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Review Article

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Role of Cytokines in Heart Failure

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Abstract

Inflammation regulates myocardial function and cytokines are considered as its key regulator. There is abundant literature suggesting that cytokines have been known to directly regulate cardiac function. However, the evidence of such regulation failed to go through the transition from bench to bedside. Large clinical trials aimed at investigating the impact of anti-cytokine therapy on heart failure failed to bring a significant change in the end points. Here we will summarize the available proof from preclinical and clinical studies.

Keywords: Heart failure; Inflammation; Cytokines

Introduction

Heart Failure (HF) is the leading cause of death and disability [1]. The knowledge about etiopathology of HF has evolved and expanded significantly from mechanical dysfunction of heart to a multifactorial pathology governed by variety of triggers and mediators [2-5]. Increased neurohumoral activation in patients with cardiac failure and its negative regulation of cardiac function has been largely the center of clinical management of HF; however, the high risk for mortality among these patients suggests that neurohormonal activation is not the only cause of HF progression. Another important regulator of cardiac function is inflammation [6,7]. The concept of immune regulation of cardiac pathology was first reported by Kawai and Takatsu [8]. Many subsequent studies reported an altered immune function in patients with congestive HF [9-11]. The study by Ognibene et al. [12] reported a detailed reversible regulation of cardiovascular function in patients receiving Interleukin (IL)-2 as immunotherapy. Subsequently, the direct regulation of cardiomyocytes contractility by cytokines was reported [13]. Numerous reports showed a strong positive correlation between cytokine and different cardiac pathology both in clinical settings as well as in research animals [14]. In spite of having compelling pre-clinical evidences supporting cytokine theory, it failed to achieve the expected results at the bedside. The clinical relation between cardiac failure and cytokine was first identified by Levine et al. [15] as an increase in serum level of Tumor Necrosis Factor (TNF) in patients with HF Clinical trials with modalities targeting inflammation fail to show an improvement in the cardiovascular health [16]. In the review, we will discuss the current status of cytokine-targeted modulation of cardiac pathology.

Activation of Immune Response

There are two major components of immune system, innate and adaptive. The innate immunity is the first line of defense and work through Pattern Recognition Receptors (PRRs) and Toll-Like Receptors (TLRs). Monocytes and macrophages are important innate immunity cells participating in inflammatory regulation of cardiovascular pathology. Activation of innate immunity cells leads to cytokine and chemokine release. Unlike innate immunity, the adaptive immunity provides a highly specific response mediated by B and T cells. In response to injury or environmental change both of these systems are activated. The initiation of innate response is mediated by PRRs present on endosomes. These PRRs are activated by Pathogen Associated Molecular Patterns (PAMPs) or Damage-associated Molecular Patterns (DAMPs) [17]. This activation of PRRs leads to two different types of signaling, one activates the production of cytokines and the other promotes the assembly of inflammasomes, which further triggers inflammatory response. Contrarily, adaptive immunity is primarily responsible for defending foreign pathogens via activation of T cells. Antigen presenting cells (APCs) process the foreign proteins to small peptides, which are up taken by major histocompatibility complexes (MHCs) leading to activation of cluster of differentiation (CD)8+ and CD4+ T cells and subsequent cytokine production and release.

Inflammation and Myocardial Infarction

Inflammation is characterized by complex molecular and cellular events that assure tissue repair and regain of physiological function. Inflammation plays a crucial role in setting of heart failure [18]. In most cases, inflammation deteriorates the cardiac function, however, abrogation of inflammatory pathways has not offered positive outcome in clinical settings. The cytokine hypothesis of heart failure proposes that endogenous cytokines promote HF via their local and systemic actions [19]. Stressed or injured myocardium releases cytokines in an attempt to repair/reduce the damage/stress. However, long-term exposure of cytokines promotes cardiac dysfunction. In case of Myocardial Infarction (MI), sudden death of cardiomyocytes activates innate immune pathways triggering inflammatory reaction [20]. This infarct healing can be divided into three overlapping phases, inflammatory, proliferative and maturation phase [21]. During the inflammatory phase cytokines and chemokines recruit leukocytes to the infarcted areas. Neutrophils and macrophages clear the wound from dead cells and matrix debris. This generates endogenous signals to activate innate immune system by DAMPs [22], leading to activation of TLRs, which further activate the pro-inflammatory cascade via NF-kB. This activation of innate immune response leads to

release of several inflammatory mediators (cytokines and chemokines) and attracts inflammatory cells like neutrophils and macrophages (Figure 1) [23].

