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Pro-inflammatory cytokines mediate GPCR dysfunction

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Abstract

Pro-inflammatory reaction by the body occurs acutely in response to injury that is considered primarily beneficial. However, sustained pro-inflammatory cytokines observed with chronic pathologies such as metabolic syndrome, cancer, and arthritis are detrimental and in many cases is a major cardio-vascular risk factor. Pro-inflammatory cytokines such as interleulin-1 (IL-1), IL-6, and tumor necrosis factor α (TNFα) have long been implicated in cardiovascular risk and considered to be a major underlying cause for heart failure. The failure of the anti-TNFα therapy for heart failure indicates our elusive understanding on the dichotomous role of pro-inflammatory cytokines on acutely beneficial effects versus long-term deleterious effects. Despite these well-described observations, less is known about the mechanistic underpinnings of pro-inflammatory cytokines especially TNFα in pathogenesis of heart failure. Increasing evidence suggests the existence of an active cross-talk between the TNFα receptor signaling and G-protein coupled receptors (GPCRs) like β-adrenergic receptor (βAR). Given that βARs are the key regulators of cardiac function, the review will discuss current state of understanding on the role of pro-inflammatory cytokine TNFα in regulating βAR function.

Introduction

Pathophysiological consequences of inflammation have long been recognized[1] but evidence of its involvement in contributing to and potentially mediating heart failure has been recognized in the last two decades[2]. Since then intense attention has been paid to pro-inflammatory cytokines that are involved in regulation of cardiac structure and function and more so on their critical role in progression of heart failure. The recognition of association between sustained elevated levels of tumor necrosis factor α (TNFα) and the stage of heart failure[3] led to the rationale of therapeutically targeting TNFα in several clinical trials[4–7]. However, counterintuitive to the evidence, anti- TNFα treatment resulted in worsening of heart failure showing our incomplete understanding on the role of TNFα in cardiac remodeling and pathogenesis of heart failure. Given these observations, it becomes imperative to revisit the role of TNFα in pathogenesis of heart failure in the context of recent advances in understanding molecular mechanisms involved in TNFα signaling.

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Studies have shown that pro-inflammatory cytokines especially TNFα blunts the responsiveness of G protein coupled receptors (GPCRs) particularly beta-adrenergic receptors (βARs) impairing contractile function of the cardiac myocytes[8–10]. Similarly, studies have also shown that βAR receptor signaling can mediate beneficial cardiac effects through TNFα receptor 2 (TNFR2) in contrast to TNFR1[11]. In addition, studies have also shown that the expression of TNFR associated factor 2 (TRAF2) could determine the outcome of the cardiac phenotype in response to TNFα[12]. Given the failure of the anti-TNFα therapy in heart failure[4–7] and the key role βARs play in regulating cardiac function, we will summarize the recent advances in understanding the cross-talk between TNFα signaling and βAR, a prototypical G-protein coupled receptor that may provide new insights into the well-known role of inflammation in mediating cardiac dysfunction and asthma exacerbation[13–18].

Cytokines and inflammation

Inflammatory response is a primordial reaction of the body to any kind of stress that could involve a simple injury to a complex infection. Despite the knowledge of the beneficial role inflammation plays, it is now recognized as a double-edged sword. The initial acute phase of the inflammatory response is multi-faceted involving synergistic activation of T and B cells in parallel with hepatic induction of acute phase proteins like interleukin 1 (IL-1), IL-6 and TNFα[19]. The acute phase is followed by a feed-forward pro-inflammatory loop that is selectively localized to the area of infection or smooth muscle injury wherein there is extravasation of leukocytes, erythrocytes, and plasma components into the injured tissue. This is classically associated with activation of macrophages, T lymphocytes and secretion of factors by activated smooth muscle cells including IL-1, C-reactive protein and TNFα leading to significant acute inflammation[20, 21]. Resolution of acute inflammation is dynamically driven by a tight interplay between anti- and pro-inflammatory cytokines. Major anti-inflammatory cytokines include IL-4, IL-6, IL-10, IL-11, and IL-13 while, transforming growth factor β (TGF-β), IL-1, TNFα, gamma-interferon (IFNγ), IL-12, IL-18 and granulocyte-macrophage colony stimulating factor are well known pro-inflammatory cytokines[22–24]. Acute phase is classically required for physiological effects of tissue repair, immune response and resolution of injury whereas often, chronic inflammatory response will lead to pathological effects. However, if left unchecked, this acute pro-inflammatory response can transition to chronic inflammation, a biochemical phenotype observed in conditions like cancer, arthritis, Alzheimer's disease, auto-immune disease[20, 25–28] including cardiovascular pathology[21]. Unlike acute inflammation, chronic inflammation is characterized primarily by tissue infiltration by lymphocytes and macrophages setting a stage and a site for generation of pro-inflammatory cytokines. As a consequence, there is an excessive production and sustained release of pro-inflammatory cytokines into the circulation. Apart from having the influence on the organ dysfunction at the site of production, higher levels of circulating pro-inflammatory cytokines can have deleterious effects on the remote organs. Since the heart is in close proximity to circulating factors, these high levels of cytokines can impact cardiac function via effects on both myocyte contractility and the extracellular matrix[29, 30] involving molecular signaling mechanism are being intensely investigated. A vast majority of the co-morbid conditions

like hypertension, diabetes, obesity and dyslipidemia that are annotated with cardiovascular risk have chronic inflammation associated with elevated levels of pro-inflammatory cytokines and, in particular TNFα which could have greater impact on cardiac function and remodeling[31–36]. In addition to co-morbid conditions associated with elevated cytokines, lung inflammation is a major cause for asthma exacerbation and less is known about how TNFα modulates lung remodeling and function.

