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Role of Stress Induced Cytokines in the Development of Heart Failure

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ABSTRACT

Comprehending the intricate mechanisms at the core of heart failure, a widespread and intricate cardiovascular ailment, is imperative for the advancement of therapeutic approaches. Stress-induced cytokines have emerged as fundamental contributors to the pathophysiology of heart failure. This review delves into the existing knowledge base, underscoring the central role played by stress-induced cytokines in the evolution of heart failure. Both empirical evidence and clinical studies underscore the substantial influence of these cytokines on adverse cardiac remodeling, dysfunction and fibrosis. Insights into the molecular pathways and signaling cascades activated by stress-induced cytokines furnish valuable information about their participation in myocardial injury and the progression of heart failure. Moreover, the abstract explores potential therapeutic interventions targeting stress-induced cytokines, aiming to alleviate cardiac damage and enhance heart failure outcomes. A thorough examination of this subject contributes to ongoing endeavors in unraveling the intricacies of heart failure, laying the foundation for the creation of focused and effective therapeutic strategies.

Key words: CCL-2, Cytokines, Heart failure, IL-1, IL-6, TNF-α

INTRODUCTION

Heart failure (HF) represents a significant global public health challenge, affecting more than 23 million individuals [1]. When it comes to survival rates, Paulus and Tschope estimated that after an HF diagnosis, the prognosis is extremely poor (at 50% and 10% at 5 and 10 years, respectively), higher than those reported for a number of other cancer types [2]. Batlle et al., proved that despite advancements in its treatment, addressing HF still involves substantial challenges. Approximately four decades ago, HF was characterized as a "neuroendocrine disease" [3]. Heart failure, according to Pfeffer et al., is defined as the incapacity of the heart to effectively pump blood to meet the needs of various tissues, or as a result of having to deal with elevated filling pressures [4, 5].

According to Iaccarino et al., the utilization of ejection fraction as a widely adopted measure of systolic function allows the classification of individuals with heart failure into two categories [6]. People with reduced ejection fraction (HFrEF) usually have compromised systolic function. On the other hand, heart failure with preserved ejection fraction (HFpEF) is used to describe individuals who manifest heart failure symptoms without notable decreases in ejection fraction. In HFpEF, disturbances in diastolic function primarily contribute to heightened filling pressures. Epidemiological studies suggest that HFpEF constitutes nearly fifty percent of all recently reported cases of heart failure [6].

Heart failure, as a clinical syndrome, can originate from diverse pathophysiological alterations, myocardial infarction, ischemia, encompassing metabolic dysregulation, pressure or volume overload, genetic disturbances in sarcomeric protein function and responses to viral infections [7]. Dick and Epelman noted that inflammatory signaling cascades are activated at both the local and systemic levels, corresponding with the onset of heart failure, regardless of the specific underlying etiology [8].

Trachtenberg and Hare examined the role of inflammation in the initial stage of heart failure in individuals with inflammatory cardiomyopathies or myocarditis [9]. Moreover, Wilson and collaborators illustrated that acute stress-induced cardiomyopathy is marked by cytokine-mediated inflammation, as detailed by Scally and colleagues [10, 11]. This complex illness has been identified as an occasional factor contributing to cardiac injury in patients with coronavirus disease 2019 (COVID-19) [12, 13].

This review delves into potential therapeutic targets for heart failure, with a specific focus on extensively studied chemokines and pro-inflammatory cytokines. The research examines conventional inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α and the CC chemokine CCL2/monocyte chemoattractant protein (MCP), along with IL-6. The discourse provides a summary of the cellular effects of these agents in the context of a failing heart and explores their potential contributions to dysfunction and the progression of heart failure. This review explores the benefits and challenges of targeting cytokines and chemokines in heart failure [14,15,16]. Kurrelmeyer et al., conducted an investigation, revealing that myocardial injury triggers the upregulation of various members in the cytokine and chemokine families. This heightened expression holds the potential to provide crucial protective benefits to cardiomyocytes [17] and might

simultaneously activate reparative programs [18].

