

Tumor Necrosis Factor-Alpha and Inflammation-Mediated Cardiac Injury

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Abstract

Experimental evidence is accumulating implicating a major role for inflammatory activation in chronic heart failure. Levels of pro-inflammatory protein mediators, such as tumor necrosis factor-alpha (TNF- α), a pro inflammatory cytokine, have been shown to be elevated in heart failure patients and appear to be directly related to pathological changes in the myocardium. Unfortunately, outcomes from clinical trials using anti-cytokine therapies to chronic heart failure patients have been largely disappointing. TNF- α is a pleiotropic cytokine, impacting tissues in a complex manner that regulates many physiological and pathological processes that can trigger differentiation, inflammation, and cell death. TNF- α is important in initiating and regulating the cytokine cascade during an inflammatory response. Most of the studies focused on the TNF- α as an immune mediator but its function in cardiac cells is not well defined. This review focuses on the role of TNF- α in acute and/or chronic cardiac conditions. We will discuss the problem with the current anti-cytokine therapies and potential problems underlying their lack of success so far.

Keywords: Tumor necrosis factor-alpha; Anti-cytokine therapy; Inflammation; Heart failure

Introduction

Inflammation and heart disease

Evidence is accumulating that there are number of age-related changes that make older people at higher risk for heart problems [1]. Cardiovascular disease has become the major cause of death, disability, and accounts for the large portion of healthcare costs in the US [2-4]. Chronic heart failure represents a major public health burden and its development and progression is associated with elevations in circulating markers of inflammation [5]. Although, it is not clear what causes age-associated chronic inflammation, both experimental and clinical evidence accumulated within the past decade, linking the chronic inflammation to the development and progression of chronic heart failure. Indeed, inflammation has been identified as a cardiovascular risk factor; therefore, treatments to lessen the inflammation and inflammation-associated cardiac damage could have significant health and fiscal impact [6-9]. Herein we review the participation of TNF- α , the "master regulator" of the immune response, as key components of the immunemediated inflammation and injury in acute and chronic heart conditions and will also explore the delicate balance between the protective roles of TNF- α and its damaging functions during the development and progression of heart disease.

Inflammatory markers

Cytokines are multifunctional proteins that play an important role in cell-to-cell communication. TNF- α is a pleiotropic cytokine that regulate a number of physiological and pathological processes, such as inflammation, development, differentiation, and cell death [10-14].

Increased expression of proinflammatory cytokines such as TNF- α , interleukin (IL)-1, IL-6, IL-8, IL-12 and interferon (INF)- γ have been reported in chronic inflammatory diseases like rheumatoid arthritis (RA), inflammatory bowel disease, psoriasis, and so forth [15]. The key role of TNF- α in the pathogenesis of the RA and other inflammatory disease was tested in patients using agents that block its biological activity such as Infliximab and Etanercept, with a favorable outcome [16,17]. Among the reported side effects associated with TNF- α inhibition in treatment of RA were infections, lymphoma and congestive heart failure in which the opportunistic infections e.g. Tuberculosis has the highest number of cases (FDA report on adverse events of TNF inhibition by Arthritis advisory committee) [18]. The success of anti-TNF- α therapy was attributed to the deactivation of the soluble TNF- α , which resulted in diminished recruitment of inflammatory cells in the peripheral blood and joints of patients with RA. Even though, the development of the anti-TNF therapies was a milestone in the therapy of RA, based on the results of the observed side effects and mortality in patients on anti-TNF therapy it was recommended that patients with congestive heart failure might not be treated with either infliximab or with etanercept.

TNF- α and cardiac injury

The role of TNF- α as a mediator of immune response has long been studied but its function in most cell type i.e. cardiac myocyte is still unclear, even though, TNF- α -activated signal transduction pathways have been postulated to contribute to adverse ventricular remodeling after myocardial infarction and to be a major contributor during the development and progression of heart failure [19,20]. TNF- α was identified in 1975 as soluble factor that causes necrosis of tumors [21]. TNF- α has also been referred to as cachectin or differentiation inducing factor (DIF), exists in two bioactive forms: transmembrane TNF- α (tmTNF- α) and soluble TNF- α (sTNF- α) [22-25].