Pro-inflammatory cytokines in comorbid conditions

Although pro-inflammatory cytokines including TNFα are elevated in chronic pathologies like cancer, arthritis, autoimmune disease[37–40], these have not yet been categorized as cardiovascular risk or comorbid condition for heart failure. Interestingly, increasing evidence has shown that cancer therapy that uses anti-epidermal growth factor receptor seems to cause collateral deleterious cardiac remodeling[41, 42]. In contrast, asthma, hyperlipidemia, hypertension, atherosclerosis, diabetes and obesity are all characterized by subtle or overt elevation of pro-inflammatory cytokine TNFα and are co-morbid conditions due to their deleterious cardiovascular effects[21, 43, 44]. These observations suggest that all chronic pathologies that have elevated pro-inflammatory cytokines perhaps may not all be conditions for cardiovascular risk. In this context, research in heart failure (HF) has long been in the realm of neuro-hormonal activation and sympathetic systems involving both the animal studies and clinically in patient populations. Blockade of these pathways demonstrated significant beneficial outcomes in a variety of patient populations including HF with reduced ejection fraction[45]. However, these neuro-hormonal blockade therapies have unfortunately been ineffective in conditions of HF with preserved ejection fraction[46, 47] and they tend to represent a major proportion of the patients admitted for HF. Interestingly, elevated serum pro-inflammatory cytokines and adverse clinical outcomes are common to both HF with reduced and preserved EF[48–51]. Given the inefficacy of the neuro-hormonal blockade in HF with preserved ejection fraction, understanding the mechanistic underpinnings of pro-inflammatory cytokines in contributing towards HF may hold a key to providing effective therapies as cytokines are universally elevated in all forms of HF. In fact, the magnitude of the elevation of pro-inflammatory cytokines in chronic HF is significantly less than what is classically observed in autoimmune diseases or acute infections. This suggests that low-grade chronic inflammation may be an important contributor to the maintenance and/or functional cardiac deterioration of patients with clinically established chronic HF[7, 52, 53]. These observations bring-to-fore the conundrum of the current understanding of some of the intricate and context-dependent mechanisms by inflammatory cells and pathways can influence HF in acute setting. However, few of these insights have been extended to assessing the role of inflammation once chronic HF has been established. In this context, a key question that remains to be addressed is whether pro-inflammatory cytokines are the “cause” or “effect” of HF. Therefore, it is important to dissect the cross-talk occurring between pro-inflammatory cytokines and neuro-hormonal signaling mechanisms as evidences show that both are elevated and underlie HF. Since βARs are one of the key regulators of cardiac function and as pro-inflammatory cytokine TNFα is universally upregulated in comorbid conditions, it is imperative to understand their interactive role, which may shed light on the key processes/pathways considered as “cardiovascular risk”.

Pro-inflammatory cytokines and cardiac dysfunction

In addition to the role of pro-inflammatory cytokines as key components of "cardiovascular risk" in comorbid conditions, broad range of cardiac diseases *per se* are also associated with elevated cytokines. These include HF[54, 55], cardiac reperfusion injury[56], myocarditis[57], cardiac allograft rejection[58, 59], and sepsis related cardiac dysfunction[60–63]. These observations indicate the importance of inflammation in HF, as biological effects of pro-inflammatory cytokines were sufficient to provoke a heart failure phenotype in experimental animals and in humans[49]. Thus, the evidence brings-to-fore the idea that heart failure progresses as a result of the deleterious effects exerted by endogenous cytokines signaling cascades on the heart and the secondary effects of the exogenous cytokines in circulation[64]. Hence, similar to sustained neuro-hormonal activation in heart failure, chronic inflammation may also contribute to worsening heart failure due to the deleterious effects of sustained inflammatory signaling. The pathophysiological effects of chronic pro-inflammatory cytokines have been reviewed extensively[29, 54] including their role in myocyte function[29] and tissue remodeling[30, 49]. Studies have documented that pro-inflammatory cytokines modulate contractile function and these effects can be classified into immediate and delayed effects. The immediate effects of pro-inflammatory cytokines are identified to be on EC coupling[19, 28–40], on nitric oxide production by NOS[65–82], on Sphingomyelinase-dependent signaling[56, 71, 74, 76, 81–95], and/or on phospholipase A2 (PLA2) and arachidonic acid (AA) activation[85, 96–102]. In contrast, to these immediate effects, delayed effects that play a key role in modulating contractile function include altered βAR signaling and loss of βAR responsiveness to its cognate βAR agonist like isoproterenol[10, 71, 103, 104].

Innate immunity in cardiac remodeling and cellular basis underlying transition to failure

Despite the idea that inflammatory cytokines could be key drivers in regulating cardiac remodeling, the role of innate immunity is starting to be appreciated[49]. Innate immunity is critical for providing defensive inflammatory response to onset of pathogen or tissue injury[239]. The protective role of this inflammatory response in the context of increased mechanical overload on the heart or cardiac injury is being recognized in its contribution to overall cardiac remodeling[240]. The concept that all inflammation in the realm of cardiac remodeling is deleterious needs to be re-visited given that innate immunity which mediates beneficial pro-inflammatory response may initially mitigate deleterious remodeling and provide benefit. However, with persistent inflammation the "adaptive inflammatory response" that occurs to maintain homeostasis can quickly become maladaptive. This graded inflammatory response or "parainflammation" occurs in the heart with the key purpose of maintaining homeostasis in response to cardiac injury which however with time transitions from being physiologic to pathological. Such a paradigm brings to fore the idea the idea that innate inflammatory response is reparative which becomes deleterious with time in presence of chronic cardiac tissue injury that occurs with increasing mechanical load. Currently, it is not known what determines this switch but the underpinning for such transition is thought to be mediated by the type of immune cells that infiltrate the myocardium and their ability to differentially activate fibroblasts to myofibroblasts[241].

