Available online on 15.01.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

TNF-α: A Benificial or Harmful Pathogenic Cytokine in Cardiovascular System

Sunny Dhiman*, Inder Kumar, Priyankul Palia, Shalini Jamwal, Pankaj Kumar

School of Pharmacy Abhilashi University Mandi H.P India

Article Info:

Article History:

Received 28 Oct 2020;
Review Completed 25 Dec 2020
Accepted 06 Jan 2021;
Available online 15 Jan 2021

Cite this article as:

Dhiman S, Kumar I, Palia P, Jamwal S, Kumar P, TNF-α, A Benificial or Harmful Pathogenic Cytokine in Cardiovascular System, Journal of Drug Delivery and Therapeutics. 2021; 11(1):114-120
DOI: http://dx.doi.org/10.22270/jddt.v11i1.4507

Abstract

Tumor necrosis factor (TNF- alpha) plays important role in pathophysiology of cardiovascular system and had been comprehensively studied over the last 20 years. These studies demonstrate both Detrimental and potentially conflicting roles of TNF-α in pathophysiology of heart. Beneficial effects of TNF-α includes cardioprotective action against ischemia, myocarditis, pressure overload and preventive action against potential adverse effects including development of atherosclerosis, reperfusion injury, hypertrophy, and heart failure. However, TNF-α is still controversial for its beneficial or harmful effects for cardiovascular system. This review includes evaluation of possible role of TNF-α in cardiovascular system specifically in pathophysiology and morphology of cardiomyocytes. Further this article mainly emphases on the claimed role of TNF-α pathways with concerning essential cardiac cellular processes which may have unswerving adaptive effects in the heart with respect to future research directions.

Keywords: Tumor Necrosis Factor, Hypertrophy, Pathophysiology, Cytokine, Pathology, Cardiovascular System.

*Address for Correspondence:

Sunny Dhiman, School of Pharmacy Abhilashi University Mandi H.P India

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 has 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, 4] 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 intracytoplasmic TNF-α receptors,[5] hence these receptors may result distinct signaling pathways.[6] Amount of Circulating TNF-α receptors are elevated by various pathophysiological factors comprising TNF-α , lipopolysaccharide (LPS), okadaic acid and phorbol esters.[7, 8] 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 cell 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 Generates Peroxinitrate 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 ischemia-induced TNF-α is released it 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-αmight 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-αand 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 nitrative 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 cNOS in HUVECs (human umbilical vein ECs) in a dose- and time-dependent manner without changing the rate of cNOS gene transcription.[48] TNF-α appears to decrease cNOS 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-SMase2 (neutral sphingomyelinase 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) adhesion 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 rooperol (a dicatechol from the South African plant Hypoxis rooperi) 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 arterioles[53], rat coronary arterioles cat carotid 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-kB, 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. [61] 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 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-a 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-kB.[70] Interestingly, the activation of NF-kB 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 lymphohistiocytic 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.[72] 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.[73] The requirement of TNF-α in the immunological defence against myocarditis was demonstrated recently in TNF-α -deficient mice exposed to encephalomyocarditis virus.[74] 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.[75]

Role of TNF-α in Atherosclerosis

The association of inflammation with atherosclerosis is now fairly well established,[76] 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.[77] Recent evidence suggests that the deposition of low-density lipoprotein cholesterol itself in vascular tissue promotes the production of TNF-α .[78] 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.[79] 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.[80] 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.[81] 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.