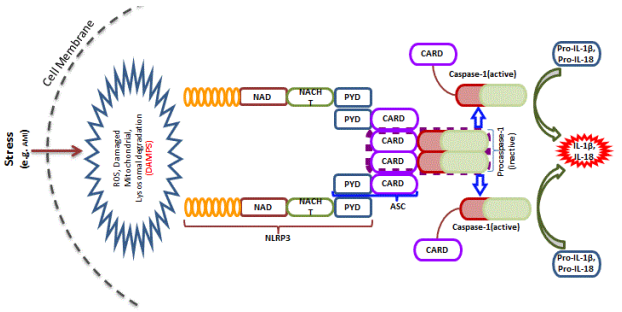

Figure 1: Assembly of NLRP3 inflammasome.

Inflammosomes are intracellular multiprotein complexes having caspase-1 activating platforms. Here we show NLRP3 (a subtype of pattern recognition receptor, PRR) inflammasome which comprises of an activated NLRP3, ASC and procaspase 1. In response to DAMPs the NLRs (here NLRP3) oligomerize and associate with their PYD to the PYD of ASC. This recruits procaspase 1 to bind to CARD of ASC which leads to activation of procaspase 1 into caspase 1. This active caspase 1 acts on pro-IL-1β/IL-18 to generate active ILIL-1β/IL-18 which is secreted out. (AMI-acute myocardial infarction, NLRP3-NOD-like receptor protein3, CARD-caspase recruitment domain, DAMPs-danger/damage associated molecular patterns, ASC-apoptosis-associated speck-like protein, NACHT-central nucleotide-binding and oligomerization domain, CARD-caspase recruitment domain, PYD-pyrin domain).

Cytokines

Cytokines are highly potent endogenous polypeptides produced by a variety of cell types and contribute to the inflammatory process. They participate in acute and chronic inflammation via a complex network of interactions. Cytokines are secreted locally in the heart or systemically in a range of cardiac conditions including, HF and ischemia-reperfusion injury [24,25]. The important pro-inflammatory cytokines, Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-1β, and IL-6 and C-reactive Protein (CRP) are all increased in HF, and their levels are positively correlated to HF severity and prognosis [15,26,27]. Here we will discuss role of some important cytokines in HF.

Tumor Necrosis Factor (TNF-α)

It (are describing TNFa or TNFR?) belongs to the TNF superfamily of type II transmembrane proteins and has been most widely investigated in cardiovascular pathology. It (TNFa?) is normally produced by activated macrophages but also by a broad variety of other tissues including lymphoid cells, mast cells, endothelial cells, fibroblasts and neuronal tissue. It is released from its membrane-integrated form via proteolytic cleavage by metalloprotease TNF-α Converting Enzyme (TACE), as soluble cytokine [28]. Increased level of serum TNF-α has been reported in patients with chronic HF [15]. It is known that TNF-α is produced in myocardium under volume overload and is present in failing but not in normal human myocardium [26,29]. It can be activated in response to initial myocardial insult (e.g. myocardial infarction) via direct antigenic stimulation i.e., viral myocarditis, acute allograft rejection). The direct functional regulation of cardiomyocyte responsiveness towards adrenergic stimulation was first shown by Gulick et al. [13]. *In vitro* treatment of cardiomyocytes by supernatant of mixed lymphocytes culture resulted in reduced maximal contractility as well as reduced cyclic AMP accumulation in cardiomyocytes in response to isoproterenol stimulation. Similar effects on cardiac function were noted *in vivo* in anaesthetized dogs by infusing recombinant human TNF-α [30]. After 24 h infusion of TNF-α, there was cardiac dysfunction, which recovered after 72 h. In papillary muscles, it produced a direct reversible negative inotropic effect, which was initially proposed to be mediated via nitric oxide [31]. However, subsequent studies provided the evidence that negative inotropic effect of TNF-α was independent of nitric oxide or any circulating factor, rather it directly reduced contractility in isolated heart and isolated cardiomyocytes via inhibiting the intracellular calcium release during systole [32]. There are two receptors characterized for TNF-α, TNFR1 and TNFR2. TNFR1 is the most widely studied TNF-receptor and is primarily targeted by TNF-α [33].