It is considered that the key aspect of the inflammatory response in the myocardium post injury involves active cross talk between the cardiomyocytes, vascular cells, fibroblasts and immune cells in that microenvironment. However, it is the necrotic cardiomyocytes that are thought to initiate the stimulus following tissue injury leading to the reparative response which could then transition to parainflammation. The charge of initial inflammatory response is thought to be mediated by resident monocytes associated with neutrophil infiltration in response to necrotic myocytes[242, 243]. These neutrophils at the sites of injury release proteolytic enzymes involved in clearance of debris from the wounded cells but may also cause collateral damage of targeting intact myocytes causing cytotoxicity. Though less is known about it, this phenomenon however has the potential for prolonging the inflammatory response providing a site for more monocyte recruitment which may decide the overall inflammatory outcome. Consistent with this idea, multiple groups have reported the observation of two key waves of monocyte infiltration into the injured myocardium[244–246]. Such a concept was based on the observation of early recruitment of $Ly6C^{hi}CCR2^{+}CX_3CR1^{lo}$ monocytes followed later by $Ly6C^{lo}CCR2^{-}CX_3CR1^{hi}$ monocytes which are thought to be involved in injury response followed by low anti-inflammatory wound resolution response. Further studies have shown that in addition to recruitment there could be a switch from recruited $Ly6C^{hi}$ to $Ly6C^{lo}$ phenotype in the monocytes[247]. It is important to note that these $Ly6C^{hi}$ monocytes are mobilized from spleen as an immediate response and currently the mechanisms that allows for mobilization of the monocytes from spleen is being actively investigated[248]. However, in this context the key component that drives both the reparative as well as long term deleterious effects is due to pro-inflammatory cytokines which mediates cardiac dysfunction by both canonical and non-canonical signaling pathways.

Pro-inflammatory cytokines and GPCR dysfunction

The role of cytokines in determining GPCR function is clearly reflected by the dysfunction of proto-typical GPCR - βAR in the heart and lung airways. A key hallmark of the contractile dysfunction in heart induced by pro-inflammatory cytokines is impaired sensitivity of βARs to catecholamines[8, 9, 105–107]. Similarly, inflammation is a known instigator of acute asthmatic response due to loss in bronchodilator capacity of lungs[108, 109]. This is also associated with impaired ability of the βARs to responds to β-agonist suggesting a loss in βAR function due to inflammation. Though less is understood about the cross-talk in lungs, studies in the cardiac systems have shown that βAR sensitization is mediated both by NO-dependent mechanisms as well as by an apparently NO- and cGMP-independent functional uncoupling of the βAR to Adenylyl Cyclase[8, 9]. Prolonged exposure to IL-1β and TNFα resulted in reduced contractility augmentation and cAMP accumulation in response to βAR stimulation with isoproterenol. These phenomena occurred without changes in βAR density, binding affinity, or phosphodiesterase activity[8, 9]. Subsequent studies have also demonstrated uncoupling of βAR stimulation to both cAMP accumulation and Ca2+ transients after prolonged exposure to the cytokines IL-1β and TNFα[110, 111].

Even though studies have implicated G-protein G_i mediated alterations in βAR signaling, the precise mechanism has not been fully defined[8]. Some studies have indicated accumulation of G_i proteins in cardiomyocyte membranes by prolonged exposure to cytokines such as

TNFα[112, 113] while, other studies have indicated otherwise[114] suggesting that more indepth studies are required to better understand the role of G_i proteins. In addition to the role of G_i proteins, mechanistic underpinnings on the influence of pro-inflammatory cytokines specifically TNFα on βAR dysfunction was identified by our studies[10]. The studies showed that βARs are desensitized when exposed to TNFα through G-protein coupled receptor kinases (GRKs) mediated phosphorylation of the receptors. Normally, GRKs desensitize βARs by phosphorylating the receptors in response to its agonist epinephrine/ norepinephrine. In contrast to this classical mechanism, TNFα non-canonically recruits GKR2 to the βAR complex and mediates desensitization accounting for the potential loss in contractile capability. Although broad deleterious effects of TNFα have long been known, this study shows that the mechanistic impact of cytokines occurs in close proximity to the βARs. Alternatively, structural and modeling studies have shown that alteration in the S-nitrosylation pathways may modulate G proteins coupling to βARs[115]. However, whether such a mechanism ensues following prolonged cytokine exposure is not known. Furthermore, in neonatal rat cardiomyocytes, it has been shown that prolonged exposure to low concentrations of TNFα is insufficient to induce iNOS or increase NO content and yet these cells show loss of βAR responsiveness[116, 117], supporting a NO-independent mechanism for βAR dysfunction.