TNF- α is produced and secreted by many cell types including: immune cells, endothelial cells, epithelial cells, smooth muscle cells, and cardiac myocytes. TNF- α can bind to two receptors; TNF receptor 1 (TNF-R1) (55-kDa) and TNF-R2 (75-kDa) [26-28]. Two distinct TNF- α receptors are also widely expressed on multiple cell surface: TNF-R1 assisting most of the activity of TNF- α , is a ubiquitous membrane receptor that is found in most cell types, however, TNF-R2 is primarily expressed by T cells and endothelial cells [29-31]. TNF-R1 can be activated by either sTNF- α or tmTNF- α , however, TNF-R2 is preferentially activated by tmTNF- α . Even though, there are some overlap and cross talk between TNF-R1 and TNF-R2, they are structurally different; therefore, TNF- α signaling through TNF-R1 and TNF-R2 can elicit distinct cellular responses depending on the cell. Binding of TNF- α to TNF-R1 can activate the transcription factor NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), regulate cytokine production, and mediate inflammation and/or apoptosis [32-35].

TNF- α was identified as the mediator of the cardiac inflammatory responses in patients with acute myocardial infarction [36,37]. In fact, myocardial TNF- α is an important contributor to myocardial contractile dysfunction and cardiomyocyte death post myocardial infarction and in chronic heart failure [20,38]. This was attributed in part to the fact that the failing heart produces robust quantities of TNF- α . Indeed, low levels of TNF- α were observed in the heart of healthy individual, however, TNF- α expression were significantly increased in patients with end-stage dilated cardiomyopathy (non-ischemic) and ischemic heart disease [39]. Moreover, Kapadia et al. demonstrated that cardiac myocytes and heart residence macrophages produce high quantity of TNF- α in response to endotoxin [40]. Therefore, accumulating evidence suggests that local myocardial TNF- α could be an important regulator of cardiac inflammation and injury. However, it remains poorly defined about whether TNF- α causes beneficial or detrimental cardiovascular effects. It has been demonstrated that chronic infusion of TNF- α in rats produces left ventricular dilatation and contractile dysfunction. Byrant et al. also shown that excessive production of TNF- α by cardiac myocytes causes severe cardiac disease supporting a detrimental effect of TNF- α on hearts of these transgenic mice, characterized by systolic dysfunction, cardiac inflammation, ventricular dilatation, congested tissue, and increased mortality [41]. Supporting data has been provided by another transgenic line of mice from Feldman's laboratory, demonstrating that overproduction of TNF- α by cardiac myocytes was enough to cause dilated cardiomyopathy [42]. In rat and dog hearts, in vivo administration of exogenous TNF- α , dose dependently reduced sarcoplasmic reticulum Ca²⁺ uptake and myofilament Ca²⁺ sensitivity leading to cardiodepressant effects [43]. As a result of extrapolation of findings from experimental animals, it was assumed that TNF- α is deleterious and by virtue of its deleterious effects to myocardial function in humans it can contribute to pathogenesis of heart disease. However, since in patients with congestive heart failure the increase in circulating TNF- α was associated with a decrease in myocardial TNF- α receptors and an increase in soluble TNF alpha receptors. It was also suggested that increased levels of circulating sTNF-Rs in patients with heart disease might have protective mechanisms; binding to circulating TNF- α will neutralize the biological actions of TNF- α and make the cytokine less active during cardiac injury [39,44]. We also see many discrepancies in the results of many clinical studies. A significant correlation between serum cytokine levels, such as TNF- α and IL-6 with the size and the severity of the myocardial infarction was reported by a number of studies [45,46]. However, other studies have not

supported the positive relationship between cytokine levels and the severity of myocardial infarction [47,48]. Whether the TNF- α upregulation is a protective mechanism in response to tissue injury or a contributor to the tissue injury via mediating inflammation and apoptosis still is open discussion. Even though, growing evidence suggests that TNF- α exerts its adverse effects by binding to its cell surface receptors; TNF-R1 and TNF-R2, little is known regarding the level of expression and the role of TNF- α receptors in the heart in particular during the development and progression of heart disease. It has been shown that there is a correlation between increased in circulating sTNF levels and the decreased expression of myocardial TNF- α receptors that was observed in patients with end stage heart failure, it was suggested that the elevated sTNF is responsible for the decrease in TNF- α receptors expression [49]. In murine model of heart failure, ablation of the TNF-R2 exacerbate heart failure whereas ablation of TNF-R1 improves survival suggesting that signaling through TNF-R1 appears deleterious to myocardial function, in contrast, to signaling through TNF-R2 in which appears to be cardioprotective [50,51]. More supporting evidence has been published suggesting the functional significance of TNF-R1 in providing signaling pathway for the deleterious effects of TNF- α in the adult mammalian heart. Al-Lamki et al. reported independent regulation and differential functions of TNFRs in myocardium; they assessed expression of TNF- α , TNF- α receptors and downstream kinases in cardiac allografts. Using TNF-R1-knockout and TNF-R2-knockout mice, they demonstrated that TNF-R1 activates apoptosis signal-regulating kinase 1 (ASK1) and mediates cardiomyocyte cell death whereas TNF-R2 activates Etk (also called Bmx), and -mediates repair via increasing markers of cell cycle entry [52].

