Cardiology Research and Cardiovascular Medicine
Zhou S and Zhai L. Cardiolog Res Cardiovasc Med 8: 196.
www.doi.org/10.29011/2575-7083.100196
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Review article

Inflammatory Causes and Immunotherapy Potential in Cardiovascular Diseases Treatment

Shijie Zhou[1*], Lidong Zhai[2]

[1]School of medicine; Case Western Reserve University; Cleveland; Ohio; USA

[2]Department of pathology; Cleveland Clinic; Cleveland; Ohio; USA

***Corresponding author:** Shijie Zhou, Email: shijie.zhou@case.edu

Citation: Zhou S, Zhai L (2023) Inflammatory Causes and Immunotherapy Potential in Cardiovascular Diseases Treatment. Cardiol Res Cardiovasc Med 8: 196. DOI: 10.29011/2575-7083.100096

Received Date: 14 June 2023 **Accepted Date:** 22 June 2023**; Published Date:** 24 June 2023

Abstract

Inflammatory profile in the cardiovascular diseases has been acknowledged widely; yet the potential of immunotherapy in the treatment of cardiovascular diseases (CVD) is not fully met. The primary and secondary inflammatory risk factors of CVD; as well as drivers of atherosclerosis from the immune system are elaborated in this review. The approaches to treat CVD in respect of immunotherapy focus on targeting cytokine response pathways; novel engineering cytokines and superkines; and targeting specialized pro-resolving mediators (SPMs) in atherosclerosis. Immunotherapy in the treatment of heart failure has gained great advancement in targeting heart fibrosis to stop and even reverse cardiac remodeling. With a deeper understanding of the roles T cells and macrophages in the development of fibrosis in heart failure; harnessing them became possible to treat heart failure. T-cell therapy with chimeric antigen receptor (CAR T-cell); as well as CRISPR gene editing therapy make personalized diagnosis and treatment possible and bring a lot of hope to concur this debilitating disease. This review attempts to summarize new understandings of inflammatory mechanisms underlying CVD and major advancements as well as challenges in CVD immunotherapy with a hope to offer a perspective on strategies to advance future therapies.

Keywords: Cardiovascular Disease; Immunotherapy; Cytokines; Engineering Cytokines; Superkines; Pro- Inflammation; Inflammation Resolution; Specialized Pro-Resolving Mediators (Spms); Heart Failure; Cardiac Fibrosis; Cardiac Remodeling; T-Cell Therapy; CAR T-Cell.

Introduction

Background

Despite steady improvements to global health over the past 30 years, ischemic heart disease and stroke continue to be the leading causes of disability-adjusted life years (DALYs) among individuals aged 50 and above [1]. Although these factors are not among the top leading causes of burden in the 25-49 age group, ischemic heart disease, stroke, along with diabetes started to emerge as significant contributors to burden in this age group [2]. Across high-income countries, such as Australia, the USA, and the UK, there is a significant slowdown in the rate of decline in cardiovascular disease (CVD) mortality since 2000 [3]. North America has even experienced increased mortality in recent years [3]. The Global Burden of Diseases, Injuries, and Risk Factor Study (GBD) found a more than half greater burden, in some countries, due to years lived with disability (YLDs) from non-communicable diseases and injuries [2]. These epidemiology transitions have been partly expedited by a rapidly aging population globally, requiring broader health services and endeavors from healthcare workers and researchers to prevent disabling outcomes caused by major cardiovascular diseases, including coronary artery disease (CAD), myocardial infarction (MI), stroke, peripheral artery disease (PAD) and congestive heart failure (CHF). CVD mortality outcome measures was included in the World Health Organization 2017 Sustainable Development Goals, with an aim to reduce premature CVD mortality by one-third by 2030 [4].