Several studies have implicated NO, derived from iNOS, as a mediator of pro-inflammatory cytokine induced loss of inotropic effect including βAR responsiveness either under basal conditions or post inotropic stimulation[70, 75, 76, 78, 111, 114, 118–131]. Series of investigations have revealed that prolonged exposure to conditioned medium of activated macrophages or to combinations of specific cytokines, adult rat ventricular myocytes lose βAR responsiveness but still maintain contraction[114, 124–128] suggesting that NO generation and βAR responsiveness can have overlapping and yet independent effects on cardiac function. This paralleled very well with cardiomyocyte induction of iNOS[125, 126], increased cGMP[114, 124] and nitrite content in the medium, and directly measured NO release[125]. Furthermore, βAR hypo-responsiveness was reversed by treatment with NOS inhibitors strongly implicating iNOS-derived NO in the pathogenesis of delayed contractile dysfunction. Moreover, adult cardiomyocytes exposed to a combination of TNFα, IL-1β, and IFN-γ had iNOS induction, increased NO synthesis, and increased cell death[132]. Importantly, these effects were prevented by the co-treatment with NOS inhibitors[127]. The functional results using specific combinations of cytokines indicated the synergistic cardio-depressant effects of the pro-inflammatory cytokines IL-1β, TNFα, and IFNγ[62, 75–77, 97, 119, 126–128, 133]. This is important given that these cytokines in combination impart significantly greater negative inotropy at a substantially lower concentration than being delivered independently. NO-mediated depression of the βAR response is primarily dependent on cGMP mechanisms, including stimulation of phosphodiesterase II (PDE II) with attendant augmentation of cAMP degradation and activation of protein kinase G (PKG) with downregulation of L-type Ca^{2+} currents due to reduction in cAMP-dependent protein kinase A (PKA) activation[65, 66, 114, 134, 135].

It has been observed that as compared with IL-1β, TNFα is a less potent inducer of iNOS[78, 116, 126] and yet leads to significant contractile dysfunction suggesting alternative mechanisms of regulation. Given this observation, GRK mediated desensitization of βARs

by TNFα may play a key role in regulating cardiac dysfunction. In that context, insights from transgenic mice with cardiomyocyte specific expression of TNFα further underscores the importance of TNFα-mediated βAR responsiveness in the pathogenesis of long-term cytokine-mediated contractile dysfunction[10, 129, 130]. Intriguingly, studies have also shown upregulation of pro-inflammatory cytokines by chronic stimulation of βAR[136] suggesting a circulatory communication loop between GPCRs and receptors involved in inflammation particularly TNFα receptors. Increasing recognition of this cross-talk in the recent years has paved ways for mechanistic understanding and may hold the key for determining the cardio-vascular risk defined for co-morbid conditions that are always associated with chronic inflammation.

GPCR Kinases (GRKs) and inflammation

GRKs are classically known to play a key role in GPCR phosphorylation following agonist stimulation leading to GPCR desensitization[137–143]. GPCR phosphorylation is immediately followed by arrestin recruitment to the receptor mediating internalization[144–146]. However, increasing evidence from recent studies has established a role for GRKs in inflammation and inflammatory diseases wherein, GRKs in addition to regulating receptor function can directly alter signaling pathways that uniquely respond to inflammation. In a classical sense, GRKs can non-canonically regulate signaling pathways. Such an idea has been well described for NFκB signaling pathway that plays a key role in the production of inflammatory cytokines. GRK2, GRK5 and GRK6 have been shown to interact with IκB and NFκB-p105 mediating their phosphorylation[147–154]. Interestingly, TLR ligands enhance GRK2 expression in primary macrophages[155]. Similarly, immune cells from sepsis patients exhibit higher levels of GRK2 suggesting that GRK2 levels and the associated non-canonical signaling pathways regulated by GKR2 may have potential clinical relevance in inflammatory diseases[156].

An alternative way GRKs can influence the production of inflammatory cytokines is by regulation of MAPK signaling pathways ERK, JNK and p38 MAPK[156]. Activation of ERK pathway leads to the induction of various inflammatory mediators (e.g. TNFα, IL-1, IL-8 and prostaglandin E2 (PGE2))[156]. However, GRK2 and 5 seem to negatively regulate lysophosphatidic acid (LPS)-induced ERK pathway in macrophages[149, 151] suggesting a cross-talk between these pathways that needs indepth investigation. The requirement for indepth understanding of this cross-talk is apparent from the studies showing that overexpression of GRK5 and/or GRK6 enhances β-arrestin2-mediated ERK activation, whereas overexpression of GRK2 and/or GRK3 abolished β-arrestin2-mediated ERK activation[157]. Critically, these effects were observed with activation of β2 adrenergic receptor, cannabinoid receptor 2, and Angiotensin 1A receptor thereby, suggesting connection between GPCRs and differential regulation of pro-inflammatory cytokines by GRKs[153, 158, 159].

The p38 MAP kinase pathway is also associated with inflammation. p38 MAPK mediates expression of many genes involved in inflammation, such as TNFα, IL-1β, IL-6, IL-8[160]. Inhibition of p38 MAPK reduced pro-inflammatory cytokine production[161] and in that context, GRK2 and p38 MAPK have bidirectional functional roles. GRK2 inhibits p38

MAPK function by directly phosphorylating it and modulating levels of GRK2 expression in turn alters p38 MAPK activation and subsequent cytokines production[162]. Also, activation of p38 MAPK inhibits GRK2-mediated GPCR desensitization by directly phosphorylating GRK2 which blocks GRK2 translocation to the membrane[163]. Consistent with this role, $GRK2^{+/-}$ hemizygous macrophages have increased p38 MAPK activation[162, 164]. In addition, p38 MAPK inhibits GRK2-mediated desensitization by acting as a non-canonical GRK for the Formyl Peptide Receptor 1 (FPR1)[163].