Anti-TNF therapy for HF

Since TNF- α is elevated in the serum of patients with heart failure [5], and the magnitude of the increase is directly correlated with the severity of disease, the presence of this potent inflammatory factor at sites of injury was implicated as a mediator of cardiac disease pathogenesis. Indeed, overproduction of TNF- α by cardiac myocytes is sufficient to cause pathological changes in the myocardium consistent with heart failure, including ventricular remodeling, interstitial fibrosis, and cardiomyocytes apoptosis [6,41]. That makes the TNF- α , an attractive therapeutic target for treatment of acute and chronic cardiac conditions. Thus it was postulated that inhibition of TNF- α may favorably modify the progression of heart failure, however, randomized trials of anti-TNF- α therapy, infliximab in the ATTACH (Anti-TNF- α Therapy Against Congestive Heart failure) trial, failed to show any improvements in patients with moderate-to-severe heart failure [53]. Result of this study was followed up by unfavorable outcomes of other anti-TNF- α clinical trials such as the RENEWAL (RENAISSANCE and RECOVER) [54]. The results of RENEWAL completely rule out any benefit of etanercept in reducing the number of death or hospitalization in patients with chronic heart failure. One interpretation of the lack of efficacy of this approach in these clinical trials with targeted anti-cytokine therapy in heart failure is that heart failure is a highly complex syndrome so the assumption that targeting a single component of the inflammatory cascade without knowing the cellular origin and the mechanism underlying their chronic expression is not a sufficient approach and the past clinical trials are the examples of it. Unlike RAs, for which TNF- α inhibitors show favorable outcome, heart failure is a complex disease that incorporates many noninflammatory conditions and the quantitative contributions of inflammatory and non-inflammatory mediators toward the

pathophysiology of heart failure is still not clear and remains to be tested. Moreover, since TNF- α is a pleiotropic protein with important regulatory functions on cardiovascular system, anti-TNF- α therapy can also inhibits the immunomodulatory effects of TNF- α , which in a long run can have adverse effects, thus, selective inhibition of TNF-R1 signaling is postulated to be more effective in relieving the deleterious effects of TNF- α in the adult mammalian heart.

Collectively, these data suggest a link between overproduction of myocardial TNF- α and pathological changes observed in the myocardium during acute and chronic heart disease, including ventricular remodeling, interstitial fibrosis, and cardiomyocytes apoptosis. It is suggested that TNF- α are elevated in chronic heart failure patient in accordance with their functional class [49]. Such an increase was found to have a linear correlation with the prognosis of chronic heart failure patients [49]. Notably, a concordant reduction in TNF- α receptors on the cardiac myocytes was noticed in heart failure patients too, which was attributed to the high circulating levels of TNF- α . Attempts to integrate TNF- α antagonist as therapeutic interventions have been suggested, with possible effectiveness for symptomatic heart failure patients [49]. Yet, variation in expression of its receptors, TNF-R1 and TNF-R2, and its regulation during cardiac disease status is not clear and needs to be studied for further understanding of their potential contributions into pathogenesis of heart diseases.

To conclude, in this review we have highlighted the contribution of the chronic inflammation to the development and progression of chronic heart failure. What is apparent from literature review is that the full understanding of the related cytokine signaling pathways in the myocardium during acute and chronic heart disease will be essential for further understanding of their potential contribution and their complex biological effects on cardiac damage. Investigation of agents that interfere with inflammatory cytokine production is needed in order to enhance our understanding on their potential contributions into pathogenesis of diseases that are associated with chronic inflammation.

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