ISSN: 2278-2648

International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.13 | Issue 1 | Jan - Mar -2024

www.ijrpp.com

DOI : https://doi.org/10.61096/ijrpp.v13.iss1.2024.31-42

Review

Role of Inflammatory Cytokines and Chemokines in the Pathological Progression of Cardiovascular Disease (CVD): A Detailed Review

Binaya Kumar Sethy[1], Mrinmoy Kumar Ghosh*[2], Sandipan Dash[3]

[1]*Assistant Professor, The School of Pharmacy, The Neotia University, Sarisa, Diamond Harbour Road,24 Parganas (South), West Bengal - 743 368.*
[2*]*Assistant Professor, Netaji institute of Pharmacy, Netaji Subhas University, Bhilai Pahari, Jamshedpur, Jharkhand – 831012*
[3]*Scholar, The School of Pharmacy, The Neotia University, Sarisa, Diamond Harbour Road,24 Parganas (South), West Bengal - 743 368.*

*Author for Correspondence: Mrinmoy Kumar Ghosh
Email: mrinmoykr.1999@gmail.com

Published on: 15 Feb 2024

Published by:
DrSriram Publications

Abstract

Over the past decades, research on the pathophysiology of cardiac dysfunction has increasingly focused on inflammation. The mediators of inflammation and indicators have become crucial for better understanding and diagnosing atherosclerotic heart disease (AHD) and congestive heart failure at the early stages of pathophysiology. CVDs include CAD (coronary artery disease) and atherosclerosis and many inflammation-mediated cardiac dysfunction, CHF, and cardiac reperfusion damage. The cytokines known as pro-inflammatory interleukin/IL-1, 6, 8, 11, 16, 17, tumour necrosis factors, granulocyte colony-stimulating factors. The cytokines that are either directly or indirectly responsible for cardiovascular disorders, coordinate responses to inflammatory factors. In this review, we have discussed the latest research on the topic as well as the cytokines and chemokines that are linked to CVD.

Keywords: Cardiovascular disease (CVD), Cardiomyopathy, Cytokines, Heart failure, Inflammation.

INTRODUCTION

Over the past ten years, inflammation has emerged as one of the major themes in the mechanism of cardiovascular disorder. Cytokines causing inflammation also indicators have become crucial management and diagnosis of illnesses with continuous and preliminary stages of progression of AHD and congestive heart disorder(1). Heart failure (CHF), atherosclerosis with related coronary artery disease, rejection of allograft, gene-associated heart disorder, and myocardial reperfusion damage are examples of CVDs. A typical reaction of bodily tissue to damage is inflammation .The mechanism by which the body responds to damage or infection is fundamental(3). It is a myocardial destructive biological response that starts with a wide range of factors starting

from infection by microbes and injury, and inflammations caused by chemicals which ultimately become a reason for cell death. Inflammation, redness, pain, and swelling are non-selective responses of the immune system. Acute and chronic (short duration & rapid onset) inflammations are the types of inflammatory reactions. Causative factor for the inflammatory response in the myocardial muscle depression .The human body may suffer injury directly in a variety of ways from protracted inflammation or its aggravation. Inflammation is significantly influenced by mediators of inflammation such as cytokines. Cytokines orchestrate inflammatory reactions (1).White blood cells, among other cell types, release cytokines, which are low molecular weight glycoproteins or regulatory soluble proteins. Additionally, one cytokine such as monocyte inflammatory protein, monocytic proteins, and cancer genes. Which stimulated secretion by macrophages against the response to a wide range of inflammatory factors, chemical, and physical fracture (3). Interleukin-1, 6, 8, 11; timer causative factors, IL-16, 17, G-CSF, and GM-CSF are mediators that produce acute inflammatory responses (2). IL 4, 5, 6, 7, and 13 are examples of cytokines that coordinate humoral responses, and IL 1, 2, 3, 4, 7, 9, 10, 12, interferons, and TNF and are examples of cytokines that coordinate cell responses. Few cytokines, such as IL-1, 6, 11, 17, and TNF-, significantly contribute to both acute and chronic inflammation. Additionally, the IL-1 family of cytokines includes two ligands (IL38, 39) that have anti-inflammatory properties as well. Chronic blood vessel inflammation characterizes CVD. Due to its large contribution to worldwide morbidity, it is a huge socioeconomic issue and a danger to public health on a global scale (3). Unfavourable outcomes from inflammatory cytokine effects might include abrupt cardiac rupture or chronic dilatation, which can set the stage for heart failure (4). Soon after heart fifers damage, the tumor produces factor interleukin-6. These cytokines can acutely control myocyte survival or death as well as initiate subsequent cellular inflammatory responses (1). Inflammation is a biologically necessary immune system response to pathogenic assaults that serves to protect the organism from harm. Inflammatory reactions and ROS can result in illness and tissue damage when they are persistent and out of control. In 2017, 17.7 million people suffered because of cardiovascular disorders.A wide family of released cytokines known as "chemokines" can cause cells to migrate Studies show evidence that chemokines are one of the factors by which they cause myocardial damage and autoimmune illnesses in addition to their fundamental advantages. One of the main factors influencing the development of atherosclerotic lesions is leukocyte invasion of the arterial wall. Overloaded lipid-consuming macrophages eventually develop into foam cells, which produce the fatty streaks seen in plaques caused by at Based on the sequence of cysteine residues, chemokines may be divided into four structural groups: Chemokines: CXCd XC. Chemokines are tiny, one-ancestor gene-derived proteins of about 71 amino acid residues. Residues of Cristine and receptor signals are two characteristics that define chemokines. (There are four types of chemokines: C chemokines, which only contain two cysteines, which consist of 2 different cysteines, those are CXC chemokines and CX3C CC. Nineteen of the fifty chemokines that have been found so far are now thought to be important in coronary artery disease. Many chemical messengers are involved in the development of cardiovascular diseases including acute myocardial infarction or atherosclerosis. Atherosclerosis can now be attributed to cholesterol and nonlipid start via immune processes including cytokine. We will outline the known or speculative roles of inflammation, especially cytokines, in the main CVD pathogenetic phases (2).

Inflammatory cytokines, chemokines, and CVDs

Inflammatory cytokines & CVDs

Cytokines

Numerous studies have demonstrated the role of pro-inflammatory cytokines including TNF, IL-1, and 6 in the pathogenesis of pathologic pain. Monocytes, which are macrophages and nonimmune cells such as fibroblasts and endothelial cells are the main sources of IL-1 secretion (4). After peripheral nerves are crushed, IL-1 expression is increased, which manifests as impacts on the central nervous system. An external stimulation can cause hyperalgesia in response to IL-1. It was discovered that IL-1 increased substance P and prostaglandin E2 (PGE2) synthesis. A particular leukotriene 1 receptor inhibitor called IL-1ra binds to the same receptor as IL-1 in a competitive way. It has been demonstrated that IL-6 is crucial for the neuronal response to nerve damage, use of leukotriene-6 antibody in animal models to suppress leukotriene-6R (5). An inflammatory cytokine with an established and significant involvement in various pain types is TNF-, sometimes referred to as cachectic. Through two cell surface receptors, TNFR1 and 2, TNF regulates the process of apoptosis and the induction of NF, kB, which causes inflammation (6). Complete Freund's adjuvant was injected intraplanar into adult rats, and this caused the levels of TNF and paw to significantly increase.