METHODS

Identify pertinent databases for conducting a literature search, encompassing platforms such as PubMed and Google Scholar. Ensure the inclusion of a broad spectrum of both experimental and clinical studies related to stress-induced cytokines in heart failure. Obtain full texts of selected articles for a detailed assessment. Extract and summarize data on study design, methodologies, and key findings, focusing on stress- induced cytokines and their implications in heart failure.

INFLAMMATORY CYTOKINES AND HEART FAILURE

Levine et al., proposed that a substantial amount of data from clinical and experimental research emphasizes the important role that inflammatory cytokines and chemokines play in the development of unfavourable cardiac remodelling and myocardial dysfunction [19]. Sanders-van et al. found elevated pro-inflammatory cytokines in the blood of people with heart failure, including HFrEF and HFpEF subgroups [20]. Abernethy et al., presented evidence suggesting an elevation in cytokine levels among patients experiencing acute decompensation [21], and these levels seem to have a connection with clinical outcomes [22]. The idea that myocardial remodelling and dysfunction can be triggered by the activation of cytokines and chemokines is supported by multiple lines of evidence, regardless of the underlying cause of heart failure. At first, pro-inflammatory cytokines show negative inotropic effects [23]. Additionally, these cytokines might contribute to cardiomyocyte apoptosis [24].

Table 1: Role of cytokines in heart failure

CYTOKINES	ROLE IN HEART FAILURE	EXPERIMENTAL EVIDENCE	REFERENCES
TNF α	Pro-inflammatory cytokines are linked with an increased risk of heart failure.	Increased expression has been noted in a number of experimental models, which may be linked to cardiac tissue dysfunction.	[25,26,27,28,29,30,31]
IL-1	connected to the onset of systolic dysfunction and heart failure	In experimental models with a variety of reasons, involving pressure overload and myocardial infarction, steady upregulation has been seen.	[32,33,34,35,36]
IL-6	Elevations are found in heart failure patients, which may be related to inflammation and heart tissue malfunction.	Experiments indicate that heart failure-related diseases are connected with increased expression of IL-6.	[37,38,39,40,41,42,43]
CCL2	Chemokine associated to inflammatory processes in heart failure.	Elevated levels are observed in instances of heart failure, participating in the attraction of immune cells and the restructuring of cardiac tissue.	[44.45,46.47,48,49,50]

TNF-α

Considerable investigation has centered around TNF-α, a versatile cytokine acknowledged as a pivotal inflammatory mediator in heart failure [19]. The significant increase in TNF-α levels circulating among HFrEF

patients in the early 1990s prompted in-depth experimental inquiries into its potential consequences for thefailing heart. Kapadia et al., proposed a persistent elevation in TNF-α expression within the myocardium, evident in both experimental models of heart failure [51, 52] and individuals with cardiomyopathic conditions [53]. Different cell types, including cardiomyocytes [25], macrophages [54], vascular cells and mast cells [55], play a role in the heightened TNF-α expression observed in hearts experiencing damage and failure.

Dunlay et al., highlighted an association between elevated mortality rates in both HFrEF and HFpEF subgroups among individuals with human heart failure and increased levels of circulating TNF-α [56, 57, 58, 59]. Asgeri et al. found that removing TNF receptors in a non-reperfused myocardial infarction model was linked to larger infarct sizes, suggesting TNF-α's role in cellular protection signaling [60]. Papathanasiou et al. found that TNF-α protected against cardiac decline in a desmin-loss cardiomyopathy model by helping form an alternative cytoskeletal network. [61]. Lacerda et al., reported that TNF-α maintained mitochondrial respiratory function after anoxia/reoxygenation injury, likely through the modulation of reactive oxygen species (ROS) and sphingolipids [62].