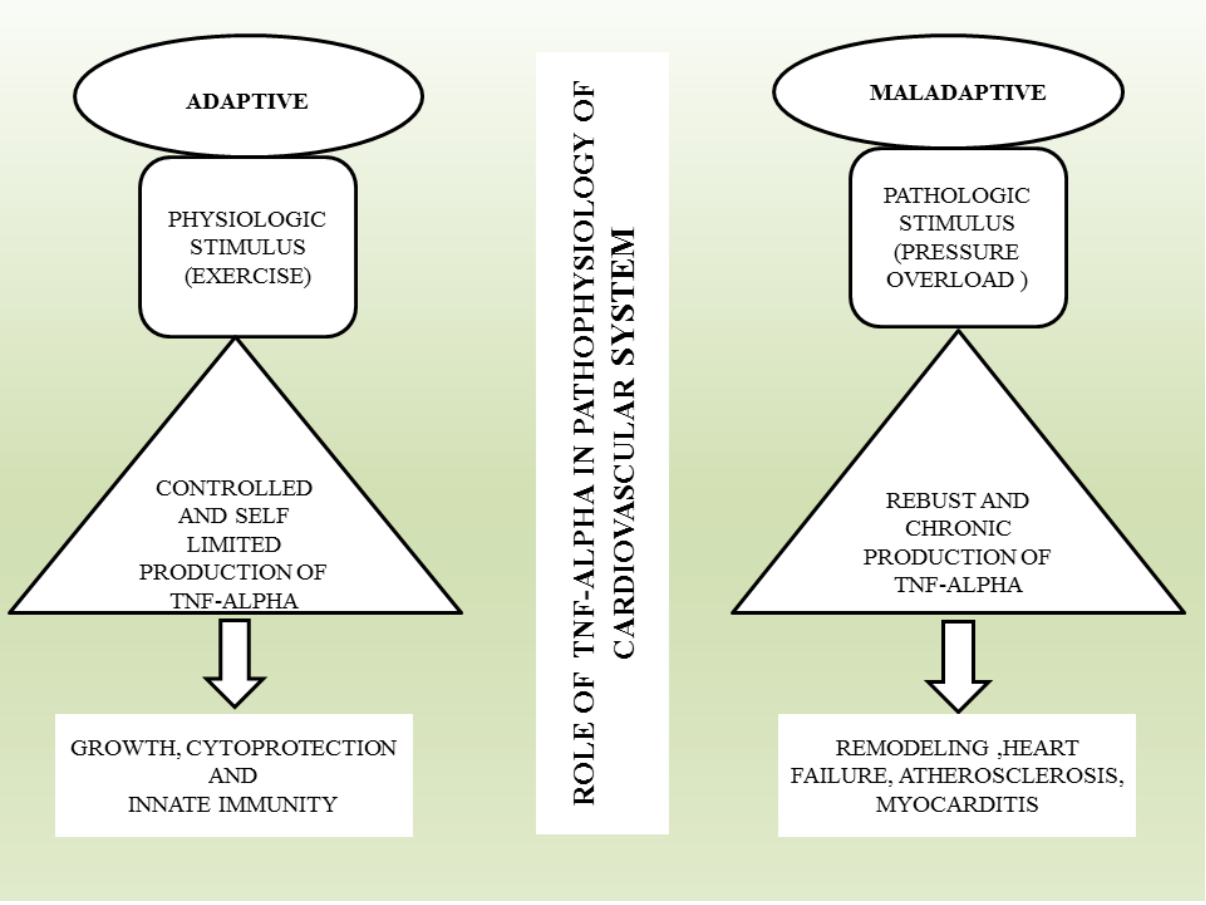

Figure1: Pathophysiological role of TNF-αin cardiovascular system

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 physiologic 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 rebust 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 pathological condition it is one of the major mediator of inflammation and other pathological effects like remodeling, hypertrophy, endothelial dysfunction, atherosclerosis. So TNF-α can be pathogenic cytokine which has both preventive and harmful.

