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Tumor Necrosis Factor- α in Heart Failure: An updated review

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Abstract

Purpose of the review—Pro-inflammatory cytokines are consistently elevated in congestive heart failure. In the current review, we provide an overview on the current understanding of how Tumor Necrosis Factor- α (TNF- α), a key pro-inflammatory cytokine potentiates heart failure by bringing imbalance and overwhelming the anti-inflammatory responses disrupting the homeostasis maintaining process.

Recent finding—Studies have shown co-relationship between severity of heart failure and levels of pro-inflammatory cytokine TNF α and one of its secondary mediator interleukin-6 (IL-6) suggesting their potential as biomarkers. Recent efforts have focused on understanding the mechanisms on how pro-inflammatory cytokines contribute towards cardiac dysfunction and failure. In addition, how unchecked pro-inflammatory cytokines and its cross-talk with sympathetic system overrides the anti-inflammatory response underlying failure.

Summary—The review offers insights on how TNF- α and IL-6 contribute to cardiac dysfunction and failure. Furthermore, this provides a forum to begin the discussion on the cross-talk between sympathetic drive and pro-inflammatory cytokines and its determinant role in deleterious outcomes.

Keywords

Heart failure; Beta-adrenergic receptor; G-protein coupled receptor kinases; Tumor necrosis factor alpha; Interleukins; Cardiac hypertrophy and dilation

Introduction

Heart failure is a complex progressive pathology, a phenotype reflective of an end organ damage as a consequence of insults/injuries including hypertension, dyslipidemia, diabetes,

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Conflict of Interest

Sarah M. Schumacher and Sathyamangla V. Naga Prasad declare that they have no conflict of interest.

Human and Animal rights and Informed Consent

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Paper of particular interest, published recently have been highlighted as:

- Of importance
- Of major importance

ischemic heart disease, post-partum cardiomyopathy, and congenital disorders^{1–4}. In response to the tissue injury to the diverse array of insults, the heart initiates tissue repair mechanisms by engaging the innate immune system. Consistent with the engagement of innate immunity, significant increase in the repertoire of pro-inflammatory cytokines is observed following cardiac insult^{5–7}. Tumor necrosis factor α (TNF α), transforming growth factor β (TGF β) and family of interleukins including IL-1, -12, -8 and -18 are among the most common pro-inflammatory cytokines observed following cardiac stress^{8, 9}. The increase in the pro-inflammatory cytokine profile is a responsive tissue repair mechanism that is considered to provide beneficial effects by mediating cardiac remodeling. Accumulating evidence indicates that the acute pro-inflammatory stage is classically followed by the anti-inflammatory response to resolve the injury^{10, 11}. However, given the diverse and unique nature of cardiac stress, the pro-inflammatory response is accentuated due to localized smooth muscle injury associated with increased extravasation of leukocytes that prolongs the pro-inflammatory cycle^{7, 12, 13}. The prolonged pro-inflammatory process if unchecked by the anti-inflammatory mechanisms transitions to chronic inflammation, aided in part by the constant cardiac stress mediated by co-morbid conditions like hypertension, diabetes etc.^{6, 14}. A key component in sustaining chronic inflammation is the infiltration of cardiac tissue by macrophages which forms the nucleating site for generation of pro-inflammatory cytokines. Thus, there is excessive production and release of these cytokines into circulation which in turn could have adverse effects on remote organs^{15, 16}. Consistent with their deleterious effects, multiple studies have suggested the use of TNF α and IL-6 as potential markers for heart failure^{16–19}. Furthermore, high levels of pro-inflammatory cytokines like TNF α can impact cardiac function by mediating signals that underlies deleterious cardiac remodeling and negative inotropic effects^{20–22}. In addition to the negative inotropic influence on the heart, there is also growing evidence of dynamic cross-regulation between sympathetic system and immune response²³. Understanding the cross-talk and regulation becomes important given that cardiac function is tightly regulated by sympathetic signaling mechanisms²⁴. In this context, we hope that our succinct review provides critical insights into immune responses focusing on integrating the cross regulation between sympathetic systems and inflammation that mediate cardiac function/dysfunction and failure.