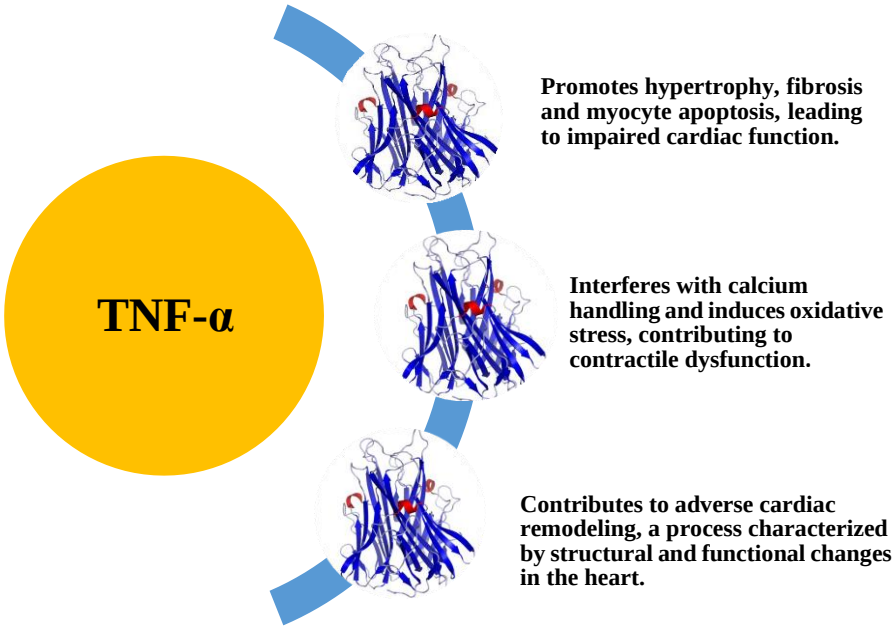

Fig 1: Role of TNF-α in heart failure

IL-1

Dinarello's study highlighted that the IL-1 family comprises 10 receptors and 11 cytokines [63]. IL-18, IL-1α/IL-1β, and the IL-33/ST2 axis have been extensively studied in the cardiovascular system [63, 64, 65, 66]. Bujak and Frangogiannis highlighted that evidence suggests IL-1 family members are crucial in heart failure and systolic dysfunction [67,68]. Dewald et al., noted a persistent increase in IL-1 expression across diverse experimental models of heart failure, including situations like cardiac infarction [69], transgenic calcineurin overexpression [70], left ventricular hypertrophy [71, 72] and diabetic cardiomyopathy [73]. Furthermore, Francis et al., suggested that IL-1β has been found in those with cardiomyopathic diseases [74]. Suetomi et al., assessed the correlation between inflammasome activation and heart failure [75]. This complex molecular

structure, consisting of various components, which are involved in the caspase-1-mediated transformation of pro-IL-1β into its active form. Kawakuchi et al., came to the conclusion that a variety of cell types, including immune cells, fibroblasts, vascular cells and cardiomyocytes, are involved in the synthesis and activation of IL- 1 in hearts that are suffering damage and failure [76, 77].

