INTRODUCTION

Tumor necrosis factor (TNF) is a member of Type II membrane proteins signalling molecules which are categorized by 150 amino acids within the C-terminus and this region is used by various TNF members to recognize their associated receptors.1 Till now two isoforms of TNF have been identified both of which have same inflammatory actions, Out of which TNF-α is minor and found more abundantly in body and is identified as main peptide involved in pathophysiology of cardiomyocytes. However TNF-Beta, sometime also known as lymph toxin is less abundant and are mainly produced by T-cells.2

TNF-α receptor and signalling pathway

TNF-α once released may interacts with two type of receptors either by high affinity receptor soluble tumor necrosis factor receptor 1 (TNFR-1), or low affinity receptor (TNFR-2).3 After interaction with receptor TNF-α persuaded cross-linking of the receptors resulting into instigation of intracellular signaling pathways. However, no such significant similarities exist between the two intra cytoplasmic TNF-α receptors,4 hence these receptors may result distinct signaling pathways.5 Amount of Circulating TNF-α receptors are elevated by various pathophysiological factors comprising TNF-α, lipopolysaccharide (LPS), okadaic acid and phorbolesters.6,7 These TNFR receptor proteins appear as condensed trashes of the extracellular regions of the type 1 and type 2 membrane-bound TNF-α receptors.9 TNF receptors don’t possess intrinsic protein kinase activity within minutes of agonistic exposure. Protein kinase activity is accomplished after phosphorylation of distinct proteins by activation of various cellular kinases. Cytotoxic effects of TNF-α may be inhibited by binding of ligand to soluble receptor. Thus flaking of soluble binding proteins may aid as a “biological buffer” and can rapidly neutralize the unwanted activities of TNF-α.10

Endogenous TNF-α production by the Heart

TNF-α is an identified multi-acting cytokine with significant local homeostatic cellular effects in various tissues. It is demarcated as “autacoid” in nature which is biologically active, distinctive from neurotransmitters or hormones and can be produced locally.11 Direct evidence to demonstrate that the heart produced TNF-α endogenously was initially difficult to prove, due to the transient presence of TNF-α in tissue. This transient presence is based on the fact that its biosynthesis is largely controlled at the translational level, with the peptide then being efficiently secreted from cells.12 These limitations were finally overcome, and it has been demonstrated that TNF-α is produced in cardiac myocytes, smooth muscle cells, and endothelial cells in response to various endotoxin independently in absence of inflammatory cells as demonstrated by numerous ex vivo and in vitro cardiac studies.13, 14 In addition, subsequent...
investigational myocardial infarction and following ischemia in isolated cardiac myocytes and fibroblasts, TNF-α expression was found to be up-regulated.15-17 Obtained data reveal that the heart has an innate capacity to produce TNF-α in response to diverse pathophysiological stimuli. A question then arising is whether TNF-α is beneficial or is just a pathogenic cytokine in cardiovascular system. Exogenous TNF-α is also associated in cardiac pathology, as seen in septic shock which results in contractile dysfunction.18 Moreover, the production of TNF-α and other cytokines from enhanced bowel permeability and bacterial translocation has been hypothesized to be involved in the deterioration in cardiac function in subjects with cardiac dysfunction and concomitant bowel edema.19

**TNF-α IN NORMAL PHYSIOLOGY OF CARDIOVASCULAR SYSTEM**

**Cardiac Morphogenesis**

TNF-α significantly involves in various processes including cell differentiation, growth, and apoptosis.20 It is relevant to speculate that whether this pleiotropic cytokine is required for normal cardiac development. However, genetic ablation of the gene’s encoding TNF-α with its two cognate surface receptors and the cardiac phenotype of the TNF-α-deficient mice,21 on gross anatomical analysis, shows only minor differences in cardiac mass when compared with controls 22. Further few cardiac studies in TNFR-1 and TNFR-2 null adult mice demonstrates absence of any discernible congenital cardiac defects.23 Collectively, these studies propose that TNF-α related pathway is not a required component for normal cardiac morphogenesis however it may act as growth factor in response to physiological stimulus in developed heart, on the other hand this pathway is compensated by various alternate signaling pathways.