Interleukin (IL)-1β

It is an important proinflammatory mediator, which is generated at the sites of injury and recruits cellular partners. Proinflammatory signals such as Lipopolysaccharide (LPS) or TNF-α initiate the synthesis of inactive-IL-1 which is subsequently cleaved by caspase 1, a cysteine protease activated by inflammasomes [17]. Interestingly, similar to TNF-α, IL-1β also desensitizes cardiomyocytes against adrenergic stimulation [13]. Blocking of IL-1 receptor (target of IL-1β) protects against ischemic cardiac dysfunction [34]. In mice, IL-1β administration induced a reversible contractile dysfunction associated with impaired response to β-receptor stimulation [35]. Patients with HF show increased serum level of IL-1β as well as cardiac expression [36,37]. Study with recombinant IL-1 receptor antagonist, Anakinra, was initially performed in patients with rheumatoid arthritis, which establishes its efficacy and safety [38-40]. This led to further clinical studies in patients with HF that we will discuss separately.

Interleukin (IL)-6

IL-6 is a controversial cytokine in terms of its biological effect on cardiac pathology. Initially IL-6 was designated as B cell differentiation factor or B cell stimulatory factor-2 [41]. IL-6 receptor is composed of IL-6R and gp130. With this discovery of IL-6 and successful identification of its sub-cellular targets, attempts were made to study the effect of loss of function of IL-6 and IL-6 receptor on heart. In general elevated levels of IL-6 expression in failing heart and circulation have been noted in clinical studies [42-44]. Genetic deletion of IL-6 did not offer protection against myocardial ischemic injury [45]. Transgenic mice expressing IL-6 and IL-6 receptor were crossed to have a sustained activation of IL-6 receptor (gp130) which led to cardiac hypertrophy [46]. IL-6 is considered to be protective in initial phase; however, persistent stimulation leads to deleterious effect [47]. However, studies involving direct manipulation of IL-6 in patients are lacking.

Targeting Inflammation in HF

The strong correlation between cardiac function and cytokines prompted clinical investigation into therapeutic efficiency of inflammation modulating agents. Broadly, three strategies have been

used modulate the inflammation, anti-inflammatory therapies, immunomodulatory therapies, and autoimmune strategies.

Pentoxifylline

The primary action of pentoxifylline is to promote blood circulation in the body. It inhibits phosphodiesterase and has been commonly used for peripheral vascular diseases. Pentoxifylline reduces platelet aggregation, thromboxane synthesis [48] and inhibits TNF-α transcription and translation [49]. In a small clinical study involving 48 patients with idiopathic dilated cardiomyopathy, it showed an improvement in NYHA functional class and ejection fraction along with reduction in circulating TNF-α [50]. Interestingly in this study, four patients died in the control group, but none in the treatment group adding to the potential of pentoxifylline. In line of the earlier findings, studies in HF patients with different etiology, pentoxifylline improved the clinical symptoms along with consistent increase in ejection fraction [51,52]. A recent meta-analysis of the clinical studies investigating the efficacy of pentoxifylline in heart failure, suggests an obvious improvement in ejection fraction of patients in pentoxifylline group [53]. However, this drug never got a full attention. Most of the studies are small and performed by the same group of investigators. Since the molecule has lost its charm for intellectual proprietary rights, which can be one of the reasons for the dampened enthusiasm in this molecule.

Thalidomide

It promotes TNF mRNA degradation thereby reduces its circulating level. It showed effectiveness in small clinical studies [54,55]. The improvement in ejection fraction was better seen in patients who could tolerate higher dose of thalidomide. However, the circulating TNF-α level did not change in either of these trials.

Dexamethasone

It is a corticosteroid, which suppresses TNF-α biosynthesis and translational and transcriptional level. A study in patients with dilated cardiomyopathy showed an improvement in ejection fraction in a subgroup of patients classified as 'reactive' [56]. However, over all there was no difference in ejection fraction between control and dexamethasone treated patients. This was the first study showing a direct relationship between anti-inflammatory agent and improvement in cardiac function.