Similarly, JNK, another MAPK member is also activated by mitogens as well as by a variety of environmental stresses and they induce transcription of AP-1, c-Jun, ATF-2, and ELK-1, all of which are important mediators of inflammatory gene transcription[165]. JNK activation of AP-1 is important for synthesis of TNFα, as well as proliferation and differentiation of lymphocytes and hence plays a vital role in immune system[166, 167]. Role of GRKs in JNK signaling, particularly related to the immune system, is not well characterized. However, studies with transgenic mice overexpressing cardiac specific GRK5 showed attenuation of JNK activation compared to controls[168]. These observations suggest that more studies are needed to determine the non-canonical cross-regulation of MAPKs by GRKs which could have significant implications as GRKs can regulate immune cell chemotaxis, inflammatory signaling and cell apoptotic pathways. Dysregulation of any one these functions will have greater impact in altering the course of many diseases. A number of studies have examined and established the role of specific GRKs in various inflammatory diseases such as neurodegenerative, autoimmune, cardiovascular diseases and sepsis[151, 152, 164, 169–204]. GRKs play numerous physiological roles and are generally involved in maintaining homeostasis. However, derangement in the processes involving GRKs often leads to pathology. Pathophysiological role of GRKs are attributed to their canonical GPCR-dependent functions such as catecholamine mediated receptor desensitization and to their non-canonical functions such as regulation of cellular signaling and inflammation. Given the nodal role GRKs could play in calibrating the receptor function as well as the inflammatory response, more comprehensive studies are needed to understand both its canonical and non-canonical functions.

GPCR-βAR activation and TNFα signaling

βAR is a proto-typical GPCR and a major regulator of cardiac contractile function[205]. βAR dysfunction is one of the classical hallmarks in heart failure. However, studies have shown that chronic activation of βARs results in induction of pro-inflammatory response in the heart. The inflammatory response profile in response to βAR activation is characterized by increased expression of TNFα, IL-1β and IL-6[206–209]. Consistent with this observation, antagonizing βARs using the β-blockers markedly reduces myocardial TNFα and IL-1β expression in the hearts[55]. Correspondingly, studies in mouse models of asthma have shown that treatment with the β-blockers attenuates inflammatory response[210] showing “quid-pro-quo” relationship between the βAR activation and induction of inflammatory response. Upregulation of TNFα, IL-1β and IL-6 in the myocardium is known to occur through the NFκB dependent mechanisms[211, 212]. Recent investigations have shown that upregulation of the inflammatory cytokines in response to β-agonist can be markedly blunted by treatment

of epidermal growth factor receptor (EGFR) blocker gefitinib[213] indicating a role for EGFR transactivation in mediating inflammatory response.

Sympathetic overdrive leads to production of inflammatory cytokines and TNFα induction is a consistent feature in various pathological conditions including obesity, rheumatoid arthritis, myocardial infarction, and kidney renal injury[30, 43, 214]. In this context, studies have shown that circulating levels of TNFα and soluble TNF receptors are independent predictors of mortality in patients with heart failure[54]. Induction of TNFα in response to sympathetic overdrive now in turn mediates cellular/physiological responses that are both beneficial acutely and deleterious chronically. TNFα that is generated in response to βAR activation is classically synthesized as a trans-membrane protein that is 26 kDa and is cleaved to 17 kDa soluble TNFα by TNFα-converting enzyme (TACE)[214, 215]. It is known that both the membrane and soluble TNFα initiate signals by binding to their receptors TNF R1 and R2. The underlying mechanism through which TNFα mediates cellular signaling and physiological effects have been detailed in multiple studies and reviews[39, 43, 214, 216, 217]. Increasing evidence has shown that downstream signaling effects mediated by TNFα are multifaceted due to differential effects that TNF R1 or R2 mediate in the cells. It is known from multiple studies that TNFR1 couples to deleterious death domain signaling pathways that mediate apoptosis[39, 218, 219]. However, it is also known that TNFR1 activation leads to NFκB activation and comprehensive studies have shown that TNFR1 can also couple to the beneficial NFκB pathway thereby “fine-tuning” the TNFα response in the cell. Such a concept is supported by the observation that TNFR1 interaction with the complex containing death domain TNFR1 protein (TRADD) and TRAF2 activates NFκB while TNFR1 interaction with TRADD-death domain containing Fas protein complex mediates apoptosis[214, 216]. In contrast to the divergent signals that can emanate from TNFR1 activation, it is understood that TNFR2 activation usually leads to beneficial signals from its interaction with TRAF2 that activates NFκB, MAPK and protein kinase B (AKT) – which are all pro-survival signals[214, 220, 221]. Given that TRAF2 is the nodal molecule that mediates the beneficial cellular signals downstream of both TNFR1 and R2, relative levels of TNFR1 and R2 expression in the tissues could determine the response to TNFα as observed in human alveolar epithelial cells[219], human heart failure[218] or renal injury[38]. However, in contrast to the idea that TRAF2 allows for beneficial signaling, high levels of myocyte-specific overexpression lead to deleterious cardiac remodeling[12] while lower levels of TRAF2 provides beneficial remodeling ischemia reperfusion injury[222]. These studies suggest that not only are the levels of TNFR1 and R2 critical in cellular responses to TNFα but also the expression levels of TRAF2 in the cells may produce counterintuitive phenotypes in pathology. This is critical given that sympathetic overdrive leading to βAR stimulation results in significant increase in TNFα. Therefore, the TNFα driven inflammatory response would be determined by the relative ratios of TNFR1 and R2 expression associated with levels of TRAF2 in various cells as βARs are universally expressed in all cell types. Corresponding to this paradigm of signaling contribution based on TNFR1 and R2 expression, βAR agonist isoproterenol treatment in the mice with TNFR2 knockout showed deleterious remodeling and worsening cardiac function compared to TNFR1 knockout and wild type littermates[223]. These findings suggest that TNFR2 signaling provides beneficial effects that counter the deleterious TNFR1-mediated signaling as

absence of TNFR2 results in increased fibrosis[223] in response to βAR agonist isoproterenol (Fig 1A).