**Cardiac contractility**

TNF-α has concentration- and time-dependent effect on cardiac contractile with minimal threshold, superficially required to induce a negative inotropic action.24 Septic shocks and various experimental conditions upsurge threshold of TNF-α action. Beside it effects of TNF-α mimics endotoxemia, with a subsequent reduction in cardiac contractility.25 A number of studies had demonstrated the presumed mechanisms of TNF-α-induced suppression of contractile function.26 Nitric oxide (NO) is reported as major mediator of TNF-α effects on contractile function and is found to be dose dependent.27 Further NO-mediated depression of contractile function is mediated by cyclic GMP signaling.28 and via attenuation in cardiac efficiency.29 NO mediated pathway generated Peroxynitrate which is found to be the major contributor for depression in cardiac contractile function.30 Beside it TNF-α is also reported to activate sphingolipids and cyclo-oxygenase signaling cascades which ultimately again lead to depression in cardiac contractility function.31 However Chronic cardiac TNF-α production may result excessive NO-dependent apoptosis which may lead to permanent impairment of cardiac functional impairment.32, 33 Overall effects of these signaling events on contractile function demonstrate reversible and irreversible depressant effects of TNF-α - on cardiac contractile function.34, 35 Captivatingly, myocardial TNF-α production has been Reported in acute ischemic condition with or without reperfusion.36, 37 If sufficient quantity of cytokine is released TNF-α can help in reducing cardiac contractility which may act as acute adaptive response as it will reduce myocardial energy demand in the context of decreased oxygen availability. TNF-α was also reported to enhance cardiac contractile recovery if given prior to an ischemic insult in an isolated perfused heart preparation, reperfusion as compared to vehicle treated control by abrogation of inhibition of sphingolipids signaling. However, the detailed mechanism underlying this adaptive effect of TNF-α on contractile recovery remains elusive. Further documented studies reveals the concept that TNF-α may confer both adaptive and maladaptive effects on cardiac contractility in a dose- and temporal-dependent manner.

**PATHOLOGIC ROLE OF TNF-α IN CARDIOVASCULAR DISORDER**

The first recognition that TNF-α might participate in the development of congestive heart failure (CHF) came in 1990 when Levin demonstrated that circulating levels of TNF-α were elevated in patients with end stage heart failure and cachexia.38 Subsequent studies demonstrated comparable elevations in IL-6 and IL-1beta.39 Furthermore, direct relationships were identified between circulating levels of TNF-α and neurohumoral activation and the degree of anemia; however, there was no relationship between cytokine levels and the degree of cachexia.40, 41 Cytokine levels were also elevated in patients with heart failure due to myocarditis.42 That the observed increases were of physiologic significance was demonstrated by studies in which injections of endotoxin into humans resulted in TNF alpha elevations, depressed left ventricular function and decreases in mean arterial pressure.43 Parenthetically, it should be noted that the different assay techniques, for example bioassays or ELISA measurements, used by various investigators provide varying values, thus obfuscating the literature to some extent. The increase in circulating TNF-α in patients with CHF was associated with a substantial decrease in myocardial TNF-α receptors and an increase in soluble TNF-α receptors; however, the stoichiometry favoured free TNF-α. Perhaps of greatest importance was the demonstration by Mann and colleagues in 1996 that the non-failing human heart does not express TNF-α, whereas the end stage failing human heart re expresses robust amounts of protein.44