Targeting soluble TNF receptors

Etanercept is an engineered human TNF receptor immunoglobulin: The concept was to trap the circulating TNF-α and prevent its subsequent effect. In small safety and efficacy studies, etanercept improved ejection fraction and quality of life along with serum cytokine profile [57,58]. In larger trial of etanercept RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) in North America and RECOVER (Research into Etanercept Cytokine antagonism in Ventricular dysfunction) in Europe and Australia, having 900 patients in each, there was no effect on primary end point and so the trials were terminated before completion [59]. On the contrary, further analysis of the RENAISSAINCE revealed an increase in risk of death, although later was nullified in Randomized Etanercept Worldwide evaluation (RENEWAL) [60]. This raised questions over the real impact of increased circulating cytokines and their role in cardiac dysfunction. However, subsequent experimental studies provided some explanations for its untoward effect, like soluble TNF binding immunoglobulins exerted cytotoxic effect by fixing the cytokines on the expressing cells [61].

Monoclonal antibodies: Infliximab, a chimeric antibody of murine Fab (antigen binding fragment) and human Fc (constant fragment) portion of IgG1. The clinical study ATTACH (Anti–TNF-αTherapy Against Congestive HF) trials showed in increased rate of mortality and HF hospitalization in patients receiving higher dose [62]. Interestingly, in rheumatoid arthritis patients with normal cardiac function, infliximab showed an increase in ejection fraction from 58.5% before treatment to 63% after supporting the complement fixation theory and nullifying inherent cardiotoxic effect [63].

IL-1 receptor antagonist

Anakinra is an antagonist against IL-1 receptor. Binding of Anakinra blocks the effect of IL-1. In MI patients Anakinra failed to improve ejection fraction although it prevented adverse cardiac remodelling [64,65]. However, in two small clinical studies, it improved exercise performance in HF patients with preserved or depressed ejection fraction [66,67].

Intravenous immunoglobulin (IVIG)

IVIG influence the level of several cytokines and cytokine modulators, resulting in the downregulation of inflammatory response [68]. In patients with ejection fraction <40% intravenous administration of immunoglobulins led to significant improvement in ejection fraction (26.62% to 31.63%), accompanied with reduced inflammatory mediators and serum BNP level [69]. However, in another study by Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) investigators in patients with recent onset of cardiomyopathy, there was no significant improvement in ventricular function which might be attributed to the difference in dosing design [70]. Further, in post-MI patients IVIG failed to improve the cardiac function or adverse remodeling raising a question towards its efficacy [71].

Immune modulation therapy (IMT)

This is another interesting approach to modulate the body immune response by exposing small amount of blood sample of patients to physio-chemical stresses, which facilitates apoptosis, and these apoptotic cells are uptaken by macrophages. This results in reduction of pro-inflammatory cytokines and increase in production of anti-inflammatory cytokines [72]. These exciting finding prompted for clinical study of IMT, where significant reduction in death and hospitalization was noted [73]. However larger study failed to show an overall effect on primary end point, although it benefitted nonischemic cardiomyopathy or patients with milder HF (NYHA class II) [74].

Conclusion

Although, the anticytokine strategies could not support the anticytokine theory in clinical conditions, it is difficult to nullify the basis of the concept. The direct functional effect of cytokines on heart and the correlation between circulating cytokine level with clinical condition suggests a strong link between the two. It raises questions about the nature of relationship between inflammation and cardiac pathology. Whether inflammation is cause' or 'effect'? Although it has

not been answered completely, but two important points are very clear, one, cytokines do participate in cardiac pathology as mechanical unloading of heart improves cytokine level and second the cytokine strategies have not shown toxicity especially in patients with normal cardiac function. It indicates that the cytokines biological effect/ mechanism of action may be different in healthy and disease conditions, meaning the target signaling pathways are behaving differently. A recent concept of 'parainflammation' has been proposed and is expected to throw some light on the outcome of these studies [16,75]. Hence, it appears that more in depth investigations are required for declassifying the mechanism of action of cytokines and also identifying the subset of patients likely to be benefitted by these strategies.

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