Types of Cytokines and CVDs

NF-κB in heart health and disease

It is understood that NFB is a transcription factor that is crucial for how practically all mammal types' cells react to various stimuli. The fast, ephemeral, and protein synthesis-independent canonical route. kinase complexes made up of catalytic subunits are activated by a variety of stimuli including microbial products and pro-inflammatory proteins. IkB is phosphorylated by IKK when it is activated, leading to its

ubiquitination and proteasomal destruction. when that, NF-B enters the nucleus to activate the target genes (7). As a result, the canonical route is regarded as an anti-apoptotic that promotes the development of several chronic inflammation illnesses (8). The not canonical process, in contrast, relies on protein synthesis and is sluggish and persistent. It includes the phosphorylation and activation of the IKK complex by the NFB-inducing kinase. The not canonical route may promote apoptosis, making it distinct from the canonical pathway in terms of its actions (7). The NFB plays a part in the processes that affect immune system cell formation and operate resistance and disease sensitivity. It prevents heart disease from forming and preserves heart health. It has been demonstrated that NF-B activation prevented cellular death following hypoxia damage (8). Doxorubicin injections were reported to cause an increase in NFB p65 activity in heart failure. Cardiac NFB binds to DNA activity rose after one day and reduced after one, two, and four weeks with prolonged stress. Cardiac damage followed by a second NFB activation caused by de novo synthesis (7). It was established that the protease inhibitor PS519 treatment eliminated NF-B stimulation, restored cardiac operation, and decreased the size of MI. The reduction of left ventricular dilatation after MI and increased early mortality were both benefits of NFB-p50 absence (9). NF-B blockage reduces myocardial damage while maintaining cardiac function by decreasing IKK activation. Carvedilol's preventing NFB p50 led to the reduction of inflammation and maintenance of heart function.In a different trial, I/R, caused an increase in NFB transcript levels of 2.1-fold, although rosuvastatin therapy decreased both this change and myocardial damage (7). Receptor-associated factor, a protein shared by tumor necrosis factor sites, was discovered to activate NFB to provide a cardioprotective effect in I/R damage. In mice with transgenic genes the IKK protein mutation that prevented NF-B from translocating to the nucleus also made the heart more vulnerable to damage from acute myocardial infarction (AMI).It has also been demonstrated that insulin's cardiovascular protection during hypoxia entails an NF-B-dependent pathway. Bagul et al. looked into the function of NFB and its modulation in cardiomyopathy with diabetes brought on by a 64% fructose diet (8). It was discovered that the diabetic rat heart had higher levels of NFB p65 mRNA and protein expression as well as binding to DNA activity. Additionally, these researchers found the increased acetylation of p65 at the lysine 310 position, both of which are associated with increased oxidative stress in the body.The nuclear translocation of p50, 65 by the diet-induced resistance to insulin was also linked to NFB activity in the diabetes heart (9). In streptozotocin-induced diabetic cardiomyopathy, the KB transcript level was dramatically elevated, and there was an inverse relationship between NFB and chosen lysosomal indicator gene expression. The enhanced iNOS activity in cardiovascular illness and the over expression of NOS in the female rat heart are both likely caused by the NF-B-p50 subunit. In trauma-hemorrhagic shock, myocardial activation of NF-B was observed as well, along with elevated TNF- and pathological changes in the cells (10). NFB-mediated suppression of SER-CA-2 concurrently with the progression of ventricular hypertrophy to heart collapse. Activation of NF that causes the p50, 52, and 65 subunits to move from the cytosol to the nucleus. The NF-B1 94TG polymorphism was strongly linked to a greater incidence of dysfunction of the left ventricle in individuals with cardiovascular disease.The functions of the NFB in the transmission of inflammatory processes brought on by certain cytokines (7).

Role of TNF-α in heart health and disease

TNF exists in two states: membrane-bound and cytoplasmic. Its primary role in the control of the immune system is made possible by its attachment to TNFR1, 2 receptors, which are found in the cell membrane (10). TNF- has a variety of impacts, including pathogenic consequences in coronary artery disease as well as physiological impacts on the cardiovascular system. Asymmetric signaling across both receptors may be one reason for such a variety of reactions. TNF- was demonstrated to be harmful in a murine model of MI by activating TNFR1, but beneficial by activating TNFR2.This may also be the reason for many research' inconsistent findings, where one study reported a harmful effect while another found a shielding effect. Patients with heart failure were shown to have increased TNF levels (11). The degree, severity, and etiology of the illness were all positively correlated with TNF gene expression in a different study that included participants who had ongoing heart failure (10). Since the overexpression of membrane-bound TNF- led to the emergence of a concentric enlarged heart phenotype while the overexpression of the soluble form of TNF is thought to be responsible for the heart's unnatural dilation (12). TNF causes protease failure and bound protein buildup, which might help explain how dysfunction of the left ventricle occurs. In mice engineered in cardiac-restricted TNF- overexpression, it was found that the early stage of reconstruction was favoured by a rise in overall MMP operation, but with aging, the ratio of MMP activity TIMP level decreased, attenuating the left heart dilation. TNF- was found to reduce myocardial flow, heart rate, contractile force, and speed of relaxing in the separate infused heart.In the past, heart dysfunction was developed as a result of PK activation. It was demonstrated that exposure to low concentrations of TNF decreased cell elasticity and led to proarrhythmic situations, which might account for the rise in atrial fibrillation (12). It was shown that experimentally induced cardiac arrest followed by pulmonary resuscitation caused a considerable rise in TNF-immunoreactivity. Because cardiomyocytes exposed to TNF exhibited a large rise in reactive oxygen species, it was hypothesized that these harmful effects were caused by oxidative stress. Research was done to determine how TNF affected the charges

that ischemia of the myocardium caused in heart function (11). A new large future study confirms a strong correlation between the onset of atherosclerotic and chronic inflammatory states, supporting the possible protective benefits of anti-TNF-therapy on cardiovascular risk in psoriatic patients.