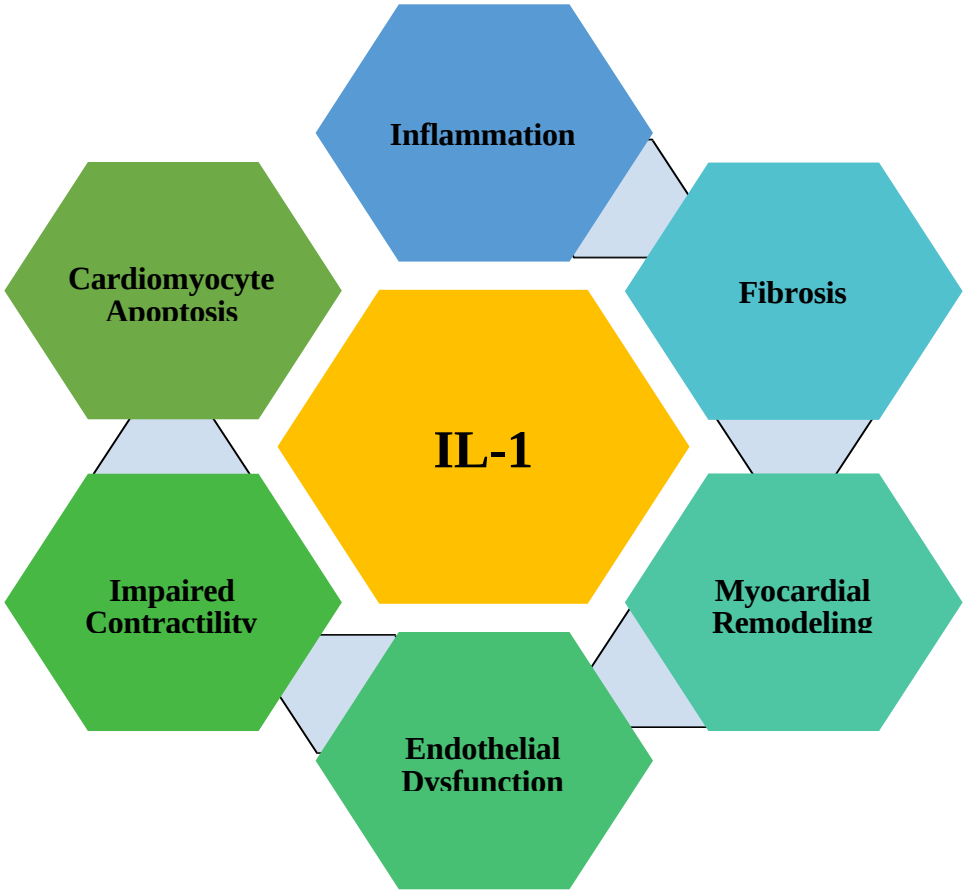

Fig 2: **IL-1's role in heart failure**

IL-6

IL-6 serves as the prototype within the gp130 cytokine family, which comprises several other cytokines associated with the progression of cardiovascular diseases [78]. Rose-John studied that notable members in this family encompass IL-11cardiotrophin-1, oncostatin-M and leukemia inhibitory factor (LIF). These cytokines transmit signals through the common signaling receptor subunit, gp130 [79], resulting in the activation of Janus kinases and subsequent induction of STAT3 phosphorylation. Baumgarten et al., observed a sustained rise in IL-6 expression in models of heart failure, irrespective of the root cause. This heightened expression is apparent across diverse cell types, including infiltrating mononuclear cells, cardiomyocytes and fibroblasts [80]. Omiya et al. proposed using RNAse regnase-1 to break down IL-6 mRNA and reduce its pro- inflammatory effects in pressure-overloaded myocardium [81].

Kubota et al. found that clinical studies suggest increased IL-6 expression in failing myocardial tissues compared to non-failing ones [82]. In contrast, some studies found no increase in IL-6 production in heart failure [83]. Rather, these investigations noted heightened levels of downstream components in the IL-6 signaling pathway, such as gp130 [84]. According to findings from Zhao et al., within the myocardium subjected to pressure overload, the genetic deficiency of IL6 was observed to improve cardiac function and reduce hypertrophy. These effects were connected with the removal of CaMKII-dependent actions on cardiomyocytes [85].