Primary residual inflammatory risk in atherogenesis and heart diseases

Atherosclerosis is a common pathology leading to major adverse cardiovascular events (MACEs), such as myocardial infarction, stroke, heart failure, and angina, which often require coronary revascularization [5]. The mortality rate from MACEs is

high. MACEs and all kinds of cardiovascular related diseases claim the life of one person in the United States every 36 seconds, which accounts for about $363 billion cost each year [6]. Atherosclerosis is characterized by lipid-laden plaque that accumulates on the endothelial layer of arteries due to high serum cholesterol and has been defined as a chronic inflammatory disease [7-8]. Strategies to reduce low-density lipoprotein (LDL) cholesterol through dietary changes and statin therapy have demonstrated a marked reduction in the mortality rate of MI, stroke, and other MACEs in the past 30 years. However, there are sizeable population of patients who succumb to the life-threatening cardiovascular adverse events eventually, despite on their lifestyle intervention or statin therapy [8–10].

Residual inflammatory risk after LDL reduction is another risk factor causing MACEs, and has therefore become the focus of CVD research as early as 1976 [8]. Lipoproteins, such as oxidized LDL, that have accumulated on the endothelial cells are believed to trigger atherogenesis and inflammatory cascades, as both innate and adaptive immune responses are activated and work simultaneously on major arteries in the cardiovascular system [11]. Atherosclerotic plaques are composed of infiltrated immune cells including activated T lymphocytes and macrophages, in addition to local inflammatory mediators [12]. Additionally, lipoprotein deposition, fibrosis, and inflammation are features of the focal lesions of the arterial intima.

From targeting "residual cholesterol risk" to "residual inflammatory risk", the understanding of atherosclerosis as a chronic inflammatory disease has reshaped the cardiovascular field and directed studies and research to target the inflammatory process and host immunity [8,13]. In the 1990s, research evidence suggested that before the onset of vascular events by many years, there usually has a low-grade systemic inflammation period.14 With many breakthroughs in immunological aspect of cancer research, immunotherapy has become a subject of interest in CVD as a potential treatment in many other chronic diseases such as autoimmune diseases, genetic disorders, and diabetes. In CVD research, immunotherapy has also demonstrated strong potential in promoting inflammation resolution, halting atherogenesis, and repairing or restoring heart injury. As such, targeting residual inflammation and manipulating immune system have become the focus of recent CVD research and clinical studies besides standard lipid-lowering methods and lifestyle modification interventions [15-16].

LDL is a heterogeneous particle composed of apolipoprotein B, cholesteryl esters, cholesterol, triacylglycerol, and phospholipids. Deposit of oxidized LDL (Ox-LDL) in the tunica intima triggers a cascade of immune response and hardening of arteries. Ox-LDL generates neoantigens known as oxidation-specific epitopes (OSEs), which are carried by dying cells, micro vesicles, and damaged proteins and lipoproteins [17] As markers of oxidative modified endogenous structures, OSEs activate the immune system to produce antibodies in order to clear them and maintain homeostasis.5,12 A sterile inflammation, as seen in atherosclerosis, can be triggered by the accumulation of OSEs via the actions of several immune cell types [18]. Excessive inflammation drives deleterious effects in atherosclerosis. The high heterogeneity of plaque and vascular leukocytes in atherosclerotic lesions makes targeting specific cell subtypes important, to inhibit inflammation while preserving the normal function of humoral immunity. One of the biggest challenges in using immunotherapy to treat atherosclerosis is the immune side effects of targeting certain important cell signaling and cytokine pathways [19]. Furthermore, inflammation associated with atherogenesis involves systemic and multiorgan involvement such as bone marrow and spleen, and is not restricted to local tissues. Current research in hematology and stem cells has provided new perspectives and opened new avenues for future possibilities in understanding atherosclerosis for the development of more potent therapies [20-22].

Secondary inflammatory risk factors in CVD

COVID-19 and other acute respiratory tract infections

A relationship between some acute respiratory tract infections (ARTI) including COVID-19 and myocarditis, acute cardiovascular events, such as acute myocardial infarction and stroke has been reported in some studies [23-24]. A two to six times increase in cardiovascular events such as MI and stroke were predicted following an acute RTI [25]. Influenza and Streptococcus pneumonia, were associated with adverse cardiac events, such as congestive heart failure, arrhythmias, and MI.26. ARTI triggers a systemic inflammatory response and upregulates pro-inflammatory cytokines (such as IL1-B, TNF-a, and IL-6) that are key mediators in atherogenesis and plaque formation [27]. These pro-inflammatory cytokines enhance monocyte recruitment to arterial walls, differentiation to macrophages, and smooth muscle cell proliferation [28]. At the same time, damage of endothelial cells of coronary vessels opens a door to macrophages migration to related areas and activates apoptosis and inflammatory response.29Another important mechanism driving COVID-related ARTI is the prothrombotic environment caused by an overactivated coagulation system and platelets. While the protein C system and other anticoagulant mechanisms were found to be inhibited [30-31] pro-inflammatory cytokines TNF-a and IL-1B increased plasminogen activator inhibitor 1 levels causing inhibition of fibrinolysis [27,32-33]. This leads to a high probability of thrombus formation and ischemia.