Role of TGF-β in heart health and disease

The human body's TGF, which consists of four primary and 25 additional members, regulates a wide range of cellular functions, including division, growth, and death (12).Multiple investigations also point to the role of elevated TGF-1 production in heart fibrosis and ventricular enlargement. TGF-1 concentration and left ventricular mass in hypertensive individuals. However, there was no association between TGF-1 levels and left ventricle diastolic performance. In rodents, aorto-caval fistula-induced sustained volume overload was found to increase cardiac TGF-1 production (13). In another investigation, elevated levels of TGF- were linked to elevated BNP stages, a large left atrial size, a thick interventricular septum, and a higher incidence of medical adverse outcomes in individuals with hypertrophic cardiomyopathy. The role of TGF was also acknowledged in the scarring of the heart in cardiomyopathy caused by diabetes. In contrast to these results, a recent study found that individuals with cardiomyopathy that is hypertrophic had lower plasma TGF1 levels, which were adversely associated with systolic dysfunction. In an obese mouse model of cardiac illness, Smad6, and TGF expressions were dysregulated in the heart tissue at both the beginning and the end of the illness. The pressure-loaded heart fibrosis was dramatically reduced by TGF type two receptor knockdown, although cardiac dysfunction and chamber enlargement remained unaffected. TGF was found to be responsible for the creation of a boundary zone, the inhibition of the inflammatory response, and the restriction of the inflammation reaction's spread into the noninfected region as a result of genetic disruption of thrombospondin-1 during heart healing following MI. When heart cells are subjected to mechanical stress, there is a rise in calcium levels within the cell that is reliant on the ryanodine receptor type 2 as well as a promotion of TGF-1, which synthesis that leads to the transcription of the gelatin gene and the formation of fibrosis in the heart (14). The persistent and improper wound healing phase, which is characterized by hypertrophic scarring and stiffness of the whole heart and results in coronary artery disease because of MI, has also been linked to TGF1 as a continuous stimulus.A further member of a group of functional Smad-suppressing elements and other negative regulators of TGF-1 signaling, SnoN is structurally and functionally similar to Ski (12). There have been several more documented effects of TGF-1 on the cardiovascular system. TGF1 treatment of primary human atrial myofibroblasts revealed that it is not only pro-fibrotic but also has the potential to promote autophagy. TGF1 levels were comparable amongst individuals who required urgent hospitalization and those who died from coronary artery disease (although without these endpoints). TGF- was shown to be high in a variety of hereditary aortic disorders, and it was also proven to promote aortic dilation (13).

Role of FGF-2 in heart health and disease

According to certain research, FGF2 has a significant role in the development of either adult or embryonic hearts as well as in pathological states such as coronary artery disease ischemia-reperfusion damage, and hypertrophy of the heart (13). The injection of FGF2 was also shown to boost the mitochondria's tolerance to calcium overload in the rat heart; the mitoconnexin 45 channel activity was found to be essential for this protective effect.These findings seem to indicate that FGF2, like other cytokines like TNF and TGF, has been linked to altering heart function in both helpful and harmful ways (14).

Interleukins in Heart Health and Disease

1. Role of IL-1

IL-1,2 are the two most researched components of the IL1, which consists of 11 pro-inflammatory cytokines that initiate and control responses that are linked to acute and chronic illnesses. IL1Ra, which binds to the IL1 receptors to control the action of these inflammatory is their natural opponent (14). IL1Ra is another cytokine that is thought to be anti-inflammatory. It has been demonstrated that IL1 has a detrimental inotropic impact on the intact heart as well as isolated heart cells. In several cardiovascular illnesses, including MI, heart failure, and septic cardiomyopathy, it has been linked to the etiology of heart failure. Increased tissue levels of IL1 (mostly IL1) are linked to cardiac IR harm, which is primarily seen clinically as acute myocardial infarction. As a result, it is thought to be a key factor in the occurrence of IR damage. Therefore, several cardioprotective measures for IR damage are linked to lower levels of IL1 in the circulatory system (15). For instance, a substance called and other phytopharmaceuticals have preventive properties. It was additionally demonstrated that reductions in IL1 mRNA concentrations were connected to the beneficial effects of a drug called ticagrelor, a kind of platelet aggregation inhibitor, on IR damage in Zucker diabetic rats. Cialis in diabetic mice and the cholesterol-lowering drug in normal rats both reduced cardiac IR harm, which was accompanied by an increase in tissue IL1 (14). Different IL1 receptor antagonists have been shown to shield the heart muscle and lessen the extent of infarction caused by acute IR damage in rats or mice. After the transplant of non-heart-beating hearts, inhibition of the generation of inflammatory cytokines such as IL-1 protects the recipient's heart function.

TGFβ1 Hypertrophic vasculature remodeling of the heart Heart fibrosis Heart disease Heart muscle cell apoptosis. TGF1's biological impact on the heart, among others Canine coronary artery disease models donor. Additionally, IL1Ras ability to block the actions of both IL1 by inhibiting the inflammatory response—which has been linked to a reduction in apoptosis—protected the myocardium from IR damage and points to the potential benefit of IL1Ra gene therapy for myocardial preservation (15). It has been suggested that IL-1 has a role in the emergence of other cardiac diseases, such as other cardiomyopathies including myocarditis and heart failure, in addition to IR damage. In dilated cardiomyopathies of many causes, it is hypothesized that the production of cytokines such as IL1, could lead to the deterioration of heart function. Numerous clinical investigations have been unable to connect IL-1 to either ischemia. Severe coronary artery disease has been associated with elevated IL1, which may lead to DCM. Various mutant mouse models of acute myocarditis have been used in certain research experiments to establish the critical function of IL1 in the onset of severe myocardial in the autoimmune myocarditis in rats was demonstrated to improve with decreased IL-1 release (16). According to Ukimura et al., IL1 mRNA only increased in certain patients with non-ischemic DCM and stayed unaltered in other people. It was hypothesized that grouping DCM patients into subgroups according to the production of cytokines may be very helpful when thinking about how to treat Cardiomyopathy patients. The most recent findings from Aleksova et al. support this viewpoint (16).

2. Role of IL-2

IL2 was first identified as a T lymphocyte-derived growth factor from bone marrow. IL2 participates in the body's normal reaction to microbial infection and guards against autoimmune disorders. The interaction between IL2 and its binding partners, which is made up of three chains results in sensors with varying degrees of IL2 affinities (16). Although IL2 has not been well-researched about coronary illness, some evidence points to its involvement in the emergence of many cardiovascular diseases. Additionally, it has been demonstrated that individuals with a recent ischemic episode or persistent angina had higher plasma levels of IL2. This may be connected to the fact that IL2 influences how receptive vascular smooth muscle cells are to angiotensin II, thereby contributing to the development of atherosclerotic. It is mentioned that following a successful coronary angioplasty surgery, the elevated IL2 in individuals with chronic angina may recover to their baseline levels (17). The term dilation of the heart was related to elevated sIL2R concentrations and a less favorable outlook for the patient. On the other hand, several research points to IL-2's potential for the treatment of AMI. Infarct diameter and LDH release were decreased by IL2 at a dosage of 55 U/ml, according to Cao et al., simulating the effects of ischemia preconditioned through a process involving the activation of kappa-opioid receptors (18).

