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The Cardiomyocyte as a Source of Cytokines in Cardiac Injury

Toshinori Aoyagi and Takashi Matsui*

Center for Cardiovascular Research, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96813

Abstract

Fibrosis induced by prolonged inflammation is a major pathophysiological feature of adverse left ventricular remodeling after myocardial infarction and pathological cardiac hypertrophy. Recent reports strongly suggest that the interaction between leukocytes, non-myocytes (mainly cardiac fibroblasts) and cardiomyocytes, possibly mediated by cytokine signaling, plays an important role in controlling the inflammatory reaction after cardiac injury. Therefore, controlling cytokine secretion from resident cardiomyocytes is one plausible strategy for preventing tissue damage.

Keywords: Cytokine; mTOR; Cardiac remodeling; Heart failure; Inflammation

Introduction

The initial inflammatory reaction is a protective response to triggers such as infection or tissue injury [1]. However, inflammation, particularly prolonged inflammation, can also damage normal tissue. For instance, reactive oxygen species (ROS) and proteases leaked from leukocytes kill normal cells [2]. Prolonged inflammatory reaction is considered part of the pathogenesis of a variety of cardiac diseases, including heart failure and adverse left ventricular (LV) remodeling [3]. This is supported by the finding that levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β, increase during heart failure [4]. In fact, elevated circulating levels of TNF-α and IL-6 have been reported as independent predictors of mortality in patients with heart failure [5,6]. However, cytokines are also known to exhibit cardioprotective effects in certain settings [7]. These findings suggest that regulation of cytokines is a potential target for development of therapies for heart failure.

Fibrosis is the final step in the inflammatory process and a major pathophysiological feature of adverse LV remodeling after myocardial infarction or in pathological cardiac hypertrophy [8]. Proinflammatory cytokines released as part of the inflammatory response accelerate the collagen deposition leading to fibrosis [1]. This has been shown in models of pressure overload-induced cardiac hypertrophy and ischemia-reperfusion injury [9,10]. Therefore, the extent of the inflammatory response following damage to cardiac tissue is a key prognostic factor for heart disease.

Cardiac fibroblasts as a source of proinflammatory cytokines

During inflammation, the injured tissue site is rapidly infiltrated by leukocytes, consisting initially of neutrophils, followed by accumulation of monocytes, and then macrophages [2]. Communication between these leukocytes and the cells surrounding the site of injury or infection is a major determinant of outcome following injury or infection [11]. While macrophages are the major source of proinflammatory cytokines, many other cardiac cells can also generate and release cytokines.

Only 25% of cells in the normal heart are cardiomyocytes; the majority of the remaining cells are cardiac fibroblasts [12]. Under pathological conditions, including myocardial infarction, cardiac fibroblasts are activated and undergo phenotypic modulation to become myofibroblasts that express the contractile protein α-smooth muscle actin (α-SMA) [13,14]. These cells are key sources of components of proinflammatory cytokines and the extracellular matrix (ECM) [12,14], and are highly responsive to cytokines, including TNF-α, IL-6 and IL-1β [14]. In particular, myofibroblasts play an important role in scar formation and fibrosis in LV remodeling following myocardial infarction [14].

Cardiomyocytes as a source of proinflammatory cytokines

Monocytes/macrophages, fibroblasts, and cardiomyocytes all elevate TNF-α expression via different transcriptional regulatory systems including the activator protein-1 (AP-1) and NF-κB [15]. Isolated cardiomyocytes have been shown to produce TNF-α under certain conditions such as treatment with lipopolysaccharide (LPS) [16-18]. IL-6 is also generated in most cells in the heart, including cardiomyocytes [16,19] and fibroblasts [20]. In contrasts, most IL-1β immunoreactivity is localized to endothelial cells and interstitial macrophages rather than the myocardium in an animal model of cardiac hypertrophy [21]. Treatment with either LPS or hypoxia-reoxygenation stimulated IL-1β production in isolated cardiac fibroblasts while isolated cardiomyocytes did not respond to either treatment [10]. Although cardioprotective effects of IL-6 have been reported as well [7], clinical studies suggest that prolonged and/or excessive synthesis of IL-6 is detrimental to the heart [6,22]. In fact, IL-6 infusion induces heart failure in a rodent model [23,24]. Previous reports demonstrated that IL-6 is produced in cardiomycoytes in response to IL-1β [19] and promotes inflammation in the heart by recruiting leukocytes [25]. Thus, inhibiting IL-6 generation in cardiomyocytes might be sufficient to suppress the subsequent inflammatory response.

Activated renin-angiotensin system (RAS) and transforming growth factor-β (TGF-β) are critical elements of the pathogenesis of LV remodeling in heart failure [26]. Angiotensin II, a component of

***Corresponding author:** Takashi Matsui, MD, PhD, Center for Cardiovascular Research, John A. Burns School of Medicine, University of Hawaii, 651 Ilalo St., BSB#311D, Honolulu, HI 96813, USA, Tel: 808-692-1554; Fax: 808-692-1973; E-mail: tmatsui@hawaii.edu

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RAS, is a major trigger of myocardial fibrosis. It acts by stimulating proinflammatory cytokine secretion from fibroblasts [27]. *In vitro*, angiotensin II induced much greater secretion of IL-6 and TNF-α secretion in co-cultures of cardiomyocytes and fibroblasts than in cultures of fibroblasts alone, suggesting that paracrine action from cardiomyocytes plays an important role in the production of proinflammatory cytokines in fibroblasts [27].