CONFLICT OF INTEREST

None

REFERENCES

1. Lee SY, Choi Y. TRAF1 and its biological functions. TNF Receptor Associated Factors (TRAFs): Springer; 2007. p. 25-31.
2. Ruddle NH. Lymphotoxin and TNF: how it all began—a tribute to the travelers. Cytokine & growth factor reviews. 2014; 25(2):83-9.
3. Vujanovic NL. Role of TNF superfamily ligands in innate immunity. Immunologic research. 2011; 50(2-3):159-74.
4. Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases: clinical and genetic advances. Archives of dermatology. 2008; 144(3):392-402.
5. Kumar S. Apoptosis: biology and mechanisms: Springer Science & Business Media; 2013.
6. Petkova-Kirova PS, Gursoy E, Mehdi H, McTiernan CF, London B, Salama G. Electrical remodeling of cardiac myocytes from mice with heart failure due to the overexpression of tumor necrosis factor-α. American Journal of Physiology-Heart and Circulatory Physiology. 2006; 290(5):H2098-H107.
7. Zhang S, He H, Day AJ, Tseng SC. Constitutive expression of inter-α-inhibitor (IαI) family proteins and tumor necrosis factor-stimulated gene-6 (TSG-6) by human amniotic membrane epithelial and stromal cells supporting formation of the heavy chain-hyaluronan (HC-HA) complex. Journal of biological chemistry. 2012; 287(15):12433-44.
8. Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. Journal of neuroimmune pharmacology. 2012; 7(1):42-59.
9. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. New England Journal of Medicine. 2013; 369(8):754-62.
10. Chu W-M. Tumor necrosis factor. Cancer letters. 2013; 328(2):222-5.
11. Shabbir A, Batool SA, Basheer MI, Shahzad M, Sultana K, Tareen RB, et al. Ziziphora clinopodioides ameliorated rheumatoid arthritis and inflammatory paw edema in different models of acute and chronic inflammation. Biomedicine & Pharmacotherapy. 2018; 97:1710-21.
12. MYERS MJ, MURTAUGH MP. Biology of Ttomor Necrosis Factor. Cytokines in animal health and disease. 2020.
13. Kao Y-H, Chen Y-C, Cheng C-C, Lee T-I, Chen Y-J, Chen S-A. Tumor necrosis factor-α decreases sarcoplasmic reticulum Ca2+-ATPase expressions via the promoter methylation in cardiomyocytes. Critical care medicine. 2010; 38(1):217-22.
14. Zhang Z, Zhu L, Feng P, Tan Y, Zhang B, Gao E, et al. C1q/tumor necrosis factor-related protein-3-engineered mesenchymal stromal cells attenuate cardiac impairment in mice with myocardial infarction. Cell death & disease. 2019; 10(7):1-15.
15. Cabrera-Fuentes HA, Ruiz-Meana M, Simsekyilmaz S, Kostin S, Inserte J, Saffarzadeh M, et al. RNase1 prevents the damaging interplay between extracellular RNA and tumour necrosis factor-α in cardiac ischaemia/reperfusion injury. Thrombosis & Haemostasis. 2014; 112(6):1110-9.
16. Selvasandran K, Makhoul G, Jaiswal PK, Jurakhan R, Li L, Ridwan K, et al. A tumor necrosis factor-α and hypoxia-induced secretome therapy for myocardial repair. The Annals of thoracic surgery. 2018; 105(3):715-23.
17. Li J, Xie C, Zhuang J, Li H, Yao Y, Shao C, et al. Resveratrol attenuates inflammation in the rat heart subjected to ischemia-reperfusion: Role of the TLR4/NF-κB signaling pathway. Molecular medicine reports. 2015; 11(2):1120-6.
18. King EG, Bauzá GJ, Mella JR, Remick DG. Pathophysiologic mechanisms in septic shock. Laboratory investigation. 2014; 94(1):4-12.
19. Sandek A, Bjarnason I, Volk H-D, Crane R, Meddings JB, Niebauer J, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. International journal of cardiology. 2012; 157(1):80-5.
20. Zhou M, Liu L, Wang W, Han J, Ren H, Zheng Q, et al. Role of licochalcone C in cardioprotection against ischemia/reperfusion injury of isolated rat heart via antioxidant, anti-inflammatory, and anti-apoptotic activities. Life sciences. 2015; 132:27-33.
21. Olleros ML, Chavez-Galan L, Segueni N, Bourigault ML, Vesin D, Kruglov AA, et al. Control of mycobacterial infections in mice expressing human tumor necrosis factor (TNF) but not mouse TNF. Infection and Immunity. 2015; 83(9):3612-23.
22. Pena E, Brito J, El Alam S, Siques P. Oxidative Stress, Kinase Activity and Inflammatory Implications in Right Ventricular Hypertrophy and Heart Failure under Hypobaric Hypoxia. International Journal of Molecular Sciences. 2020; 21(17):6421.
23. Burchfield JS, Dong J-W, Sakata Y, Gao F, Tzeng H-P, Topkara VK, et al. The Cytoprotective Effects of Tumor Necrosis Factor Are Conveyed Through Tumor Necrosis Factor Receptor–Associated Factor 2 in the Heart. Circulation: Heart Failure. 2010; 3(1):157-64.
24. Schumacher SM, Prasad SVN. Tumor necrosis factor-α in heart failure: an updated review. Current cardiology reports. 2018; 20(11):117.
25. Yang F-L, Subeq Y-M, Chiu Y-H, Lee R-P, Lee C-J, Hsu B-G. Recombinant human erythropoietin reduces rhabdomyolysis-induced acute renal failure in rats. Injury. 2012; 43(3):367-73.
26. Yin J, Tu C, Zhao J, Ou D, Chen G, Liu Y, et al. Exogenous hydrogen sulfide protects against global cerebral ischemia/reperfusion injury via its anti-oxidative, anti-inflammatory and anti-apoptotic effects in rats. Brain research. 2013;1491:188-96.
27. Zhai J, Guo Y. Paeoniflorin attenuates cardiac dysfunction in endotoxemic mice via the inhibition of nuclear factor-κB. Biomedicine & Pharmacotherapy. 2016; 80:200-6.
28. Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. Journal of intensive care. 2016; 4(1):1-10.
29. Hedayat M, Mahmoudi MJ, Rose NR, Rezaei N. Proinflammatory cytokines in heart failure: double-edged swords. Heart failure reviews. 2010; 15(6):543-62.
30. Du L, Dronadula N, Tanaka S, Dichek DA. Helper-dependent adenoviral vector achieves prolonged, stable expression of interleukin-10 in rabbit carotid arteries but does not limit early atherogenesis. Human gene therapy. 2011; 22(8):959-68.
31. An J, Du J, Wei N, Guan T, Camara AK, Shi Y. Differential sensitivity to LPS-induced myocardial dysfunction in the isolated Brown Norway and Dahl S rat hearts: roles of mitochondrial function, NFκB activation and TNF-α production. Shock (Augusta, Ga). 2012; 37(3):325.
32. Lind M, Hayes A, Caprnda M, Petrovic D, Rodrigo L, Kruzliak P, et al. Inducible nitric oxide synthase: good or bad? Biomedicine & Pharmacotherapy. 2017; 93:370-5.
33. Lee J-Y, Kim JH, Chae G, Lee B-K, Ha K-S, Kwon Y-G, et al. Cyclic AMP prolongs graft survival by suppressing apoptosis and inflammatory gene expression in acute cardiac allograft rejection. Experimental & molecular medicine. 2010; 42(1):69-79.
34. Torzewski M, Wenzel P, Kleinert H, Becker C, El-Masri J, Wiese E, et al. Chronic inflammatory cardiomyopathy of interferon γ–overexpressing transgenic mice Is mediated by tumor necrosis factor-α. The American journal of pathology. 2012; 180(1):73-81.
35. Razazi K, Boissier F, Surenaud M, Bedet A, Seemann A, Carteaux G, et al. A multiplex analysis of sepsis mediators during human