3. Role of IL-4

In addition to the mast cells and inflammatory cells, active T cells in the body also generate IL-4, a multifunction multifaceted mediator. IL4 is known to regulate cell proliferation, and apoptosis, as well as the transcription of several proteins in diverse kinds of cells. It is crucial for the development of naïve T cells that assist H-helper type 2 cells (19).There are two main types of IL-4 receptors, type I, II receptors, which are how IL4 exerts its impact on cells. While type 2 receptors, known as IL13R1, may bind both IL4, 13, type 1 receptors in the body known as IL4Rs, primarily bind to IL4, but type 2 receptors, known as IL13R1, are capable of binding either cytokines. It was demonstrated that individuals with coronary artery disease, as well as those who have persistent angina pectoris, have higher blood levels of IL4. However, other clinical studies that examined the tissue expression of IL4 in rat or mouse hearts were unable to identify any modifications in IL4 expression levels as a result of MI. It's important to note that recent experimental findings have revealed that the infusion of IL4 is advantageous for the healing of tissues following MI. Recombinant IL4, a long-acting IL4 complex, was shown to accelerate tissue healing, decrease the size of infarction, and improve heart function in the mouse model of AMI after coronary artery closure. It was proposed that injured tissue, including infarcted hearts, can be repaired by the activation of reparative (M2) macrophages via IL4 (18).

Role of IL-6

A sticky cytokine called IL-6 has pleiotropic effects on the process of hem inflammatory processes, and the immune system's reaction. It serves as a key mediator of fever as well as the acute phase of immunological reaction and is released in reaction to illnesses and harm to tissues to promote immune response. Contrary to individuals with persistent heart failure, AMI patients' elevated blood IL6 levels were substantially linked with their hypothyroidism status. (19). IL6 was shown to be increased in patients with cardiovascular shock while plasma IL6 levels in MI patients with and without cardiogenic shock were examined. This finding suggests that IL6 is a predictive factor for MI sequelae. A rise in IL6 has been linked to worse cardiovascular results in patients having acute coronary syndrome, as well as a higher risk of serious adverse cardiac events, such as cardiac arrest, in patients with stable coronary heart disease, according to a clinical study. Several experimental investigations have suggested that IL6 plays a significant part in cardiac IR damage. Serum IL6 levels from rabbits were shown to be considerably higher 2 hours after resuscitation and 4 hours after left coronary artery

blockage (20). Additionally, it has been demonstrated that after MI levels of IL6, IL6R, and mRNA. As contrasted with the wild-type mice, the size of infarcts was reduced in IL6 deficient Heart Failure Rev animals after 1 hour of ischemia and 3 hours of resuscitation indicating that IL-6 plays a role in the development of infarct size in the early stages of resuscitation (18). Hartman et al.'s recent investigation in rats, however, demonstrated that blocking the IL6R receptors with monoclonal MR16-1 antibodies did not stop the IR-induced remodeling of the heart. Tocilizumab, an IL6R antagonist, on the other hand, reduced the inflammatory response and the ejection of troponin T among individuals with ST-elevation MI, raised VCAM levels while the individuals were in the hospital, and did so without compromising their coronary flow reserve. The majority of experimental and clinical investigations have indicated that IL6 has a detrimental effect on MI, making it likely that IL6 and its binding partners might be targets for therapeutic approaches. On the other hand, numerous research confirmed that IL6 has a neutral or even beneficial function in MI. According to Gabriel et al.'s research. In hospital stay, the elevated IL6 levels in patients with AMI did not correspond with infarct size or coronary artery disease, but they did when the same patients developed heart failure 12 weeks later. The infarct size of IL6 animals matched that seen in wild-type mice, according to an experimental investigation. Additionally, the size of the infarct was not decreased in preconditioned IL6(-/-) mice, and it was hypothesized that IL-6 plays an essential role in late preconditioned through activation of iNOS and COX-2 and JAK/STAT signalling (19) .Congestive heart failure that is related to idiopathic dilated cardiomyopathy (IDCM), which was associated with raised blood IL6 stages, had an unfavorable outlook in individuals with high IL6 levels (20). The ventricle expression of IL-6 was shown to be greater among individuals with IDCM compared to those with ischemic myocardium in the examination of cardiac tissues from end-stage heart failure patients. These findings suggest that IL6 is directly produced in the heart during the onset of several cardiomyopathies (18).

4. Role of IL-8

The cytokine IL8 is generated by a variety of kinds of cells, including monocytes, neutrophils, fibroblasts, endothelium, epithelial, and cancerous cells. Initially thought to work as a chemotactic factor for neutrophils and lymphocytes, it has since been demonstrated to have a variety of pro-tumor effects, such as promoting vasculature and survival of cancer cell signals. Patients undergoing cardiac transplantation and those with AMI both had elevated levels of IL8, indicating that IL8 may play a role in myocardial IR damage (20). An in vivo experimental model of IR in rats has revealed elevated circulating IL8 levels, while a real-world instance of IR within rabbits' hearts has shown IL8 gene activation in the myocardial.In this rabbit model of coronary IR damage, it was also discovered that inhibiting IL8 with a neutralizing monoclonal antibody targeted towards rabbit IL8 reduced the amount of necrotic. In line with prior research, the stimulation of the enzyme heme oxygenase and hypoxia-inducible factor-1 is linked to decreased IL-8 release and smaller infarcts in a rabbit model of myocardial IR. The production of HO1 by HIF1 has been proposed as a possible method for inhibiting the IL8-mediated inflammatory processes brought on by IR (21). Additionally, it has been demonstrated that in those suffering from AMI, the elevated level of circulating IL-8 serves as an indicator of the onset of coronary artery disease.In AMI patients with heart failure, it is linked to a slower recovery of the left ventricle within the first six-week period following PCI. A major case research that examined the relationship between IL8 serum levels and the likelihood of MI found that, curiously, the amount of IL8 in the bloodstream was linked to a lower likelihood of Ami in women and a slightly higher risk in males (22). A rise in circulating CD135+ progenitor cells appears to be related to elevated plasma IL8 levels in MI patients, indicating that this pathway may aid in the development of new vessels and enhanced heart function after MI. Infarct size or MI-induced dysfunction of the pulmonary artery in rats was shown to be reduced by the specially designed introduction of endothelial cells overexpressing neutrophil membrane IL8 receptors, IL8RA (21).