More recently, COVID-19 infection was shown to cause acute cardiac injury along with acute kidney injury and thrombosis, as part of disease complications, besides acute respiratory distress

syndrome [34]. For COVID-19, the angiotensin-converting enzyme 2 (ACE2) protein and cytokine release syndrome in response to direct viral infection in the myocardium lead to secondary inflammatory damage to the heart and multi-organ failure [35] Although people with pre-existing cardiovascular disease and co-morbidities are known to be more susceptible to cardiac manifestations from COVID-19 infection, emerging research has demonstrated that low- risk individuals, such as young adults and children, also develop a variety of cardiac-related complications from coronavirus infection, including myocarditis, cardiomyopathy, heart failure, and pediatric inflammatory multisystem syndrome [36-39] Clinical elevation of cardiac biomarkers such as troponins, CK-MB, D-dimers, are indicating tissue damage from a strong systemic inflammatory response to COVID-19 infection29. Blood clots are formed in the blood vessels causing ischemia after the coronavirus enters through the endothelial layer. People who had been infected by the COVID-19 show significant higher incidents of thrombosis with thrombocytopenia in two weeks post-infection compared with those who had influenza and who received mRNA COVID-19 vaccine [35]. cardiovascular diseases along with neurological issues are among the most reported long COVID-19 complications [40].

Microbiota and cardiovascular disease

The human microbiota, particularly the gut microbiome, has been strongly associated with aging and immune function. The gut microbiota is influenced by both genetics and the environment and affects genetic expression, protein metabolism, and immune cell metabolites. Chronic inflammatory diseases, a category which includes but is not limited to, Alzheimer's disease, rheumatoid arthritis, diabetes, eczema, asthma, IBD, IBS, and CKD present a disturbed bacteria system in the gastrointestinal system. Dysbiosis of the gut microbiota activates a pro-inflammatory status, which favors atherogenesis [41-43]. Chronic low-grade inflammation originating from the gut increases the permeability of the endothelial layer, which facilitates the transfer of bacteria and metabolites from both bacteria and food into the bloodstream, enhancing the risk of systemic inflammation [44-45]. A "microbiota- metabolite-gene" regulatory axis demonstrated a direct impact on carotid atherosclerosis and the incidents of stroke [46].

Bacterial Periodontal infection

The association between periodontal disease (PD) and CVD, which is independent of other known CVD risk factors, has long been recorded [47]. As a part of the residual inflammatory risk that leads to CVD, PD is also a chronic inflammatory disease mostly caused by microbiological etiology, which in turn has posed an inflammatory burden to the immune system. Depending on the stages of development, PD can affect gingiva, bone, and periodontal ligaments supporting the teeth. The interaction between the oral flora and host immune system is the underlying cause of PD and inflammatory response. From gingivitis, a local inflammation, to the development of deep periodontal pockets where gingiva, bone, and supporting periodontal ligament are gone, a systemic inflammation known as chronic periodontitis has formed. Elevated systemic inflammatory markers, including TNF-a, IL-1, IL-6, IL-8, and circulating neutrophils, are observed in patients with chronic periodontitis. Cross-reactive autoantibodies against bacterial antigens, especially those against HSP60 and HSP27, may contribute to atherosclerosis in periodontal infected patients [48-49]