**Role of TNF-α in endothelial dysfunction**

TNF-α regulates NOS expression and/or activity, which exerts direct effects on NO production; for example, human aortic ECs treated with TNF-α for 8 h had induced iNOS mRNA expression, but down-regulated eNOS expression.45, 46 Other studies have also shown that TNF-α significantly decreased eNOS expression in ECs.47 Unlike eNOS, iNOS is transcriptionally regulated and not normally produced in most cells. iNOS-derived RNS (reactive nitrogen species) initiate an ONOO− (peroxynitrite)-mediated mechanism and therefore contribute to nitritative stress and impair endothelial function. Several mechanisms have been suggested for the induction/activation of NOS by TNF-α. Yoshizumi et al. demonstrated that TNF-α markedly reduced mRNA levels of eNOS in HUVECs (human umbilical vein ECs) in a dose- and time-dependent manner without changing the rate of eNOS gene transcription.48 TNF-α appears to decrease eNOS mRNA levels by increasing the rate of mRNA degradation. Another study, however, suggested that TNF-α increases eNOS activity in HUVECs.49 Activation of eNOS by TNF-α requires activation of Akt (protein kinase B), a known eNOS activator, via Sph1P (sphingosine-1-phosphate) receptor activation. Sph1P receptor is activated by Sph1P, a sphingolipid involved in proliferation, survival, migration and differentiation of these cells, generated through N-Smae2 (neutral sphingomyelinate 2) and SK1 (sphingosine kinase 1) activation. TNF-α-mediated
Activation of eNOS is accompanied by increased NO generation, which exerts protective effects on DC (dendritic cell) adherence to endothelium induced by TNF-α itself. It has also been suggested that TNF-α may increase iNOS expression by activating NF-κB (nuclear factor κB).50 TNF-α-induced iNOS mRNA expression in microvascular ECs could be decreased by ruopecoll (a dicatetechol from the South African plant Hynopis rupestris) administration, which is an anti-inflammatory agent in the treatment of several inflammatory disorders.51 In HUVECs, the effect of TNF-α on iNOS expression was not affected by statin treatment, whereas reduced eNOS expression was reversed by rosuvastatin and ceruvastatin by inhibiting HMGCoA (3-hydroxy-3-methylglutaryl-CoA) reductase and subsequent blocking of isoprenoid synthesis.52 Evidence suggests that TNF-α impairs endothelium dependent and NO-mediated vasodilation in various vascular beds, e.g. mouse coronary arterioles53, rat coronary arterioles cat carotic arteries and bovine small coronary arteries Picchi et al. demonstrated that endothelial dysfunction in prediabetic metabolic syndrome is a result of the effects of TNF-α and the subsequent production of O2− (superoxide radical).54-56

Role in cardiac hypertrophy

TNF-α expression and peptide production are up-regulated in the adult heart in response to pressure overload and in response to stretch in isolated cardiac myocytes.57 These hemodynamic loads elicit cardiomyocyte hypertrophy and extracellular matrix remodeling as phenotypic alterations that are thought to be adaptive responses in order to maintain normal cardiac contractility and homeostasis. In support of the requirement of TNF-α in hypertrophic adaptive cardiac growth, it was shown that mice deficient in TNF-α have a significantly reduced right ventricular hypertrophic response to chronic hypoxia compared with wild type littermate controls. These studies strongly suggest that TNF-α binding to its cognate receptor and the subsequent activation of the downstream signalling cascade play a role in the postnatal adaptive myocardial growth response to multiple biomechanical stresses. The signaling pathways downstream of TNF-α that direct this hypertrophic growth have not been extensively explored to date. However, in neonatal cardiac myocytes, a role for reactive oxygen species in TNF-α-mediated hypertrophic growth has been described.58 TNF-α has also been shown to up-regulate angiotensin II Type 1 receptors in cardiac fibroblasts,59 and an interaction between TNF-α and the renin–angiotensin pathway in cardiac hypertrophic growth probably warrants investigation. NF-κB, in turn, has been shown to be an important nuclear regulatory peptide in cardiac hypertrophy in cardiac myocytes.60 The experimental role of TNF-α in cardiac hypertrophy has been supported in human studies where cardiac TNF-α levels were measured in subjects with inherited hypertrophic cardiomyopathy (HCM) and compared with non-hypertrophic control subjects. The HCM subjects had a significantly higher level of TNF-α on right ventricular biopsy samples compared with control subjects. Moreover, following nonsurgical septal reduction.