Role of IL-10

Many different cell types, including Th2 cells, monocytes, and macrophages, as well as dendritic cells, human B cells, eosinophils, mast cells, epithelial cells, and tumor cells, generate the cytokine known as IL10. Both the kind of cell kind that produces IL10 and the cellular type that responds to it define the biological actions of this cytokine. Two IL-10 receptor-1 and two IL-10 receptor-2 proteins make up the receptor combination via which IL10 functions. The JAK-STAT3 signaling pathway is activated by IL10 binding to the receptor complex, which ultimately affects how many genes are expressed in the nucleus (23). A type of cytokine called IL10 has multiple impacts on inflammatory and immunological control. It has an anti-inflammatory effect by preventing the release of cytokines that cause inflammation. Due to its capacity to reduce NO generation, stop ROS from being released, and control TNF-mediated cellular damage, it was also proposed that it functions as an oxidant.It has been shown that artificial MI in rats drastically reduced membrane-bound IL-10 protein and mRNA levels in the heart, and this was associated with impaired cardiac performance, which eventually led to a condition known as congestive heart failure (24). Contrarily, administration of certain cardioprotective substances is linked to a rise in IL-10 level, which in turn leads to enhanced cardiac function and/or a smaller size of an infarct. The extracellular vesicles generated by cardio-

sphere cells have been found to give cardioprotection in vitro and in vivo. It is now believed that this cardiovascular protection may be achieved via modulating IL10 production and secretion (21). According to research by Chen et al., lower limb ischemia-induced remote ischemic preconditioning, which causes cardioprotection relying on STAT5, is linked to greater amounts of IL10.

5. Role of IL-18

A member of the IL1, IL18, sometimes referred to as an interferon-inducing aspect, is generated by macrophages and other cells. IL18 functions as a proinflammatory cytokine in a variety of immunological and inflammatory diseases by attaching to the receptors. This cytokine has been demonstrated to stimulate immunity mediated by cells after microbial infection in conjunction with IL12. Natural killer cells and specific T cells respond to IL18 by releasing interferon, which is crucial for stimulating macrophages or other types of cells (25) . Elevated circulating IL18 levels were seen in MI patients, indicating that IL18 may serve as a marker of developing heart injury. Elevated tissue IL18 levels and IL18 mRNA concentrations during IR in a spirofused human atrial myocardium model suggest that indigenous IL18 contributes significantly to IR-induced cardiac damage. In an animal model of MI, increased cardiac IL-18 mRNA and circulation IL18 were seen after MI (26). IL18 mRNA as well as protein levels were increased in the cardiac tissue of individuals with end-stage coronary artery disease, but IL-18 binding protein (IL-18BP), the constitutive inhibitor of IL-18 function, saw a downregulation in transcript levels. One of the main participants in the inflammatory response connected to MI is IL18, NLR3 inflammasome regulates this response. Recent research suggests that targeted suppression of the NLR3 inflammasome may have therapeutic promise for AMI by shrinking the size of infarcts and maintaining heart function in a porcine MI model (27). It has been shown that the treatment of IL-18 caused post-infarct mice hearts to have decreased cardiac function, which was reversed by cardiac extracellular matrix metalloproteinase inducer (EMMPRIN) gene silencing. It was proposed that EMMP knockdown may be a possible treatment method to mitigate the post-infarct adverse effects of IL18 because it was discovered that EMMP silence decreased the levels of MP9 (28). It's important to note that for those with steady CAD, a variant within the IL18 gene, either alone or in combination with a variation in the MP-9 gene, can be observed to affect the likelihood of new medical conditions like MI, stroke, or unstable angina pectoris (29). In conclusion, the pathogenic process of several CVDs, especially those associated with myocardial ischemia like CAD, is mediated by the inflammatory factor IL18 (7).

Inflammatory Chemokines and CVDs

Chemokines

The placement of particular physically significant cysteine residues inside the finished protein plus the chemokine's main amino acid sequence serve as its defining characteristics. These combine to produce bonds of disulfide that keep the cycle monomer's three-stranded core sheet, C/terminal helix, and brief, unorganized N terminus, which is essential for receptors stimulation, in place. Chemokines may be divided into four subfamilies: CXC, and CC variations in the exact arrangement of the two cysteines nearest to the N/terminus. These are placed next to one another immediately in CC chemokines, but CXC chemical messengers contain a single variable amino acid between them. While XC chemokines among which there are two variants among humans and one in mice, do not have the initial and third cysteines of the motif, the only CX 3C chemokine does have three amino acids between these two cysteines. Many different animals have large numbers of CC and CXC chemokine genes identified among them. There are non-allelic variants that can occur, such as CCL3L1, CCL3 in humans and CCL21 a, CCL21/CCL21 in rodents (30). Occasionally all individuals of a breed. Significant genetic variety is produced via allelic and copy number variations, which affects the propensity for and intensity of certain illnesses (31). Even though chemical messengers were initially named after particular functions, a systematic nomenclature was introduced in 2002. It consists of a family title, the letter L, followed by a number based on the year when the gene was initially isolated.While rodent CCL8 is a CCR8 receptor while human CCL3 appears more functionally similar to human CCL3L1/CCL3, human CCL8 binds with the human CCR2 receptor (32). An N terminal signal peptide is present in the production of all chemokines, but it is eliminated after the chemokine has been guided to the endoplasmic reticulum for secretion. Two chemokines, CX 3CL1, have an extended C terminus that includes the transmembrane domain and a stalk-like structure that resembles a mucin. The cycle part of this maintains these chemokines on the cell surface, but it can be broken by proteolysis to release them into the environment outside of the cell. Other chemokines, such as CCL6, CCL9, and CCL23, have a prolonged N terminus that may be cut off using a protease to improve their ability to activate receptors. A GPCR not included in the category of a CKR, formyl peptide receptor-like 1, may be activated by an N terminal peptide that has been cut off from a CCL22 variation. Chemokine variants can be produced by alternatively splicing RNAs. For instance, six different versions of human CXCL12 have been identified, each with a unique C-terminus and set biological characteristics (33).