Innate immune response in cardiac remodeling and heart failure

The heart maintains cardiac tissue homeostasis like any other organ/tissue systems by engaging the innate and adaptive inflammatory responses. Traditionally, the innate immune response is associated with infections²⁵ and thus, difficult to envision its role as a part of initial inflammatory response²⁶. However, it has come to be recognized that heart also encodes the classical germ-line encoded pattern recognition receptors that initiate repair upon detecting pathogen-associated molecular patterns (PAMPs or damage-associated molecular patterns (DAMPs)^{6, 27, 28}. There is increasing appreciation that the pattern recognition receptors can detect molecules of self-origin like DAMPs providing the link between cardiac tissue injury/damage to the initial pro-inflammatory response^{7, 29}. In the context of the cardiac injury, the DAMPs could include mitochondrial components, dsRNA, heart shock proteins released from damaged/necrotic cardiomyocytes, or degraded

extracellular matrix components like Hyaluronan fragments^{6, 30, 31}. These molecules engage the recognition pattern receptors to mediate robust inflammatory response with infiltration of neutrophils and monocytes that initiate tissue repair. Given the robustness of the inflammatory response “sans” the pathogenic infection in the cardiac tissue, it has been referred to as “sterile infection”. Thus, innate inflammatory response is mediated by an ensemble of components involving macrophages, dendritic cells and poly-morphonuclear granulocytes through cytokines, chemokines and activation of complement system^{32–34}.

A key determinant in the robust innate inflammatory response is the pattern recognition receptors that are activated by DAMPs or PAMPs which are primarily represented by Toll-like receptors (TLRs) and C-type lectin receptors (CLRs)^{35–37}. In addition to these classical pattern recognition receptors, there are also intercellular receptors like retinoic acid inducible gene 1-like receptors (RLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs)^{34, 38, 39}. Together this repertoire of pattern recognition receptors sense the DAMPs and/or PAMPs to mediate the initial repair response to resolve the damage. Although the roles of pattern recognition receptor are well described in immune cells, less is known about their roles in cardiac systems, especially in cardiomyocytes. In this context, it is important to note intense studies are in progress defining the roles of pattern recognition receptors in human hearts and in conditions of failure. It is known that human hearts express the ensemble of pattern recognition receptors including TLRs, CLRs and NLRs^{38, 40, 41}. Thus, expression of these set of receptors in human heart provides may provide a quick and robust inflammatory repair response to cardiac stressors including injury to cardiac tissue or infection^{34, 37, 42}.

The primary purpose of this response is to resolve the source underlying disruption of homeostasis with aim to restore cardiac function. However, given that co-morbidities like hypertension, dyslipidemia, diabetes are sustained cardiac stressors, in turn, ensues in prolonged inflammatory response leading to persistent low grade inflammation. This low grade inflammation that occurs in the absence of any identifiable infection and is termed “parainflammation”⁴³. Occurrence of this low grade inflammation suggests that the heart is not able to restore homeostasis by resolving the initial inflammatory response⁴⁴. Consistent with this idea, human heart failure has long known to be associated with elevated levels pro-inflammatory cytokines (TNF α and IL-6)^{19, 45} and reduced level of circulating regulatory T cells (Tregs, known to suppress immune response)^{46–48}. In addition, Tregs from heart failure patients have innately reduced functional capability to suppress cytokines production^{46, 47}. Accordingly, rodent studies have shown that transfer of Tregs from healthy to hypertension-induced cardiac hypertrophic rats in reverse remodeling and amelioration in cardiac function⁴⁸ supporting the idea that resolution of the inflammatory response may not occur efficiently paving the way for a low grade inflammation that could transition into a sustained low-grade pathological pro-inflammatory response.

An integral part of the inflammatory response with progression of heart failure is the simultaneous observation of graded increase in the pro-inflammatory cytokine profile. However due to the complexity of the immune response, a key question that remains to be addressed is whether pro-inflammatory cytokines are the “cause” or “effect” of HF. Thus, despite evidence that inflammatory cytokines are associated with heart failure, anti-cytokine

therapies have not achieved significant success^{49, 50}, in part, due to incomplete understanding of the beneficial vs. deleterious role these play in cardiac remodeling⁵¹. It is known that pro-inflammatory cytokines bind to their cognate receptors to mediate their effects through a key transcription factor - nuclear factor kappa B (NF- κ B)^{52, 53}. NF- κ B is engaged by both the innate immune response as well as by the pro-inflammatory cytokines^{6, 54}. Increasing evidence shows that NF- κ B can be activated by canonical and non-canonical pathways reviewed indepth in Bartekova et al.,⁹. Canonical activation of NF- κ B involves the activation of I κ B kinase that predominantly mediates p65/p50 dimer to be translocated to the nucleus to initiate transcription^{9, 55, 56}. Non-canonical activation involves IKK α kinase complex predominantly mediating p52/RelB complex translocation to the nucleus^{57, 58}. Despite these complexities in activation, NF- κ B is well known to mediate both beneficial and deleterious effects reflecting the beneficial vs. deleterious role of inflammation in cardiac remodeling and failure.

