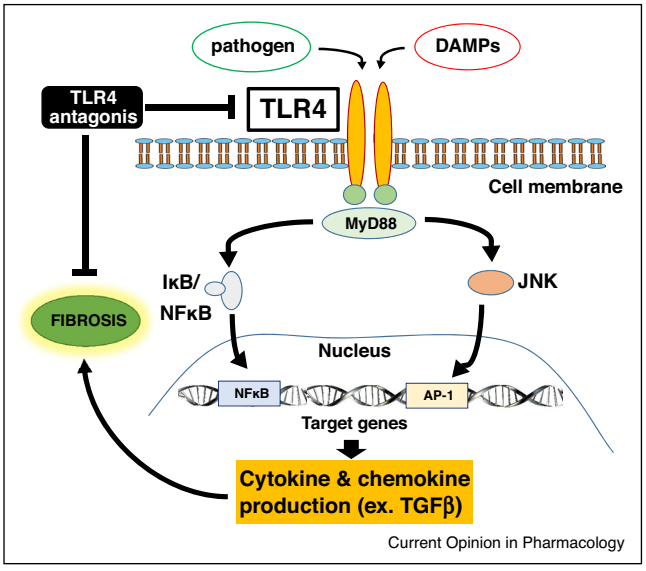
Innate immune response

Innate immunity is a pre-programmed (non-specific) first-line of defense, classically mediated by myeloid-derived cells that upon injury produce cytokines and activate the complement system. The innate immune-system plays a crucial role in the initiation and progression of the subsequent healing cascade.

Toll-like receptors

TLRs are transmembrane proteins, members of the family of pattern recognition receptors, involved in innate and adaptive immune responses in the identification of pathogens and in sensing endogenous danger-associated molecular patterns released from necrotic or dying cells [8]. The activation of TLRs triggers a downstream signaling cascade comprising activation of transcription factors, such as activator protein 1 and NFκB, followed by secretion of pro-inflammatory chemokines and cytokines, recruitment of phagocytes, and activation of the complement system (Figure 1) [9]. TLRs are expressed in innate immune cells and have also been identified in several cardiovascular cells, including cardiomyocytes and endothelial cells [10]. This suggests that TLR signaling could be important in the development of myocardial diseases and therefore, TLRs present a valuable therapeutic target.

Figure 1



Myeloid differentiation primary-response protein 88 (MyD88)-dependent mechanism of Toll-like receptor (TLR)-4 activation of pro-inflammatory responses. TLR-4 antagonists can block the inflammatory cascade and provide cardioprotective effects. AP-1: activator protein-1; DAMPs: danger-associated molecular patterns: IkB, inhibitor of kB; JNK: c-Jun-N-terminal kinase; NFkB: nuclear factor kappa B.

Of the TLR family, TLR4 is the most studied, and it is expressed in cardiac cells ~10-fold higher than most other TLRs [8]. TLR4 expression is significantly higher in patients with atrial fibrillation and is an independent predictor of atrial fibrillation recurrence [11]. Metformin, a first-line medication for type 2 diabetes, displays potential cardioprotective roles during lipopolysaccharide-induced inflammatory responses by attenuating TLR4 activity [12••]. Ischemia-reperfusion (I/R) injury in hearts could also be treated with the application of TLR4 antagonists, since rats treated with such drugs demonstrated a decrease in infarct size [13]. In addition, the administration of the tricyclic anti-depressant amitriptyline curiously improved LV pressure recovery in I/R-induced rats [14], and moderate levels of tricyclics proved to alter TLR4 levels [15]. TLR4 signaling may also play an important role in angiotensin (Ang) II-induced hypertension. Crosstalk between AngII and TLR4 within the brain increased NFκB activity and sympathetic impulses contributing to hypertension progression and cardiac dysfunction in rat models [16]. In summary, TLRs are novel candidate molecules that connect myocardial injury and circulating inflammatory mediators, and therefore uncover potential therapeutic approaches to model the immune system.

Macrophages

During pathological cardiac remodeling and healing, both resident and circulating macrophages play crucial cardioprotective roles. In the inflammatory phase that follows cardiac injury, Ly-6Chi monocytes are recruited from the bone marrow and spleen to help resident macrophages remove dead/damaged tissue and cells, as well as, produce the necessary enzymes to facilitate extracellular matrix remodeling and vascularization [17]. Several subsets of cardiac macrophages have been defined; however, for the purpose of this review, we will only refer to the M1 and M2 phenotypes. Classically activated macrophages (M1, Ly-6C^{hi}CD206^{-}CD204^{-}) associate with pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS)-derived nitric oxide, tumor necrosis factor (TNF)-α, and interleukin (IL)-12 [18]. Secreted IL-12 further activates CD4 T-cells promoting the pro-inflammatory phenotype [17]. M1 macrophages display potent phagocytotic properties necessary to clear necrotic tissue [19]. Upon ingestion of apoptotic cells, macrophages release anti-inflammatory cytokines promoting a shift in the macrophage population towards a reparative phenotype that may restrain inflammatory injury and attenuate adverse cardiac remodeling [20]. Alternatively activated macrophages (reparative/M2, Ly6C^{lo}CD206^{+}) express IL-10, chitinase 3-like 3, and resistin like-beta and upregulate arginase-1 and CD206 [18]. M2 macrophages inhibit CD4 T-cell and granulocyte activity and display anti-inflammatory properties [17]. Interestingly, targeted depletion of either M1 or M2 population with clodronate liposomes leads to impaired cardiac healing evidenced by increased left ventricular dilation, reduced vascularization, and increased mortality post myocardial injury [21]. Several mechanisms have been reported that exert cardioprotective effects by promoting M2 macrophage polarization. In an I/R MI mouse model, a selective A2B adenosine receptor (A2BR) agonist reduced tissue injury by increasing phosphorylated Akt (p-Akt) levels [22]. The majority of p-Akt was colocalized to CD206^{+} cells, suggesting that A2BR activation promotes M2 polarization, and therefore, an anti-inflammatory response. Db/db diabetic mice that received fibroblast growth factor-9 treatment for two weeks post-MI exhibit reduced monocyte infiltration, increased M2 macrophage differentiation and anti-inflammatory cytokines (IL-10 and IL-1RA), and improved cardiac function [23••]. Similarly, Miao *et al.* showed that hydrogen sulfide supplementation, in a mouse MI model, ameliorated pathological remodeling and cardiac dysfunction by enhancing M2-polarized macrophage levels at the early stage of MI [24]. When using cardiosphere-derived cells (CDCs) de Couto *et al.* demonstrated that infiltrating macrophages can be primed to acquire a cardioprotective phenotype in ischemic heart and mitigate ischemic injury through activation of an anti-apoptotic program in cardiomyocytes [25••]. Unexpectedly, while the expression of M1 markers was decreased they did not observe an increase in M2 markers. These results highlight the heterogeneity of macrophage populations and raise important questions