These findings suggest that the interaction between leukocytes, cardiac fibroblasts and resident cardiomyocytes plays an important role in control of the inflammatory reaction after cardiac injury. While non-myocytes, including cardiac fibroblasts and myofibroblasts, play a key role in inflammation and collagen deposition, controlling cytokine secretion from resident cardiomyocytes is one possible strategy for preventing tissue damage caused by prolonged inflammation in LV remodeling after myocardial infarction and pathological hypertrophy. Cardiac fibroblasts regulate global myocardial function at a number of levels in both adaptive and maladaptive response to cardiac injury. For example, they regulate cytokine synthesis, ECM synthesis, ECM degradation [14]. Most recently, it was shown that cardiac fibroblasts can be reprogrammed to cardiomyocyte-like cells [28]. Since cytokines appear to be so central to the regulation of the inflammatory reaction in cardiac fibroblasts, controlling cytokine regulation in these cells might affect other cardioprotective events. On the other hand, cardiomyocyte contribution to the inflammatory reaction is more limited. Therefore, targeting cytokine production in cardiomyocytes might be a safer and more straightforward strategy for regulating the inflammatory reaction (Figure 1).

The inflammatory response is regulated by the mammalian target of rapamycin (mTOR)

Rapamycin, a natural product of the bacterium *Streptomyces hygroscopicus*, was approved for clinical use an immunosuppressant for organ transplant patients. However, clinical studies reported that rapamycin and other mTOR inhibitors can cause distinct inflammatory diseases, including pneumonia [29]. *In vitro* study revealed that mTOR inhibition by rapamycin promotes production of proinflammatory cytokines by immune cells by stimulating the transcription factor NF-κB [30]. Rapamycin also increases production of bioactive IL-1β by increasing processing by caspase-1 in bone marrow-derived macrophages [31]. Recently, we reported that mTOR activation in cardiomyocytes suppresses the inflammatory reaction in the early stage of pressure-overload induced cardiac pathological hypertrophy, as evidenced by decreased production of IL-6 and IL-1β and less accumulation of macrophages, resulting in preserved cardiac function [17]. mTOR activation reduced the production of cytokines, especially IL-6, in LPS-stimulated cardiomyocytes *in vitro* [17]. In an animal model, anti-IL-6 treatment prevented adverse LV remodeling after myocardial infarction [32]. These results suggest that suppressing release of proinflammatory cytokines from cardiomyocytes, especially IL-6, may be sufficient to inhibit LV remodeling, thereby preventing heart failure.

Conclusion

In large clinical trials, anti-TNF-α agent was unable to prevent heart failure [33]. Since cytokines can also exhibit cardioprotective effects in some settings, the target cell type (leukocytes, cardiac fibroblasts or cardiomyocytes), the timing (acute or chronic phase following myocardial infarction) and the extent of inhibition must all be considered in designing a therapy using anti-inflammatory agents [14,15]. Although the main source of cytokines in the heart is the cardiac fibroblast [14], cardiomyocytes contribute to the inflammatory reaction, particularly via secretion of IL-6 and TNF-α [17,27]. As discussed above, controlling the chain reaction of inflammation that occurs in resident cardiac cells, including cardiomyocytes, by inhibiting proinflammatory cytokine secretion can prevent cardiac damage during LV remodeling in an animal model. Advanced cell therapy or molecular biology techniques that target proinflammatory cytokine production specifically in cardiomyocytes may be an effective way to control regional inflammation following cardiomyocyte injury.

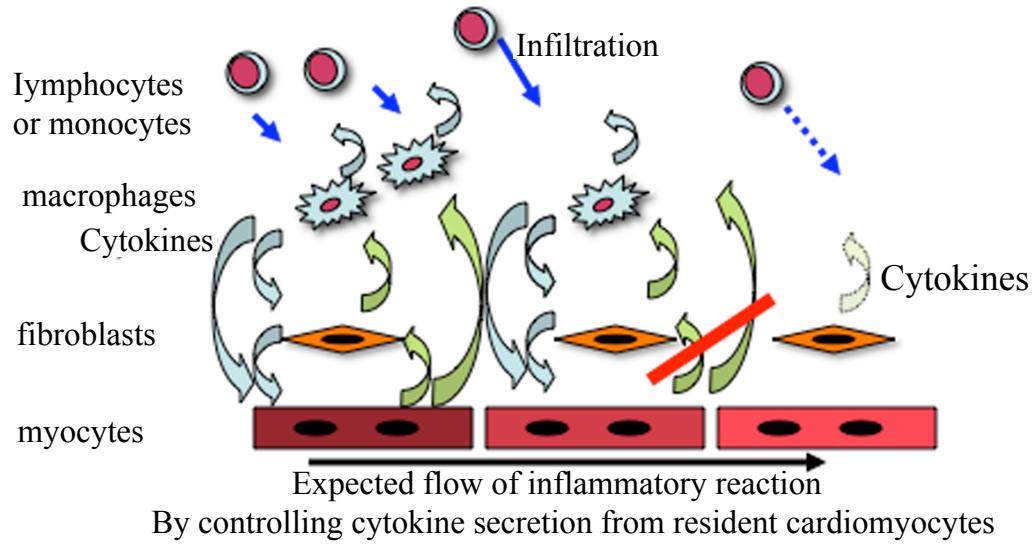

Figure 1: A speculated model of serial inflammatory reaction in the heart following injury.

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