Types of Chemokines & CVDs

1. CCL2, CCL3, CCL4, and CXCL2 & CVDs

Many investigations in the field of cardiovascular research have focused on CCL2. Numerous cells, notably macrophages as endothelial and epithelial cells, generate it (34). It is believed to be crucial in several pathologic processes, including cholesterol and reconfiguration following MI. A higher baseline level of CCL2 was linked to both conventional CVD risk factors and an increased risk of mortality or MI in a sizable sample of individuals with ACES. In the animal's heart, CCL2 was discovered to rise during reperfusion but not after a persistent infarction had been present for one or two hours. Taken shared, our results indicate that this chemokine is more closely linked to disease than hypoxic or ischemic due to its strong reperfusion regulation and correlation with a well-known inflamed marker like CRP (35). Over the last twenty years, several preclinical investigations have been carried out to learn more about the mechanism of action of CCL2 and other chemokines in the myocardial response to injury. In-depth research on this subject by Frangipanis, with colleagues revealed a link between CCL2 and cardiac fibrosis in a rat model of hypoxia with death (36). After repeated cycles of short IR, CCL2 was found in the ischemic myocardium and was linked to LV dysfunction, increased collagen content, and macrophage infiltration. These effects were reduced in CCL2 in mice. Furthermore, repeated IR boosted the proliferative ability of progenitors derived from wild-type mice, but this capacity was suppressed in fibroblasts from CCL2 null-hearts. Since no changed gene expression in genes linked to cardiac fibrosis was discovered at the molecular level, it was determined that the profibrotic activities of CCL2 are likely linked to reduced macrophage recruitment. use the same experimental model in a separate investigation. Intriguingly, Tarzami and colleagues discovered a survival route in the target cardiac myocytes themselves, a protective impact of CXCL2-dependent production in myocardial ischemia sans restoration. CCL2 significantly reduced the cell death brought on by oxygen in myocytes from the heart in vitro. CCL2 and receptors appear to be one of the primary players in the transition from physiological to pathological conditions in the circulatory system. They are among the chemical messengers influencing these processes. Mononuclear cells, a source of fibrogenic mediators such as TGF and Fibroblast Development Factor, are chemotactically drawn to CCL2. Additionally, it stimulates gelatin and TGF1 production in monocytes. It has also been claimed that CCL2 changes the phenotypic and activity of fibroblasts. Additionally, it could play a significant role as a mediator in the attraction of fibroblast cells. Monocyte-mediated inflammation and several related phenomena are brought on by activation of the CCL2/CCR2 axis; increased CCR2 fluorescence intensity on monocytes has been seen in both people with high blood pressure and animal models. Angiotensin II vascular inflammation and remodeling were less pronounced in CCR2 rats compared with animals, and long-term therapy with antibodies toward CCL2 improved diastolic function without producing myocyte enlargement or fibrosis within a model of the fibrosis and enlargement caused by suprarenal aortic narrowing. Control rodents, on the other hand, exhibited responsive fibro and hypertrophic (37). A mouse model of CCL2 genetic deletion provides more evidence for CCl's role in the transition from hyperplasia to cirrhosis (50). Injection of Ang II inhibited the growth of fibrosis in gelatine induction, it is TGF induction and TNF mRNA expression in CCL2 Knock Out rats. The nonadaptive enlargement of the heart in this condition requires CCL2 activation (38). An intriguing clinical investigation discovered that, despite receiving an elevated dose of ACE inhibitor therapy, patients with heart failure had greater levels of circulation CCL2 than normal controls. On the reverse side, CCL2 has also been shown to have angiogenesis and cardioprotective effects. In a mouse model of MI, Morimoto, and associates looked into the impact of cardiac CCL2 overexpression on LV dysfunction and remodeling. The intriguing results showed that cardiac overexpression of CCL2 improved ventricular function and remodeling while decreasing infarct extent and formation of scars, pointing to a contentious role for CCL2 in the body's reaction to MI. Dewald & colleagues also discovered that CCL2 suppression may have the same negative effects as corticosteroid therapy in individuals with MI, namely, a reduction in the ability to heal after damage (39).

CCL5

Two research studies published recently demonstrated the impact of cxcl suppression in MI. In the initial study, administration of polyclonal anti-CCL5 antibodies dramatically lowered post-infarction HF and infarct diameter in a mouse model, and this was associated with decreased recruitment of leukocytes inside the infarcted hearts (40). In the second investigation, mice that had their left coronary arteries permanently severed in vivo and were monitored for a variety of periods (up to 21 days) demonstrated a beneficial reduction in infarct size when compared with regulates when given chemical inhibitors, particularly CCL5 restriction, which decreased cardiac injury/inflammation and increased survival. Reactivity of oxygen species release, circulating concentrations of CXCL1 and CCL2, and post-infarction cardiac infiltration of leukocytes were all correlated with this therapy (41).

CXCL8, CXCL1, and CXCL5.

CXCL8 (IL-8) is a chemokine that attracts neutrophils and is important for both heart failure and the early stages of reperfusion damage. In ischemia-repercussed myocardium, CXCL8 mRNA was observed to rise, suggesting that it may play a role in neutrophil-induced myocardial damage by encouraging ligand-specific adhesion to cardiac myocytes (42). According to research by Damas and colleagues, patients with congestive heart failure (CHF) gradually developed higher circulation levels of CXCL8, 1, 5 along with a rise in the functional class. Recent research suggests that elevated levels of CXCL8 may have a role in reperfusion-related damage among individuals with ST-elevation myocardial infarction exacerbated by heart failure. These individuals showed poorer recovery in the left ventricle during the initial six-week period following PCI (43). In 2001, Chandrasekhar and coworkers discovered that cardiac IR in rats activates NFB and causes neutrophil invasion via LIX, which is a homolog of CXCL8 in humans. The expression of LIX was discovered to be increased by reactive stress in produced heart cells, as well as by resident myocardial cells during IR. Furthermore, they found that LIX not only attracted and activated neutrophils but also boosted the chain of inflammatory reactions by inducing the local generation of mediators with detrimental inotropic and proapoptotic effects. CXCL8,1,5 levels in the blood were investigated by Damas and colleagues in individuals with varying degrees of heart failure. They discovered that all three chemical messengers significantly increased in these individuals and that CXCL8, 1 (44).

CXCL12

The CXCL12, also known as stromal cell-derived factor 1, is implicated in heart remodel and hypertrophy. Haematopoiesis, cardio genesis, vasculogenic, and neurogenesis are all significantly influenced by this cxcl (45). It is believed that the elevated production of CXCL12 in ischemic tissue acts as a positive signal to entice stem cells to the heart. CXCR4, which is expressed in a variety of cells, such as those from the megakaryocytic descent, is the primary receptor for CXCL12. The mobilization of bone marrow stem cells is the primary purpose of CXCL12 interaction with CXCR4 (44). According to research by LaRocca and peers, CXCR4 physically interacts with the adrenergic receptor type 2 and influences the signaling that follows. Cardiac myocytes contain CXCL12, CXCR4, which lowers contractility in response to isoproterenol, an agonist of the -adrenergic receptor. According to a recent study, continuous drug administration to CXCR4 and WT mice for three weeks inhibited the development of heart hypertrophy. Biochemical and circulatory measures were taken. In comparison to WT livestock, mice displayed worsening fractional shortening and ejection fraction, as well as increased levels of markers of apoptosis and decreased activity of the mitochondria. Cardiac fibrosis also increased in severity. In rats, a CXCR4 gene transfer decreased apoptosis and enhanced mitochondrial and cardiac function (43). Due to the homing of vascular progenitor cells and activation of CXCL12, apelin-14 improved vasculature and heart healing. Six and thirty days after a permanent infarction, EPO reduced the number of apoptotic cells in the peri-infarct region. Furthermore, EPO administration increased the homing of Sca1(+) and CXCR4 toward a CXCL8 gradient into the ischemic myocardium as well as the mobilization from bone marrow-derived stem cells . It's important to note that local cardiac stem cells did not benefit from EPO (42). In an intriguing study, Hwang and Kloner looked at the possible advantages of giving rats with permanent coronary ligation several soluble factors (SFs), including CXCL12. The fact that administration of a single SF to the ischemic heart in the clinical context had little impact served as the foundation for our investigation. Their findings showed no improvements in cardiac function or smaller infarcts (4).