In addition to the divergent signals that are initiated by activation of TNFR1 and R2, TNFR1 and R2 can be differentially and/or selectively activated by the ligand TNFα. The selectivity depends on whether TNFα is membrane bound or is in the soluble format. It is considered that membrane bound TNFα is the prime activating ligand for TNFR2[39, 217, 218] and is thought to primarily mediate the beneficial signals in response to TNFα. Such an idea is supported by the observation that cardiac-specific overexpression of non-cleavable TNFα leads to concentric hypertrophy while, overexpression of secreted TNFα leads to dilated cardiomyopathy[17, 18]. Furthermore, membrane bound TNFα in endothelial colony forming cells protects against senescence in inflammatory environment suggesting a key role in cell proliferation[224]. Consistently, significant reduction in apoptosis and amelioration in deleterious cardiac remodeling was observed in TNFα knockout mice ($TNF^{-/-}$) following myocardial infarction[225]. In this context, it is important to note that myocardial infarction is associated with significant upregulation of sympathetic hormones epinephrine/norepinephrine, which would elevate TNFα. Given the absence of TNFα in the $TNF\alpha^{-/-}$ mice, a major portion of the βAR agonist epinephrine mediated deleterious signals via TNFα are absent reflecting in better cardiac function and remodeling. Understanding the complexity in TNFα signaling is important as βAR-TNFα signaling axis underlies deleterious manifestation in many pathologies including cardiovascular disease. Since increase in sympathetic drive activates βAR downstream signaling, it is critical to delineate mechanistic pathways that mediate TNFα upregulation. Determination of these pathways would be key as it may provide insights into potentially novel therapeutic targets.

TNFα and βAR signaling

There is increasing appreciation that in response to increased sympathetic stimuli there is an upregulated pro-inflammatory response. However, there are circumstances wherein, activation of innate immune response occurs that is independent of sympathetic overdrive leading to release of potent cytokines like IL-1β, IL-6 and TNFα. It is known that upregulation of these cytokines is associated with pathogenesis of metabolic syndrome, airway disease such as asthma and heart failure. Both asthma and heart failure are associated with increased TNFα mRNA and protein[226] and circulating levels of TNFα[2, 29]. In this context, it is known that TNFα treatment leads to cardio-depressant effects and previous studies have identified that TNFα may mediate these effects through βARs[8, 9]. The negative inotropic function mediated by TNFα is thought to involve both immediate and delayed signaling pathways, with immediate effects through altered intracellular $Ca2+$[96], spingolipid mediators[79], and nitric oxide synthase[78]. Despite these interesting observations, the mechanistic underpinnings for the TNFα-mediated βAR dysfunction are not well understood and whether any of the classical pathways that mediate βAR dysfunction are recruited in the TNFα-driven mechanisms.

βARs are one of the most powerful regulators of cardiac contractility and lung relaxation function[205, 227]. Diminished response of βAR signaling to catecholamines (sympathetic hormones) occurs through a process defined as βAR desensitization that contributes to the

pathogenesis of heart failure and potentially to asthma exacerbation. Desensitization of βARs is mediated by phosphorylation of the C-terminal tail of the receptor by G-protein coupled receptor kinases (GRKs), protein kinase C (PKC) and protein kinase A (PKA). Among the plethora of kinases that regulate βAR phosphorylation and desensitization, GRK2 is a predominant player as inhibition of GRK2 recruitment to the βARs through a dominant negative strategy of using C-terminal of GRK2 (GRK2-Ct) results in beneficial cardiac remodeling[228]. Since GRK2 is consistently upregulated in response to pro-inflammatory cytokine TNFα in various tissues[229], we assessed whether GRK2 is upregulated in the cardiac tissues to TNFα. Our studies revealed that cardiac GRK2 is upregulated in the transgenic mice with cardiac specific overexpression of TNFα even before identification of cardiac dysfunction by echocardiography[10].

The observation of GRK2 upregulation in response to TNFα in the hearts suggested that GRK2 maybe the proximal link and the underlying mechanism for the observation of TNFα-mediated cardio-depressant effect through regulation of βAR dysfunction[8, 9, 14]. Our studies further showed that GRK2 is the key molecule involved in β2AR desensitization as cardiomyocyte specific GRK2 null mice have preserved β2AR function in response to TNFα. However, in contrast to GRK2-ct transgenic mice ameliorating cardiac dysfunction in response to transverse aortic constriction (TAC) or myocardial infraction (MI), chronic TNFα treatment resulted in cardiac dysfunction associated with βAR desensitization. These studies suggest the presence of a novel mechanism by which GRK2 can be recruited to the βAR complex to mediate phosphorylation instead of the classical G-protein beta-gamma (Gβγ) subunits [230–232]. Interestingly, our studies further showed that the recruitment of GRK2 to the βAR complex could be mediated by TNFR2 as marked reduction in GRK2 recruitment was observed in TNFR2 knock out cells[10]. Thus, TNFα-induced βAR desensitization mediated by GRK2 in conditions of heart failure is observed to be independent of Gβγ subunits[10] (Fig 1B). Correspondingly, a recent study reported elevated GRK2 and decreased β2AR expression in dendritic cell cytomembranes of adjuvant induced arthritis model[233] further supporting the view that GRK2 function is regulated under conditions of inflammation. Accordingly, treatment of lung epithelial cells with glucocorticoids (anti-inflammatory agent) resulted in significant inhibition of GRK2 expression[234]. However, the involvement of TNFR2 in GRK2 recruitment to the plasma membranes in response to TNFα is counterintuitive[10] given the beneficial role of TNFR2 signaling. A potential beneficial role that can be envisioned by this pathway could be the ability of TNFα signaling to dampen the cardiac function in the face of pre-existing sympathetic drive thus providing relief to the mechanically overloaded heart. Such a mechanism could be the integral part of the beneficial role TNFR2 could play in presence of chronic βAR agonist as absence of TNFR2 (TNFR2 knockout mice) leads to deleterious cardiac remodeling in response to β-agonist isoproterenol[11, 223] (Fig 1A). These intriguing observations indicate that more comprehensive studies are warranted to better understand the signaling axis between TNFα/TNFR2 and βAR pathways, as less is known about the adaptor molecules involved and the mechanism of TNFR2 signal transduction[235].