septic shock: A preliminary study on myocardial depression and organ failures. Annals of intensive care. 2019; 9(1):64.
36. Zhang Y, Cao Y, Xin L, Gao N, Liu B. Association between rs1800629 polymorphism in tumor necrosis factor-α gene and dilated cardiomyopathy susceptibility: Evidence from case–control studies. Medicine. 2018; 97(50).
37. Hu H, Zhai C, Qian G, Gu A, Liu J, Ying F, et al. Protective effects of tanshinone IIA on myocardial ischemia reperfusion injury by reducing oxidative stress, HMGB1 expression, and inflammatory reaction. Pharmaceutical biology. 2015; 53(12):1752-8.
38. Lecour S, Minners J, Rochette L, Opie L, Sack M, editors. Tumor necrosis factor alpha confers cardiac preconditioning: Possible role of mitochondrial K-ATP channel mediated event. Circulation; 1999: LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
39. Tomé-Carneiro J, Larrosa M, Yáñez-Gascón MJ, Dávalos A, Gil-Zamorano J, Gonzálvez M, et al. One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacological research. 2013; 72:69-82.
40. Hori M, Yamaguchi O. Is tumor necrosis factor-α friend or foe for chronic heart failure? Circulation research. 2013; 113(5):492-4.
41. Askevold ET, Gullestad L, Dahl CP, Yndestad A, Ueland T, Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Current heart failure reports. 2014; 11(2):146-55.
42. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. Circulation research. 2019; 124(11):1568-83.
43. Charbonney E, Tsang JY, Li Y, Klein D, Duque P, Romaschin A, et al. Endotoxemia following multiple trauma: risk factors and prognostic implications. Critical Care Medicine. 2016; 44(2):335-41.
44. Putko BN, Wang Z, Lo J, Anderson T, Becher H, Dyck JR, et al. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: evidence for a divergence in pathophysiology. PloS one. 2014; 9(6):e99495.
45. Nagpure B, Bian J-S. Interaction of hydrogen sulfide with nitric oxide in the cardiovascular system. Oxidative medicine and cellular longevity. 2016; 2016.
46. Ghebre YT, Yakubov E, Wong WT, Krishnamurthy P, Sayed N, Sikora AG, et al. Vascular aging: implications for cardiovascular disease and therapy. Translational medicine (Sunnyvale, Calif). 2016; 6(4).
47. Yamagata K, Suzuki S, Tagami M. Docosahexaenoic acid prevented tumor necrosis factor alpha-induced endothelial dysfunction and senescence. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2016; 104:11-8.
48. Yoshizumi M, Perrella MA, Burnett Jr J, Lee M-E. Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. Circulation research. 1993; 73(1):205-9.
49. Liang J, Nagahashi M, Kim EY, Harikumar KB, Yamada A, Huang W-C, et al. Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. Cancer cell. 2013; 23(1):107-20.
50. Zhang J, Wu G, Dai H. The matricellular protein CCN1 regulates TNF-α induced vascular endothelial cell apoptosis. Cell biology international. 2016; 40(1):1-6.
51. Li J, Hao J. Treatment of neurodegenerative diseases with bioactive components of Tripterygium wilfordii. The American Journal of Chinese Medicine. 2019; 47(04):769-85.
52. Panth N, Paudel KR, Parajuli K. Reactive oxygen species: a key hallmark of cardiovascular disease. Advances in medicine. 2016; 2016.
53. Carreras A, Zhang SX, Peris E, Qiao Z, Gileles-Hillel A, Li RC, et al. Chronic sleep fragmentation induces endothelial dysfunction and structural vascular changes in mice. Sleep. 2014; 37(11):1817-24.
54. Picchi A, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM, et al. Tumor necrosis factor-α induces endothelial dysfunction in the prediabetic metabolic syndrome. Circulation research. 2006;99(1):69-77.
55. Aoki N, Siegfried M, Lefer AM. Anti-EDRF effect of tumor necrosis factor in isolated, perfused cat carotid arteries. American Journal of Physiology-Heart and Circulatory Physiology. 1989; 256(5):H1509-H12.