Role of TNF-α in Heart failure:

Scientist also found strong association between circulating level of TNF-α and the degree of heart failure.62 In heart failure, the biosynthesis of TNF-α has been postulated to arise from endogenous cardiac production in response to biomechanical stress, including stretch, ischemia, and immune activation, and putatively from extraneous sources, such as from endotoxin exposure from bowel edema, from liver congestion, and from neurohumoral activation of adipolysis.63 Multiple experimental studies in the last decade have now demonstrated that TNF-α can induce multiple components of the heart failure phenotype, including left ventricular dilatation and dysfunction. These data support the concept that the production of this cytokine may contribute to the pathogenesis of progressive heart failure, and, therefore, would be a feasible therapeutic target in the management of heart failure. Interestingly due to the accumulating evidence associating TNF-α and other cytokine levels with prognosis in heart failure.64 The concept of the activation of a portfolio of cytokines in a similar way to activate the neurohormonal system in heart failure has been proposed.65 Thus data presented suggest that activation of TNF-α signaling may have divergent effects on cardiac Pathophysiology.

TNF-α in Cardiac ischemic syndromes:

Myocardial TNF-α production has been well documented during acute myocardial ischemia with or without reperfusion. In an experimental study, TNF-α is thought to mediate cardioprotection via an enhancement of innate myocardial tolerance to ischemia. This was demonstrated where mice deficient in both TNF-α cell surface receptors developed larger myocardial infarcts compared with wild-type littermate controls, following an acute myocardial infarction.66 TNF-α may promote an intrinsic cell survival programme in response to ischemia and that this protective effect is abrogated by the inflammatory cascade induced by TNF-α during reperfusion. As with the experimental data in myocarditis, the divergent effects of TNF-α in ischemia/reperfusion probably are dependent on the absolute levels within the distinct temporal periods of ischemia and reperfusion. A biologic concept called preconditioning has been described where a transient non-lethal ischemic ‘trigger’ or endogenous molecules produced/released by ischemia enables the tissue to become more resistant/tolerant to subsequent ischemic injury. Such ischemic preconditioning is apparent within minutes, and lasts for 2–3 hr. A second phase of delayed preconditioning reappears 12–24 hr later, and lasts for 3–4 days.67 Interestingly, in classic ischemic preconditioning, the initial ischemic trigger or administration of the endogenous preconditioning mimetic adenosine has been shown to attenuate subsequent ischemia-mediated TNF-α production.68 These experiments suggest that a component of the preconditioning trigger modulates subsequent ischemia/reperfusion induced TNF-α production. Hypothetically, a preconditioning trigger may maintain TNF-α within adaptive physiologic levels that could putatively promote innate cell survival, as opposed to exacerbating reperfusion inflammation. This hypothesis, if proven, may support the concept that transient production of physiologic amounts of TNF-α may promote innate cellular survival pathways. The role of TNF-α in delayed preconditioning has been more firmly established. A role of TNF-α in delayed preconditioning has now been confirmed by numerous investigators.69 Interestingly, TNF-α-mediated up-regulation of MnSOD is thought to be in part via transactivation of NF-κB.70 Interestingly, the activation of NF-κB is thought to be essential in the activation of the late preconditioning programme.