TNFα based therapy and clinical outcomes

Among the pro-inflammatory cytokines, TNFα is consistently elevated in majority of the chronic conditions such as inflammatory bowel disease, rheumatoid arthritis, psoriasis, asthma, and heart failure. Comprehensive studies have shown that circulating levels of TNFα and soluble TNFR could be independent predictors of heart failure[54]. Given the consistent elevation of TNFα in these pathologies, a logical idea would be to develop anti-TNFα therapies. Consistent with this idea, anti-TNFα therapies have worked and have been approved for treatment of inflammatory bowel disease, rheumatoid arthritis and psoriasis[26]. However, such therapies have been a failure in human heart failure patients as anti-TNFα resulted in time- and dose-related increase in death and heart failure hospitalization[54]. These negative clinical outcomes could be due to several reasons. Although TNFα levels are elevated in the HF, it may not be directly responsible for disease progression. Part of the complexity in the failure of anti-TNFα therapy for heart failure could be due to the inherently different and opposing signaling effects arising from the TNFR1 and TNFR2 receptors (Fig 1A). In that context, less is known about the detailed mechanism of TNFR2 signaling components and adaptor proteins, which could underlie/explain the opposing actions of TNF receptors in the heart. Furthermore, there may be several other pathways operating in congruence at the same time like pathways activated by elevated catecholamines. Another possibility is that anti-TNFα therapy is beneficial but is offset by unintended, unanticipated, and/or unrecognized mechanisms of actions, such as βAR desensitization by recruiting GRK2 to the receptor complex through non-canonical Gβγ-independent mechanisms[10] (Fig 1B). Thus, in the context of heart failure, identification and validation of the molecules that may reflect specific perturbations of cardiac β-adrenergic system due to the elevated levels of TNFα is necessary. This will help in generation of precise therapeutic targets to improve the cardiac function altered due to chronic inflammation. Moreover, the effect of circulatory TNFα and localized generation of TNFα on the regulation of cardiac function has not been delineated. Given the role of TNFR1 and R2, further studies are warranted for clearly delineating the differential recruitment and activation of signaling components following activation of TNFR1 and R2. Such an idea may hold some promise given the observation in mouse models that TNFR1 and R2 have opposing effects on activation of NFκB in conditions of heart failure[223, 236]. These findings suggest a more nuanced approach for targeting TNF pathways in heart failure is required. The methods could be based on selective antagonism/blockade of TNFR1 associated signaling pathway and activation of TNFR2 thus harnessing the beneficial spatial, temporal and molecular components of TNFα signaling.

Summary and future outlook

Although understanding differential roles of TNFα on mediating TNFR1 and R2 signaling is important, it is also important to delineate the multiple arms of cross-talk that occurs with βARs in the context of cardiac function. Determining the underlying molecular mechanism between TNFα and βARs (Fig 1)is key since βARs are universally expressed and thus may have differential cellular consequences based on the cell type as circulating levels of TNFα is elevated in pathology (Fig 2). While all the studies on understanding the paradigm of cross-talk between TNFα-βARs is focused towards kinase-mediated desensitization of

βARs, a key aspect that has not been studied in the cross-talk is the role of phosphatase-mediated resensitization of βARs. Indepth studies would be required as increasing evidence indicates that the phosphatase-driven mechanisms may not be passive homeostatic process but a tightly regulated mechanism[237, 238] contributing to the pathology. Such observations open up to the possibility that TNFα-mediated signaling mechanisms could also regulate βAR function by modulating phosphatase functions and resensitization within the paradigm of cross-talk between TNFα and βARs. Consideration of these complex layers of regulation by TNFα signaling and the dissection of beneficial versus deleterious pathways mediated by TNFRs will hold the key for developing successful therapies that may harness the benefits of the TNFα (Figs 1 & 2).