Given that human heart failure is associated with an elevated pro-inflammatory cytokine milieu, a key question studies have been focused on determining whether biological effects of pro-inflammatory cytokines are adequate to provoke a phenotype of heart failure in experimental animals and in humans⁷. However, increasing evidence supports the prevailing idea that heart failure progression occurs as a result of deleterious signaling exerted by pro-inflammatory cytokines secreted by the hearts in addition to the secondary effects accruing from circulating cytokines⁵⁹. Thus, chronic sustained inflammation contributes to worsening of heart failure phenotype reminiscent of the sustained neuro-hormonal activation in heart failure. In this context, pathological effects of chronic pro-inflammatory cytokines have been extensively reviewed^{51, 60} including their role in cardiomyocyte function⁶⁰ and ventricular remodeling^{7, 61}. Studies have shown that pro-inflammatory cytokines directly modulate cardiac contractile output wherein, this modulation can be mediated by immediate and delayed effects. The early immediate outcomes encompass effects on EC coupling^{19, 28–40}, NOS leading to nitric oxide generation^{62–79}, Sphingomyelinase signaling^{68, 71, 73, 78–93}, and phospholipase A2 (PLA2) and arachidonic acid (AA) activation^{82, 94–100}. In contrast, the delayed effects also play a role in modulating contractile function by altering β AR signaling wherein, loss of β AR responsiveness to β AR agonists like isoproterenol underlies the reduction in contractile responses^{22, 68, 101, 102}.

Tumor Necrosis Factor- α (TNF α)

One of the key pro-inflammatory cytokines that has been extensively studied including its use for therapeutic strategies and as a potential biomarker associated with heart failure is TNF α ^{19, 45, 49, 50}. One of the key mediators of the TNF α signaling in the cells is through NF- κ B, which again reflective of the dual role TNF α plays in cardiac physiology and pathology¹⁰³. The downstream cellular effects of TNF α are mediated by two cognate receptors, TNF receptor 1 or 2 (TNFR1 or 2)¹⁰⁴. Classically, it is considered that TNF α activation of TNFR1 is deleterious while, TNFR2 is beneficial and the relative ratio of their expression in a given tissue system would potentially drive the phenotypes^{104–106}. In addition to the divergent roles the receptors play in TNF α signaling, it is known that these receptors can be shed from various cells to generate soluble TNFR1 or 2 (sTNFRs). Circulating TNF α may bind to these receptors depleting the available pool of TNF α to bind

and activate membrane TNFRs on cells^{86, 107}. However, it is important to note that the role of these sTNFRs are not yet well understood in the overall cardiac pathophysiology⁵¹. Furthermore, TNF α as an inflammatory ligand has two forms a) the membrane bound form and b) the secreted form^{108, 109} adding another layer of complexity in the overall development of pathophysiology. Despite the complexities of TNF α signaling, multiple studies have shown that cardiomyocyte specific expression of TNF α results in depressed cardiac function that is gene dosage dependent^{110, 111}. Consistently, studies have shown that TNF α *per se* mediates negative inotropic effects in vitro and in vivo^{112–114} and is discussed later in the review. Such findings indicate that the pro-inflammatory cytokine TNF α could cross-talk with the beta-adrenergic receptor (β AR) system and thereby, underlie the negative inotropic phenotype observed in heart failure.