Role of TNF-α in Myocarditis

TNF-α is thought to play an integral role in the inflammatory reaction present in myocarditis.71 Robust over expression of this cytokine in the absence of microbiologic pathogens has been shown to result in lethal myocarditis in mice. Less abundant expression of TNF-α, again in the murine model, results in a lymphohistocytic interstitial inflammatory infiltrate, with progressive heart failure. In humans with
myocarditis, TNF-α mRNA expression levels correlated positively with left ventricular volumes and inversely with left ventricular systolic function. Together, these data support an adverse effect of TNF-α in myocarditis, and this is consistent with the proposed roles of TNF-α in activating endothelial cells, recruiting inflammatory cells, enhancing inflammatory cytokine production, and inducing negative inotropic effects. In contrast to these disease-enhancing effects, TNF-α is thought to be important in host-defence against microorganisms, a probable advantageous effect of this cytokine in response to microbial-induced myocarditis. The requirement of TNF-α in the immunological defence against myocarditis was demonstrated recently in TNF-α-deficient mice exposed to encephalomyocarditis virus. The TNF-α-deficient mice developed severe myocarditis with 100% mortality within 14 days. In contrast, 67% of the wild-type control mice were alive at 14 days. The requirement of TNF-α was confirmed by rescuing the TNF-α-deficient mice by treatment of these mice with recombinant TNF-α prior to inoculation with the viral infection. Clinically, immunosuppression with agents such as prednisone, cyclosporin, and immunoglobulin's has had disappointing results in randomized clinical studies of patients with acute myocarditis. No clinical trials directly suppressing TNF-α have been reported. However, numerous experimental studies in animals do suggest that this line of therapy may have beneficial effects, only if administered prior to the introduction of the pathogenic insult.

**Role of TNF-α in Atherosclerosis**

The association of inflammation with atherosclerosis is now fairly well established, and the expression of pro-inflammatory cytokines such as TNF-α have been identified throughout the full spectrum of atherosclerotic development. In fact, in humans, TNF-α has been identified in the endothelial and smooth muscle cells from the early intimal thickening stage of atherosclerosis to subjects with established occlusive atherosclerosis. Recent evidence suggests that the deposition of low-density lipoprotein cholesterol itself in vascular tissue promotes the production of TNF-α. Putative roles for TNF-α in atherosclerosis include recruitment of inflammatory cells, promotion of vascular smooth muscle cell adverse remodeling and as a pro-inflammatory factor in plaque rupture itself. No direct studies have been performed to establish whether anti-TNF-α therapy does modulate atherosclerosis, and there is little evidence to support the use of anti-inflammatory agents as anti-atherosclerotic agents. However, indirect evidence is promising where the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin reduced monocyte expression of TNF-α levels by 49% in hypercholesterolemic patients compared with patients on diet alone. These data support the clinical studies that suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy may have protective effects against coronary events independent of those achieved with cholesterol reduction alone. In a pilot study, subjects with coronary artery disease, when treated with irbesartan (angiotensin II Type 1 receptor antagonist), demonstrated a reduction in TNF-α levels. Finally, experimental evidence suggests that the new insulin-sensitizing agent troglitazone, via its ability to inhibit TNF-α-mediated upregulation of monocyte chemo attractant protein-1, may have anti-atherosclerotic effects. Summarized role of TNF-α is shown in Fig. 1.

![Pathophysiologic role of TNF-α in cardiovascular system](image-url)
CONCLUSION

TNF-α may be involved in both physiology and pathological state of cardiovascular system but the concentration of TNF-alpha play important role in these state. As in case of pathogenic stimuli like exercise, swimming etc., TNF-α is released in controlled and self-limited manner but in case of pathologic stimuli like pressure overload as in hypertension patient there is robust and chronic production of TNF-α which further cause various cardiovascular disorder like hypertrophy, heart failure, myocarditis etc. So from whole reviewed literature it is concluded that TNF-α is beneficial in physiology of heart but concentration required is very low so its absence didn’t attenuate physiology but in case of pathologic condition it is one of the major mediator of inflammation and other pathologic effects like remodeling, hypertrophy, endothelial dysfunction, atherosclerosis. So TNF-α may be pathogenic cytokine which has both preventive and harmful.

CONFLICT OF INTEREST

None

REFERENCES