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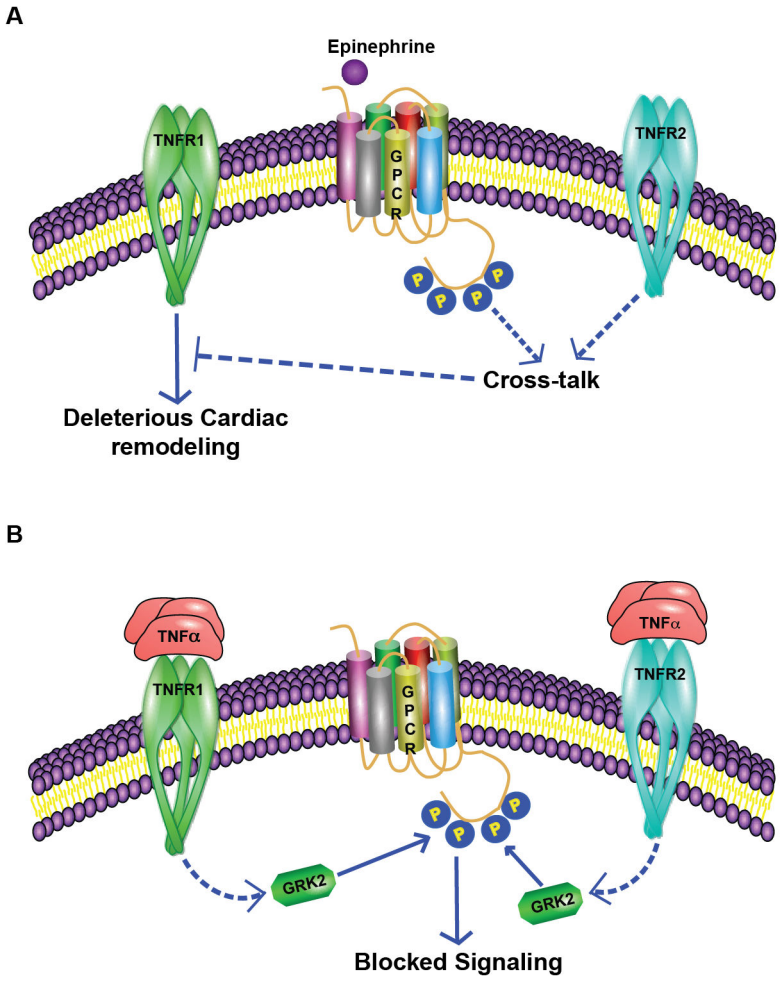

Figure 1. Intricate cross-talk between TNFα receptor signaling and βAR pathways

A, The downstream effects of TNFα are mediated by both TNFR1 and R2 receptors. In this context, chronic administration of βAR agonist isoproterenol in mice leads to cardiac remodeling which is however worse in TNFR2 knockout mice. These observations suggest that cross-talk between βAR and TNFR2 signaling acts as a brake on the deleterious signals initiated by TNFR1[11]. **B**, Correspondingly, chronic TNFα treatment results in loss of βAR response to its agonist isoproterenol. Studies have shown that TNFα is able to mediate non-canonical Gβγ-independent recruitment of GRK2 to the βAR complex mediating its phosphorylation even in the absence of βAR-agonist. Since pro-inflammatory cytokine TNFα is elevated in diabetes, hypertension, and obesity which are all cardiovascular risk factors, this unsuspected inhibition of βAR function by TNFα could underlie the cause of heart failure. βARs are one of the most powerful regulators of cardiac function and a key hallmark for heart failure is βAR dysfunction[10].

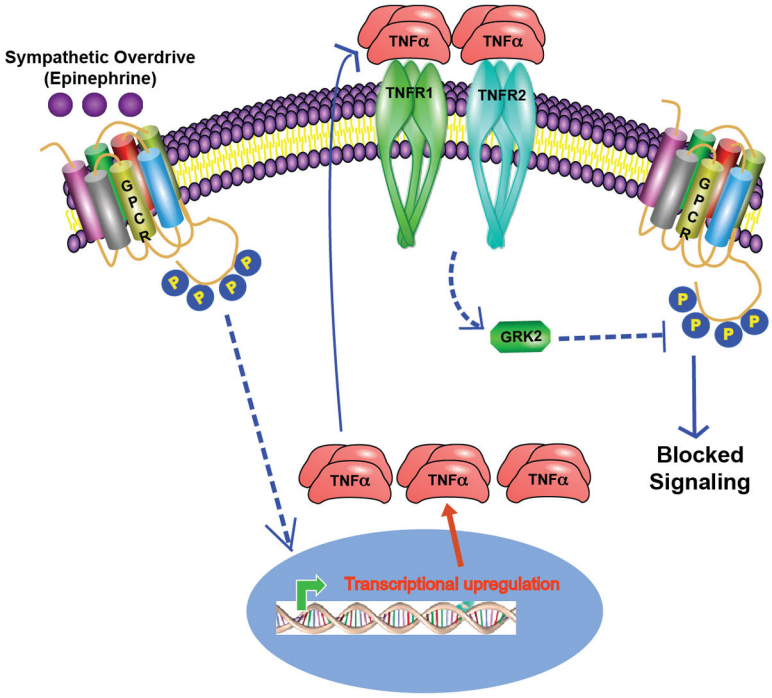

Figure 2. Sympathetic overdrive involves an active cross-talk between βAR and TNFα-mediated downstream signaling

It is known that epinephrine binding to βAR activates downstream signaling playing a role in cardiac contraction. However, it is well established that sustained sympathetic overdrive leads to deleterious cardiac dysfunction and is associated with βAR dysfunction. In addition, increasing evidence shows that sympathetic overdrive leads to generation of pro-inflammatory cytokines including TNFα. Increased TNFα would bind to TNFR1 and R2 receptors that will non-canonically recruit GRK2 to βAR complex inhibiting βAR signaling. This inhibition of βAR signaling in other words represents βAR dysfunction, a phenotype observed in conditions of heart failure. Therefore, in this context it is important to note that sympathetic overdrive in addition to directly altering βAR function could have consequences that are mediated by altering TNFα and shows an additional pathway that regulate βAR function in various cell types.