Cross-talk between inflammatory cytokines and sympathetic system

Sympathetic overdrive and elevated levels of pro-inflammatory cytokines underlie the progression of heart failure and a key concern has been whether these parallel pathways cross-talk and contribute to the pathology. In this regard, many studies have consistently shown that an increase in pro-inflammatory cytokine TNF α leads to negative inotropy both in “in vitro” and “in vivo” settings^{113, 114}. Given that β ARs are key regulators of cardiac inotropic responses, these observations show that pro-inflammatory cytokines like TNF α could directly alter β AR function to induce negative inotropy. Similarly, chronic activation of β ARs by sympathetic system results in induction of pro-inflammatory response characterized by increased expression of TNF α , IL-1 β and IL-6 in the hearts^{115–118}. Consistently, antagonizing β ARs using the β -blockers markedly reduces myocardial TNF α and IL-1 β expression in the hearts¹¹⁹ indicating a “quid-pro-quo” relationship between the sympathetic β AR activation and induction of inflammatory responses. As discussed in the earlier part of the review, upregulation of TNF α , IL-1 β and IL-6 in the myocardium occurs through the NF- κ B dependent mechanisms^{120, 121}. In addition, studies have shown increase in the pro-inflammatory cytokine profile following sympathetic β -agonist is markedly blunted by epidermal growth factor receptor (EGFR) blocker gefitinib¹²² adding another layer of complexity to dynamic cross-talk between inflammatory cytokines and sympathetic systems. Thus, accumulating evidence from multiple studies portrays the existence of a dynamic cross-talk between sympathetic activation and pro-inflammatory responses that determines the ultimate cardiac phenotype.

Pro-inflammatory milieu (TNF α) modulates cardiac sympathetic response:

TNF α is a known negative cardiac depressant and thought to mediate these effects through β ARs^{113, 123}. As discussed, TNF α is thought to mediate these effects by engaging immediate and delayed signaling mediators. The immediate effects include alterations in Ca²⁺⁹⁴, spingolipid mediators⁷⁶ and nitric oxide synthase⁷⁵. However, the mechanistic underpinnings of the delayed signaling mediators are still an area of intense study. Despite the knowledge that TNF α drives negative inotropy through β ARs, less has been known on whether traditional pathways that mediate β AR dysfunction are engaged by the TNF α -driven mechanisms. Sympathetic hormones (catecholamines) mediate cardiac contractility through β ARs^{24, 124}. Diminution in β AR signaling to catecholamines occurs through β AR

desensitization contributing to the pathogenesis of heart failure. β AR desensitization is mediated by phosphorylation of the receptor by G-protein coupled receptor kinases (GRK 2, 3, 5 & 6), protein kinase C (PKC) and protein kinase A (PKA). Among them, GRK2 is a predominant player^{125–127} as blocking recruitment of GRK2 to the β ARs through a strategy of deploying C-terminal of GRK2 (GRK2-Ct) results in beneficial cardiac remodeling¹²⁶. In this context, GRK2 is consistently upregulated in response to pro-inflammatory cytokine TNF α in various tissues¹²⁸ and our studies identified that cardiac GRK2 is upregulated in mice with cardiac overexpression of TNF α which occurs before cardiac dysfunction²².

GRK2 upregulation in response to TNF α in these hearts indicates that GRK2 could be the proximal link in mediating cardio-depressant effects of TNF α through β AR dysfunction^{113, 123, 129}. Studies showed that GRK2 is key in mediating β 2AR desensitization following TNF α as cardiomyocyte conditional GRK2 knock-out mice had preserved β 2AR function despite elevated TNF α . In contrast to the known benefits afforded by cardiomyocyte specific expression of GRK2-Ct, expression of GRK2-Ct was not able to ameliorate cardiac dysfunction in response to TNF α . This indicates the presence of a yet unknown mechanism by which GRK2 can be recruited to phosphorylate β AR instead of the traditional G-protein beta-gamma ($G\beta\gamma$) subunits^{130–132}. Furthermore, recruitment of GRK2 to the β AR complex is mediated by TNFR2 as there was marked reduction in GRK2 recruitment to β ARs in TNFR2 knock out cells²² potentially indicating mechanisms that could be independent of $G\beta\gamma$ subunits. However, such a role for TNFR2 is counterintuitive as TNFR2 is considered to play beneficial role compared to TNFR1 signaling²². In conditions of heart failure with significant pre-existing sympathetic overdrive, TNFR2 signaling could provide beneficial effects by dampening cardiac function in presence of TNF α by mediating non-canonical β AR desensitization. Such mechanisms could underlie the beneficial role TNFR2 may play in presence of chronic β AR agonist as studies have shown that absence of TNFR2 (TNFR2 knockout mice) results in deleterious cardiac remodeling to β -agonist isoproterenol^{133, 134}. These observations indicate a dynamic relationship exists between the sympathetic β AR activation and pro-inflammatory cytokine TNF α .