56. Ahmad M, Zhang Y, Zhang Y, Papharalambus C, Alexander RW. Role of isoprenylcysteine carboxyl methyltransferase in tumor necrosis factor-α stimulation of expression of vascular cell adhesion molecule-1 in endothelial cells. Arteriosclerosis, thrombosis, and vascular biology. 2002; 22(5):759-64.
57. Wu Y, Qin C, Lu X, Marchiori J, Feng Q. North American ginseng inhibits myocardial NOX2-ERK1/2 signaling and tumor necrosis factor-α expression in endotoxemia. Pharmacological research. 2016; 111:217-25.
58. Han J, Zou C, Mei L, Zhang Y, Qian Y, You S, et al. MD2 mediates angiotensin II-induced cardiac inflammation and remodeling via directly binding to Ang II and activating TLR4/NF-κB signaling pathway. Basic research in cardiology. 2017; 112(1):9.
59. Siddesha JM, Valente AJ, Sakamuri SS, Yoshida T, Gardner JD, Somanna N, et al. Angiotensin II stimulates cardiac fibroblast migration via the differential regulation of matrixins and RECK. Journal of molecular and cellular cardiology. 2013; 65:9-18.
60. Zou J, Li H, Chen X, Zeng S, Ye J, Zhou C, et al. C/EBPβ knockdown protects cardiomyocytes from hypertrophy via inhibition of p65-NFκB. Molecular and cellular endocrinology. 2014; 390(1-2):18-25.
61. Tang F, Lu M, Yu L, Wang Q, Mei M, Xu C, et al. Inhibition of TNF-α–mediated NF-κB Activation by Ginsenoside Rg1 Contributes the Attenuation of Cardiac Hypertrophy Induced by Abdominal Aorta Coarctation. Journal of Cardiovascular Pharmacology. 2016; 68(4):257-64.
62. Papathanasiou S, Rickelt S, Soriano ME, Schips TG, Maier HJ, Davos CH, et al. Tumor necrosis factor-α confers cardioprotection through ectopic expression of keratins K8 and K18. Nature medicine. 2015; 21(9):1076.
63. Lubrano V, Balzan S. Consolidated and emerging inflammatory markers in coronary artery disease. World journal of experimental medicine. 2015; 5(1):21.
64. Eskandari V, Amirzargar A, Mahmoudi M, Rahnemoon Z, Rahmani F, Sadati S, et al. Gene expression and levels of IL-6 and TNFα in PBMCs correlate with severity and functional class in patients with chronic heart failure. Irish Journal of Medical Science (1971-). 2018; 187(2):359-68.
65. Gullestad L, Ueland T, Vinge LE, Finsen A, Yndestad A, Aukrust P. Inflammatory cytokines in heart failure: mediators and markers. Cardiology. 2012; 122(1):23-35.
66. Prabhu SD, Frangogiannis NG. The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circulation research. 2016; 119(1):91-112.
67. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. The Lancet. 2013; 381(9861):166-75.
68. Gedik N, Maciel L, Schulte C, Skyschally A, Heusch G, Kleinbongard P. Cardiomyocyte mitochondria as targets of humoral factors released by remote ischemic preconditioning. Archives of medical science: AMS. 2017; 13(2):448.
69. Robertson FP, Fuller BJ, Davidson BR. An evaluation of ischaemic preconditioning as a method of reducing ischaemia reperfusion injury in liver surgery and transplantation. Journal of clinical medicine. 2017; 6(7):69.
70. Thirupathi A, De Souza CT. Multi-regulatory network of ROS: the interconnection of ROS, PGC-1 alpha, and AMPK-SIRT1 during exercise. Journal of physiology and biochemistry. 2017; 73(4):487-94.
71. Chemaly M, McGilligan V, Gibson M, Clauss M, Watterson S, Alexander HD, et al. Role of tumour necrosis factor alpha converting enzyme (TACE/ADAM17) and associated proteins in coronary artery disease and cardiac events. Archives of Cardiovascular Diseases. 2017; 110(12):700-11.
72. Philip J, Xu Z, Bowles NE, Vallejo JG. Cardiac-specific overexpression of melanoma differentiation–associated gene-5 protects mice from lethal viral myocarditis. Circulation: Heart Failure. 2013; 6(2):326-34.
73. Benjamin MM, Khalil RA. Matrix metalloproteinase inhibitors as investigative tools in the pathogenesis and management of vascular disease. Matrix metalloproteinase inhibitors: Springer; 2012. p. 209-79.
74. Wang D, Li T, Cui H, Zhang Y. Analysis of the indicating value of cardiac troponin i, tumor necrosis factor-α, interleukin-18, Mir-