CXCL13 and CXCL16

Waehre or coworkers investigated chemokines that were linked to changes in the extracellular matrix's structure and Small Leucine-Rich Proteoglycans activity. The kinetics, assembly, and spatial organization of fibrils are controlled by SLR, which are proteins able to bind different forms of collagen. They discovered that CXCL13's association with its receptor, CXCR5, was crucial for cardiac remodeling and possibly regulated proteoglycans and the quality of the cardiac ECM. The hereditary ablation of the CXCR5 receptor worsened dilatation and increased mortality, perhaps due to the absence of an increase in SER, hence it was shown that this relationship is beneficial (46). Additionally, they discovered that CX3CL1, CCL5, CXCL16 controlled SLR transcription and posttranslational changes in fibroblasts of the heart in a model that exhibited pressure overload-dependent right ventricular remodeling. Thus, during stress overload, these mediators of inflammation may contribute to the onset and growth of right-sided cardiac remodeling (50).

CX3CL1 and XCL1/2

Recently, two chemokines—CX3CL11/2, commonly known as lymphotactin—were shown to be connected to HF. Chemokine CX3C1 is the only component of the CX3C class and has a peptide structure that differs from the normal structure found in other chemokines that It was discovered to be an accurate indicator of death in HF patients (47). By stimulating the MAP pathway, it is hypothesized to induce myocardial damage and

HF. TNF modulates the way it is expressed. Both CX3CL1,1/2 were discovered to be implicated in the rejection of transplanted hearts as a result of infection with CMV in a rodent heart replacement paradigm. (24)

2. CCL21

CCL 21 is a chemokine that is referred to as homeostatic and is involved with the remodeling of tissues. It was independently associated with mortality in chronic and acute post-MI heart failure, and its content in serum from patients with heart failure was greater than in controls. Intriguingly, after a week of post-MI HF, animals missing the CCL21 receptor, CCR4, showed enhanced survival and reduced rise in indicators of myocardial dysfunction, but over time, they displayed myocardial dysfunction and increased wall stress (48). For the mediators participating in the procedure, the choice between compensated remodeling versus repair for restoration appears to be a fork in the road. It is unclear whose input may tip the scales in Favor of recovery. In this situation, the effects on ANS also could be quite important (49).

CONCLUSION

It is commonly believed that inflammation plays a significant role in the pathophysiology of cardiac dysfunction. Numerous massive prospective investigations show that different inflammatory cytokines predict unfavorable events related to cardiovascular disease, such as MI, ischemic stroke, and sudden cardiac death, robustly and separately.

REFERENCES

1. Gencer, S., Evans, B. R., van der Vorst, E. P. C., Döring, Y., & Weber, C. (2021b). Inflammatory Chemokines in Atherosclerosis. *Cells*, *10*(2), 226. https://doi.org/10.3390/cells10020226
2. Sánchez-Martín, L.; Estecha, A.; Samaniego, R.; Sánchez-Ramón, S.; Vega, M.Á.; Sánchez-Mateos, P. The chemokine CXCL12 regulates monocyte-macrophage differentiation and RUNX3 expression. Blood 2011, 117, 88–97. [CrossRef] [PubMed]
3. Zernecke, A.; Shagdarsuren, E.; Weber, C. Chemokines in atherosclerosis: An update. Arterioscler. Thromb. Vasc. Biol. 2008, 28, 1897–1908. [CrossRef]
4. Miller, M.C.; Mayo, K.H. Chemokines from a Structural Perspective. Int. J. Mol. Sci. 2017, 18, 2088. [CrossRef]
5. Monika Bartekova, Jana Radosinska, Marek Jelemensky, Naranjan S. DhallaJournal:Heart Failure ReviewsVolume:23Issue:5Year:2018Pages:733—758
6. Tilborghs S, Corthouts J, Verhoeven Y, Arias D, Rolfo C, Trinh XB, van Dam PA (2017) The role of nuclear factor-kappa B signaling in human cervical cancer. Crit Rev Oncol Hematol 120:141–150
7. Sun SC (2012) The noncanonical NF-κB pathway. Immunol Rev 246(1):125–140
8. Caamaño J, Hunter CA (2002) NF-kappaB family of transcription factors: central regulators of innate and adaptive immune functions. Clin Microbiol Rev 15(3):414–129
9. Tian M, Yuan YC, Li JY, Gionfriddo MR, Huang RC (2015) Tumor necrosis factor-α and its role as a mediator in myocardial infarction: a brief review. Chronic Dis Transl Med 1(1):18–26
10. Waters JP, Pober JS, Bradley JR (2013) Tumour necrosis factor in infectious disease. J Pathol 230(2):132–147
11. Frangogiannis NG (2008) The immune system and cardiac repair. Pharmacol Res 58(2):88–111
12. Jarrah AA, Schwarskopf M, Wang ER, LaRocca T, Dhume A, Zhang S, Hadri L, Hajjar RJ, Schecter AD, Tarzami ST (2017) SDF-1 induces TNF-mediated apoptosis in cardiac myocytes. Apoptosis. https://doi.org/10.1007/s10495-017-1438-3
13. Tian M, Yuan YC, Li JY, Gionfriddo MR, Huang RC (2015) Tumor necrosis factor-α and its role as a mediator in myocardial infarction: a brief review. Chronic Dis Transl Med 1(1):18–26
14. Dinarello CA (2011) Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 117(14):3720–3732
15. Opal SM, De Palo VA (2000) Anti-inflammatory cytokines. Chest 117(4):1162–1172
16. Weisensee D, Bereiter-Hahn J, Schoeppe W, Löw-Friedrich I (1993) Effects of cytokines on the contractility of cultured cardiac myocytes. Int J Immunopharmacol 15(5):581–587
17. Morgan DA, Ruscetti FW, Gallo R (1976) Selective in vitro growth of T lymphocytes from normal human bone marrows. Science 193:1007–1008
18. Kim HP, Imbert J, Leonard WJ (2006) Both integrated and differential regulation of components of the IL-2/IL-2 receptor system. Cytokine Growth Factor Rev 17(5):349–366
19. Liao W, Lin JX, Leonard WJ (2011) IL-2 family cytokines: new insights into the complex roles of IL-2 as a broad regulator of T helper cell differentiation. Curr Opin Immunol 23(5):598–604

20. Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE (1999) The IL-4 receptor: signaling mechanisms and biologic functions. Annu Rev Immunol 17:701–738
21. Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 6(10): a016295
22. Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M (2012) IL-6/IL-6 receptor system and its role in physiological and pathological conditions. Clin Sci (Lond) 122(4):143–159
23. W. Xuan, Y. Liao, B. Chen et al., "Detrimental effect of fractalkine on myocardial ischaemia and heart failure," Cardiovascular Research, vol. 92, no. 3, pp. 385–393, 2011.
24. D. N. Streblow, C. Kreklywich, Q. Yin et al., "Cytomegalovirusmediated upregulation of chemokine expression correlates with the acceleration of chronic rejection in rat heart transplants," Journal of Virology, vol. 77, no. 3, pp. 2182–2194, 2003.
25. Dusi V, Ghidoni A, Ravera A, De Ferrari GM, Calvillo L. Chemokines and Heart Disease: A Network Connecting Cardiovascular Biology to Immune and Autonomic Nervous Systems. Mediators Inflamm. Epub 2016 May 3:. doi: 10.1155/2016/5902947.
26. F. Kuwahara, H. Kai, K. Tokuda et al., "Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation?" Hypertension, vol. 43, no. 4, pp. 739–745, 2004.
27. M. Sopel, A. Falkenham, A. Oxner, I. Ma, T. D. G. Lee, and J.-F. Legar ´ e, "Fibroblast progenitor cells are recruited into the ´ myocardium prior to the development of myocardial fibrosis," International Journal of Experimental Pathology, vol. 93, no. 2, pp. 115–124, 2012.
28. S. B. Haudek, J. Cheng, J. Du et al., "Monocytic fibroblast precursors mediate fibrosis in angiotensin-II-induced cardiac hypertrophy," Journal of Molecular and Cellular Cardiology, vol. 49, no. 3, pp. 499–507, 2010
29. L. Gullestad, P. Aukrust, T. Ueland et al., "Effect of highversus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure," Journal of the American College of Cardiology, vol. 34, no. 7, pp. 2061–2067, 1999.
30. L. Gullestad, P. Aukrust, T. Ueland et al., "Effect of highversus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure," Journal of the American College of Cardiology, vol. 34, no. 7, pp. 2061–2067, 1999.
31. H. Morimoto, M. Takahashi, A. Izawa et al., "Cardiac overexpression of monocyte chemoattractant protein-1 in transgenic mice prevents cardiac dysfunction and remodeling after myocardial infarction," Circulation Research, vol. 99, no. 8, pp. 891–899, 2006
32. O. Dewald, P. Zymek, K. Winkelmann et al., "CCL2/monocyte chemoattractant protein-1 regulates inflammatory responses critical to healing myocardial infarcts," Circulation Research, vol. 96, no. 8, pp. 881–889, 2005.
33. R. Roberts, V. DeMello, and B. E. Sobel, "Deleterious effects of methylprednisolone in patients with myocardial infarction," Circulation, vol. 53, no. 3, pp. I-204–I-206, 1976.
34. F. Montecucco, V. Braunersreuther, S. Lenglet et al., "CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice," European Heart Journal, vol. 33, no. 15, pp. 1964–1974, 2012.
35. V. Braunersreuther, F. Montecucco, G. Pelli et al., "Treatment with the CC chemokine-binding protein Evasin-4 improves post-infarction myocardial injury and survival in mice,"Thrombosis and Haemostasis, vol. 110, no. 4, pp. 807–825, 2013
36. G. L. Kukielka, C. W. Smith, G. J. LaRosa et al., "Interleukin-8 gene induction in the myocardium after ischemia and reperfusion in vivo," The Journal of Clinical Investigation, vol. 95, no. 1, pp. 89–103, 1995
37. J. K. Damas, L. Gullestad, T. Ueland et al., "CXC-chemokines, ˚ a new group of cytokines in congestive heart failure—possible role of platelets and monocytes," Cardiovascular Research, vol. 45, no. 2, pp. 428–436, 2000.
38. J. K. Damas, H. G. Eiken, E. Øie et al., "Myocardial expression of ˚ CC- and CXC-chemokines and their receptors in human endstage heart failure," Cardiovascular Research, vol. 47, no. 4, pp. 778–787, 2000
39. T. Husebye, J. Eritsl, H. Arnesen et al., "Association of interleukin 8 and myocardial recovery in patients with St-elevation myocardial infarction complicated by acute heart failure," PLoS ONE, vol. 9, no. 11, Article ID e112359, 2014.
40. B. Chandrasekar, J. B. Smith, and G. L. Freeman, "Ischemiareperfusion of rat myocardium activates nuclear factor-κ b and induces neutrophil infiltration via lipopolysaccharide-induced CXC chemokine," Circulation, vol. 103, no. 18, pp. 2296–2302, 2001
41. B. Chandrasekar, P. C. Melby, H. M. Sarau et al., "Chemokinecytokine cross-talk: the ELR+ CXC chemokine LIX (CXCl5) amplifies a proinflammatory cytokine response via a phosphatidylinositol 3-kinase-NF-κ B pathway," The Journal of Biological Chemistry, vol. 278, no. 7, pp. 4675–4686, 2003.
42. E. P. C. van der Vorst, Y. Doring, and C. Weber, "MIF and ¨ CXCL12 in cardiovascular diseases: functional differences and similarities," Frontiers in Immunology, vol. 6, article 373, 2015

43. T. J. Larocca, D. Jeong, E. Kohlbrenner et al., "CXCR4 gene transfer prevents pressure overload induced heart failure," Journal of Molecular and Cellular Cardiology, vol. 53, no. 2, pp. 223–232, 2012
44. J.-F. Wang, Z.-Y. Liu, and J. E. Groopman, "The α-chemokine receptor CXCR4 is expressed on the megakaryocytic lineage from progenitor to platelets and modulates migration and adhesion," Blood, vol. 92, no. 3, pp. 756–764, 1998.
45. E. R. Wang, A. A. Jarrah, L. Benard et al., "Deletion of CXCR4 in cardiomyocytes exacerbates cardiac dysfunction following isoproterenol administration," Gene Therapy, vol. 21, no. 5, pp. 496–506, 2014.
46. P.-Y. Chu, J. Mariani, S. Finch et al., "Bone marrow-derived cells contribute to fibrosis in the chronically failing heart," The American Journal of Pathology, vol. 176, no. 4, pp. 1735–1742, 2010.
47. L. Li, H. Zeng, and J.-X. Chen, "Apelin-13 increases myocardial progenitor cells and improves repair postmyocardial infarction," American Journal of Physiology—Heart and Circulatory Physiology, vol. 303, no. 5, pp. H605–H618, 2012.
48. S. Brunner, J. Winogradow, B. C. Huber et al., "Erythropoietin administration after myocardial infarction in mice attenuates ischemic cardiomyopathy associated with enhanced homing of bone marrow-derived progenitor cells via the CXCR-4/SDF-1 axis," The FASEB Journal, vol. 23, no. 2, pp. 351–361, 2009.
49. L. Calvillo, R. Latini, J. Kajstura et al., "Recombinant human erythropoietin protects the myocardium from ischemiareperfusion injury and promotes beneficial remodeling," Proceedings of the National Academy of Sciences of the United States of America, vol. 100, no. 8, pp. 4802–4806, 2003.
50. H. Hwang and R. A. Kloner, "The combined administration of multiple soluble factors in the repair of chronically infarcted rat myocardium," Journal of Cardiovascular Pharmacology, vol. 57, no. 3, pp. 282–286, 2011.