Sympathetic signals modulate immune response:

Given that dynamic “quid-pro-quo” relationship, wherein TNF α mediates β AR dysfunction, thereby reducing the ability of β ARs to respond to sympathetic stimulation. Simultaneously, sympathetic overdrive in turn elevates inflammatory cytokine TNF α setting up a deleterious feed-forward feed-back loop. A feature observed in many pathologies including that obesity, rheumatoid arthritis, myocardial infarction, and kidney renal injury^{61, 135, 136}. The sympathetic nervous system (SNS) is integral to the overdrive that mediates increased pro-inflammatory cytokines profile. SNS innervates both primary organs and lymphoids like bone marrow, thymus, and secondary lymphoid tissues, including the spleen and lymph nodes^{137–141}. This innervation of noradrenergic fibers provides direct communication between the nervous system and cells of the immune system through the catecholamine neurotransmission. In addition, circulating catecholamines released from the adrenal medulla also influences immunocompetent cell activity^{142–144}. In this context, it is

important to note that the functional response displayed by the immune cells in part is mediated by the β ARs on these cells in response to catecholamines^{141, 145–148}.

The SNS driven catecholamine effects are mediated by the most commonly expressed member of adrenergic receptor family (composed of α 1, α 2, β 1, β 2 and β 3¹⁴⁹), the β 2ARs, that are found in the majority of immune cells except T-helper 2 cells^{150–153}. However, studies have shown that the expression of the repertoire of adrenergic receptor members can be altered in pathology, like upregulation of α 1- and α 2ARs in certain lymphoid compartments¹⁵⁴. Though a speculation, the differences in receptor subtype expression in various immune cells may underlie the apparent controversial effects of catecholamines with regards to their pro- and anti-inflammatory effects that could be dependent on cell type, activation state, and other circumstances^{153–155}. For example, α AR stimulation enhances while β AR stimulation inhibits lymphocyte proliferation, antibody secretion, and pro-inflammatory cytokine production^{150–152}. Further, β 2AR activation is known to increase NK cell number and activity¹⁴⁴, whereas α AR drives bone marrow-derived lymphocyte production^{156, 157} mimicking acute psychological stress and exercise^{144, 156, 157}. In contrast to acute catecholamine release, chronic elevation of catecholamine levels decreases lymphocyte and NK cell numbers in the peripheral blood without altering immune cell distribution¹⁵⁸. Despite these differential effects, accumulating evidence indicates that sympathetic overdrive leads to an increase in pro-inflammatory cytokine response resulting in neuro-inflammation and pain in fibromyalgia¹⁵⁹ while causing negative inotropy in heart leading to heart failure.

An important aspect that needs recognition is the parallels observed between the sympathetic and immune systems. It is well known that the “fight-or-flight” response triggers SNS and hypothalamic-pituitary-adrenal (HPA) axis activation in an attempt to overcome the effects of the stressors with an aim to return homeostasis^{156, 157}. Similarly, during acute stress the innate immune system is activated to release pro-inflammatory cytokines that prepares the body to fight infections or limit injury¹⁶⁰. However, in the context of inflammation, chronic stress is believed to induce a shift from an adaptive response to immunosuppression, potentially through receptor desensitization or downregulation, with detrimental outcomes for the host¹⁶¹ that are associated with low grade inflammation. This low grade inflammation due to chronic stress has a negative impact in the context of cardiac function, as evidenced in the co-morbidities of numerous pathologies like cardiovascular disease, metabolic syndrome and arthritis among others^{162, 163}. Given the dynamic cross-talk between SNS and inflammatory response, it is possible that the stress-induced immunomodulation is mediated by the SNS activation which maintains a low-grade inflammation. This in turn causes negative inotropy, leading to increase in epinephrine/norepinephrine levels and keeping this SNS-inflammatory cytokine cycle active. At a cellular level, epinephrine/norepinephrine released from the nerve endings or adrenal medulla results in adrenergic activation and GRK2 upregulation in lymphocytes, leukocytes and other immune cells¹⁶⁴ which in turn underlies the chronic immune response that seems to occur in the absence of active infection. However, it is important to note that the immunomodulatory effects by epinephrine/norepinephrine could be different depending on pathology like rheumatoid arthritis and multiple sclerosis which are associated with decreased PBMC GRK2 levels^{165, 166} in contrast to heart failure¹⁶⁷.