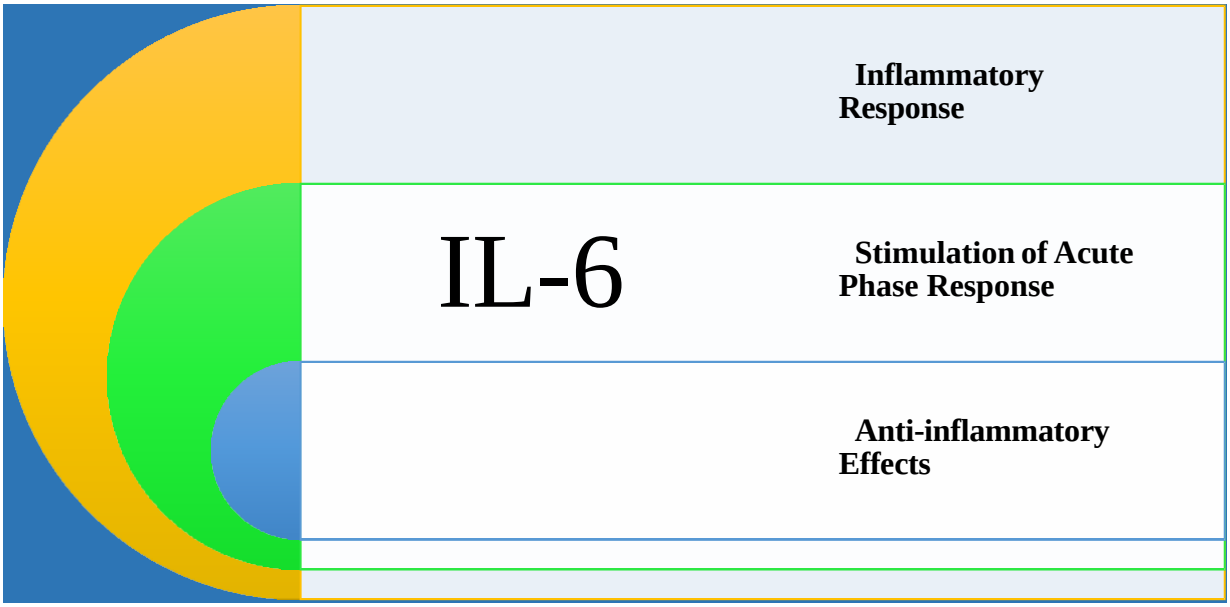

Fig 3: Role of IL-6 in heart failure

CCL2

As per the discoveries by Sokol and Luster, Chemokines, ranging in size from 8 to 12 kDa, are small cytokines characterized by chemotactic qualities. They play a crucial role in coordinating cell migration and spatial organization throughout developmental processes, maintaining homeostasis and influencing inflammatory responses [86]**.** Lafuse et al., have documented a consistent and significant increase in the expression of CCL2 within experimental models designed to replicate cardiac remodelling, injury and heart failure [87]. In hearts afflicted by infarction or failure, CCL2 is detected in multiple cell types, including vascular smooth muscle cells, cardiomyocytes and endothelial cells [88] and mononuclear cells [89]. As per Chen and Frangogiannis, the increase in CCL2 levels might be linked to the activation of Toll-like receptor (TLR) signaling and neurohumoral cascades, or pathways influenced by pro-inflammatory cytokines [90,91]. Frangogiannis et al., have also reported that research involving human patients demonstrates an upregulation of CCL2 in failing hearts, with increased expression observed in myocardial specimens obtained from individuals with dilated [93], ischemic [92], or hypertrophic cardiomyopathy [94].

The findings of Hayashidani et al., suggest that CCL2 is involved in adverse dysfunction, remodelling and fibrosis in both non-infarctive and infarctive heart failure models. In myocardial infarction

models, the improvement of adverse remodelling was noted when CCL2 was eliminated, along with the application of anti-CCL2 gene therapy [95]. However, this improvement came with the drawback of delayed dead cardiomyocyte phagocytosis, leading to granulation tissue formation [19]. In a model simulating ischemic fibrotic cardiomyopathy, CCL2 contributed to fibrotic remodeling, macrophage recruitment, and systolic dysfunction [96, 97, 98, 99]. Moreover, within a left ventricular pressure overload model, the neutralization of CCL2 alleviated diastolic dysfunction, leading to a reduction in fibrosis. Substantiating these experimental findings, clinical studies highlighted by Stumpf et al., associate elevated circulating CCL2 levels with more severe symptoms and worsened systolic dysfunction in patients experiencing heart failure with reduced ejection fraction (HFrEF) [100]. Moreover, Hohensinner et al., also conveyed that elevated circulating CCL2 levels in advanced heart failure patients were associated with higher mortality rates [101].