1 and Mir-146b for viral myocarditis among children. Cellular Physiology and Biochemistry. 2016; 40(6):1325-33.
75. Zhang Y, Zhao J, Lau WB, Jiao L-Y, Liu B, Yuan Y, et al. Tumor necrosis factor-α and lymphotoxin-α mediate myocardial ischemic injury via TNF receptor 1, but are cardioprotective when activating TNF receptor 2. PloS one. 2013; 8(5):e60227.
76. Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. New England Journal of Medicine. 2015; 372(21):2039-48.
77. Skjøt-Arkil H, Barascuk N, Larsen L, Dziegiel M, Henriksen K, Karsdal MA. Tumor Necrosis Factor-Alpha and Receptor Activator of Nuclear Factor-κB Ligand Augment Human Macrophage Foam-Cell Destruction of Extracellular Matrix Through Protease-Mediated Processes. ASSAY and Drug Development Technologies. 2012; 10(1):69-77.
78. Zeya B, Arjuman A, Chandra NC. Lectin-like oxidized low-density lipoprotein (LDL) receptor (LOX-1): a chameleon receptor for oxidized LDL. Biochemistry. 2016; 55(32):4437-44.
79. Yang C-Q, Li W, Li S-Q, Li J, Li Y-W, Kong S-X, et al. MCP-1 stimulates MMP-9 expression via ERK 1/2 and p38 MAPK signaling pathways in human aortic smooth muscle cells. Cellular Physiology and Biochemistry. 2014; 34(2):266-76.
80. Bekkering S, Stiekema LC, Moens SB, Verweij SL, Novakovic B, Prange K, et al. Treatment with statins does not revert trained immunity in patients with familial hypercholesterolemia. Cell metabolism. 2019; 30(1):1-2.
81. Umebayashi R, Uchida HA, Okuyama Y, Kakio Y, Hanayama Y, Shikata K, et al. The clinical efficacy of angiotensin II type1 receptor blockers on inflammatory markers in patients with hypertension: a multicenter randomized-controlled trial; MUSCAT-3 study. Biomarkers. 2019; 24(3):255-61.