In conditions of heart failure, it is well known that sympathetic overdrive is coupled with elevated pro-inflammatory cytokine profile. Studies have found a persistent relationship between circulating TNF α and soluble TNF receptors and mortality in patients with heart failure⁵¹. Given the evidence, it is perhaps easy to speculate that sympathetic overdrive induces TNF α which mediates cellular/physiological responses that initially may be beneficial but becomes deleterious with time. In terms of the molecular signaling, TNF α produced in response to β AR activation is synthesized as a 26 kDa trans-membrane protein which can also be cleaved into a soluble 17 kDa soluble TNF α by TNF α -converting enzyme (TACE)^{135, 168}. As detailed previously TNF α mediates its effects through TNFR1 or R2 via NF κ B “fine-tuning” the cellular response. TNFR1 and R2 mediated responses are complex as they engage multiple pathways like TNFR1 interaction with the death domain TNFR1 protein (TRADD) and TRAF2 activates NF κ B, while its engagement with TRADD-death domain containing Fas protein complex mediates apoptosis^{135, 169}. While TNFR2 activation leads to beneficial effects through its interaction with TRAF2 that activates NF κ B, MAPK and protein kinase B (AKT) that are pro-survival signals^{135, 170, 171}. TRAF2 is the nodal molecule that mediates beneficial signals downstream of both TNFR1 and R2 and thus its expression could be a key determinant of TNF α response in conditions of heart failure. Interestingly, high levels of myocyte-specific overexpression of TRAF2 leads to deleterious cardiac remodeling¹⁷² while lower levels of TRAF2 provides beneficial remodeling in ischemia reperfusion injury¹⁰³. Thus, expression levels of TRAF2 in cells may produce counterintuitive phenotypes in pathology. This is critical as sympathetic overdrive leads to β AR stimulation, increasing TNF α whose downstream effects would be determined by the ratio of TNFR1 and R2 expression and driven by levels of TRAF2 in various cells. In addition to this paradigm of cross-talk mediated by SNS, the pathophysiological phenotype is also further determined by whether TNF α is membrane bound or is in the soluble format. It is thought that membrane bound TNF α activates TNFR2^{104, 173, 174} initiating beneficial responses to TNF α . Correspondingly, studies show that cardiomyocyte-specific expression of non-cleavable TNF α leads to concentric hypertrophy, while expression of secreted TNF α results in dilated cardiomyopathy^{108, 109}. More importantly, the key role of TNF α in cardiac pathophysiology is documented by findings showing reduction in apoptosis and amelioration in deleterious cardiac remodeling in TNF α knockout mice (TNF KO) upon myocardial infarction (MI)¹⁷⁵. It is known that MI is associated with upregulation of sympathetic hormones elevating TNF α , and thus, the absence of TNF α in TNF α KO mice ameliorates the major β AR agonist epinephrine driven deleterious signals via TNF α . These exciting observations lead to the idea to target elevated TNF α in humans with an idea to sequester the circulating TNF α thus reducing the deleterious effects in heart failure. To accomplish the sequestration of elevated TNF α two approaches were employed wherein, a) genetically engineered TNF receptor was used a decoy to bind and potentially clear circulating TNF α and b) to use a chimeric monoclonal antibody that would bind and neutralize TNF α . The clinical trial using the genetically engineered humanized TNF receptor Etanercept named RENAISSANCE and RECOVER were terminated prematurely due lack of accrued benefits⁵⁰. Critically, greater portion of patients on Etanercept had worsened prognosis compared to placebos^{7, 50}. Similar to the observation with Etanercept, use of monoclonal antibody Infliximab neutralizing TNF α also resulted in early termination of the clinical trial due worsening heart failure⁴⁹. The failure of the heart failure clinical trial was a

disappointing that lead to a period of cessation of studies in this area. However, given that the underlying mechanisms for worsening in heart failure following anti-TNF α treatment in not well understood, it is imperative that more effort and resources need to be dedicated to gain insights as elevated TNF α is consistently associated with heart failure. This is all the more important given that anti-TNF α antibody Infliximab provides beneficial effects in Crohn's disease and rheumatoid arthritis⁷ reflecting the complexity of the disease etiologies. Finally, it argues to the idea that unique engagement of the certain pathways could provide beneficial effects in certain pathologies while resulting in deleterious outcomes in others. Such an observation with anti-TNF α treatment suggests that better understanding of the mechanisms would allow for selectively leveraging the beneficial components of the anti-TNF α treatment in the complex etiology of heart failure.