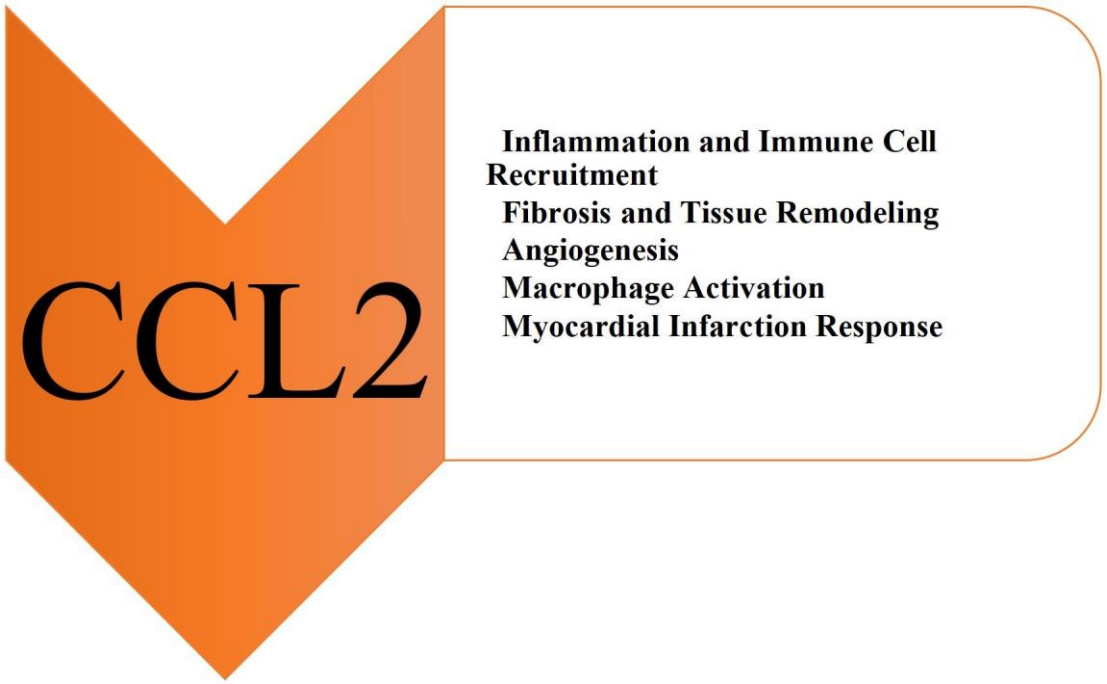

Fig 4: Role of CCL2 in heart failure

CONCLUSION

Stress-induced cytokines are crucial in heart failure, driving cardiac remodeling, dysfunction, and fibrosis. Both experimental evidence and clinical studies have shed light on the substantial impact of stress-induced cytokines, offering valuable insights into the molecular mechanisms and signaling pathways implicated in myocardial injury.

As our comprehension deepens regarding the involvement of these cytokines in the intricate landscape of heart failure, a promising opportunity emerges for targeted therapeutic interventions. Strategies directed at mitigating the effects of stress-induced cytokines not only hold the potential to ameliorate cardiac damage but also to enhance overall heart failure outcomes. The exploration of effective therapeutic modalities

targeting these cytokines opens new avenues for personalized and precise treatments, advancing the management of heart failure.

Looking ahead, continued research into the specific roles, regulation and interactions of stress-induced cytokines will be of utmost importance. This research will deepen our understanding of heart failure and guide new therapies. Ultimately, deciphering the complexities of stress-induced cytokines in heart failure lays the groundwork for transformative breakthroughs that have the potential to revolutionize the approach to treating this prevalent cardiovascular condition.

Conflict of interest- The authors declare that there is no conflict of interest.

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