Conclusions

A key focus of our review was to bring-to-fore the current state of understanding regarding the dynamic cross-talk between the pro-inflammatory cytokines and SNS which have independent and interdependent effects on cardiac function and pathology. Our discussion was to focus on how the active feed-forward and feed-back between SNS and inflammatory cytokines effects cardiac function and pathology [Fig 1]. This is all the more critical given the failure of anti-TNF α , indicating that an indepth understanding of the complexity of TNF α activity in context of TNF α - β AR signaling axis may shed light on deleterious manifestations in heart failure. On the same note it is also important to understand the conundrum of upregulation of pro-inflammatory pathways following sympathetic overdrive, a hallmark feature of heart failure. Thus, molecular delineation of these bi-directional pathways will pave the way for comprehensive understanding of the mechanism while simultaneously providing insights into potentially novel therapeutic strategies/approaches.

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Figure 1:

The schematic illustration describes the current understanding on the cross-regulation of pro-inflammatory cytokines and the neuro-hormonal-beta-adrenergic receptor (B-adrenergic receptors) axis. Cardiac stressors like changes in hemodynamic load or hypoxia leads to cardiac injury and in response pro-inflammatory cytokines including tumor necrosis factor α (TNF α) are employed as first step in the defense mechanism. This is followed by cardiac tissue repair and injury resolution phase primarily mediated by anti-inflammatory cytokines. However as TNF α inhibits B-adrenergic receptor function, it results in the inability of these receptors to respond to sympathetic drive fundamentally impeding cardiac responses to changes in mechanical demand. Reduced B-adrenergic receptor response leads to a feed-back increase in sympathetic hormones that in turn results in feed-forward elevation in pro-inflammatory cytokine TNF α which leads to self-perpetuating cycle that is now independent of pro- and anti-inflammatory response which was initiated due to injury. This cycle of increased TNF α now inhibits B-adrenergic receptors thereby, leading to feed-back and feed-forward cycle resulting in deleterious signaling mechanisms that underlies cardiac hypertrophy, deleterious remodeling and heart failure.

Table:

Changes in expression of the tumor necrosis factor (TNF) superfamily of ligands in Heart Failure.

Member of TNF Family	Ligand	Expression in Heart Failure
TNFSF1	LT α	NA
TNFSF2	TNF α	Elevated
TNFSF3	LT β	Unchanged
TNFSF4	OX40L/CD252/gp34	Unchanged
TNFSF5	CD40L/CD154/gp39	Elevated
TNFSF6	FasL/CD95/Apo1	Elevated
TNFSF7	CD27L/CD70	Elevated
TNFSF8	CD30L	Unchanged
TNFSF9	4-1 BBL	Unchanged
TNFSF10	TRAIL	Elevated
TNFSF11	RANKL/TRANCE	Elevated
TNFSF12	TWEAK	Unchanged
TNFSF13	BAFF/APRIL	Elevated
TNFSF14	LT γ /LIGHT	Elevated
TNFSF15	TL1	NA
TNFSF16	GITRL/TL6	NA

Abbreviations: NA – Data not available.

Ligand: LT α – Lymphotoxin α ; TNF α – Tumor necrosis factor α ; LT β – Lymphotoxin β ; Apo1 – Apoptosis 1; TRAIL – TNF α -related apoptosis inducing ligand; RANKL – Receptor activator of NF- κ B ligand; TRANCE – TNF α -related activation induced cytokine; TWEAK – TNF-like weak inducer of apoptosis; BAFF – B-cell activating factor; APRIL – A proliferation inducing ligand; LT γ – Lymphotoxin γ ; LIGHT – Lymphotoxin-related inducible ligand that competes for glycoprotein D binding to Herpes Simplex virus entry mediator on T-cells; TL1 – TNF-like 1; GITRL – Glucocorticoid-induced TNF receptor ligand; TL6 – TNF-like 6.