Drivers of inflammatory profile in atherosclerosis of CVD

Age-related somatic mutations

Accumulating evidence has shown a relationship between CVD at an early subclinical stage and aging [50-51]. Age-dependent risk factors, in particular somatic mutations, have garnered increased attention in recent years because of their potential application in personalized medicine. Among them, loss-of-function somatic mutation in the Epigenetic modifier enzyme TET2 (Ten Eleven Translocation) has been shown to be associated with increased CVD.52,21 TET2 is responsible for producing an epigenetic regulatory enzyme which facilitates the conversion of 5-methylcytosine in DNA into 5-hydroxymethylcytosine through oxidation. This mutation causes mosaic blood cells to mix with healthy blood cells, and mutant cells gain a proliferative advantage over normal healthy cells [52-54]. Mechanistically, TET2 loss-of-function in macrophages led to increased NLRP3 inflammasome-mediated interleukin-1B secretion which enhanced atherosclerosis progression [21]. Furthermore, TET2-deficient macrophages are more likely to expand in the atherosclerotic vascular wall, leading to enhanced proatherogenic activities of macrophages with marked increases in proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha.[21]. Of note, in the context of resolving inflammation in innate myeloid cells like macrophages and dendritic cells, TET2 has been identified as a key regulator that specifically inhibits the transcription of interleukin-6 (IL-6) [55]. These studies could lead to new therapies or preventive care strategies for atherosclerosis by monitoring somatic mutations including TET2 mutations.

Dysregulation of Metabolism

Another major driver of atherogenesis is metabolic syndrome (MetS) or metabolism dysregulation [56]. MetS is characterized by atherogenic dyslipidemia (i.e., elevated triglycerides and apolipoprotein B-containing lipoproteins, and low high-density lipoproteins), insulin resistance, elevated blood pressure, and a large waistline, and is widely acknowledged as a common risk factor for atherosclerotic CVDs [57-59] MetS has become a global

pandemic, because not only is it implicated in CVDs, but is also causally associated with a cluster of other medical conditions, such as cholesterol gallstones, fatty liver, obstructive sleep apnea, depression, gout, musculoskeletal diseases, and polycystic ovarian syndrome [57].

MetS correlates with chronic inflammation and oxidative stress from oxidant-antioxidant imbalance, which is present in patients diagnosed with both atherosclerosis and MetS. A variety of antioxidant defense systems play crucial roles in maintaining reactive oxygen species (ROS) homeostasis around vascular endothelium cells [60]. In a variety of MetS, such as excess accumulation of body fat around the abdomen, elevated triglycerides, hyperglycemia, and hypertension, there is consistent evidence of elevated oxidative stress and inflammatory response, such as elevated IL-6, TNFa, and C-reactive proteins (CRPs)(Reference). Non-invasive measurements of subclinical atherosclerosis found increased pulse wave velocity, intima-media thickness, and increased plaque thickness in patients with high waist circumference or elevated fasting glucose [61-62]. Therefore, modification of metabolic syndrome components through lifestyle and dietary changes are crucial interventions to prevent atherosclerosis and CVDs.

Novel immunotherapies for the treatment of CVD

Targeting cytokine response pathway

Cytokines are actively involved in the atherosclerotic inflammatory process by regulating immune cell proliferation, differentiation, and effector functions, [63]. The therapeutic potential of targeting cytokines and their receptors have long been the focus of a lot of research with the goal to halt the atherogenesis progression and make the inflammation pathways under the control.

However, the complexity of immune responses in the progression of atherosclerosis makes targeting cytokine receptor pathways challenging. Immunotherapy research in the field of cardiovascular diseases is primarily centered around investigating the interactions between innate and adaptive immune cells, as well as their release of cytokines and chemokines with immune-regulatory and activating properties. In the context of atherosclerosis, inflammation plays a critical role as a regulator, and it can occur separately from lipid-related factors [64]. One of the most successful studies to target a proinflammatory mediator pathway is the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, which targeted the interleukin (IL)-1B-IL6-CRP axis. The findings from this trial provided evidence that targeting specific inflammatory pathways related to atherosclerosis can effectively decrease the risk of CVD and mortality in individuals with ongoing inflammation, regardless of their low-density lipoprotein (LDL) levels [65].

However, many other unsuccessful clinical trials that also targeted inflammatory pathways suggest that therapies for atherosclerosis must focus on pathways with specificity and associate atherosclerosis inflammation. For example, the Cardiovascular Inflammation Reduction Trial (CIRT), which tested low-dose methotrexate in patients with myocardial infarction, failed to reach its CVD events reduction endpoint, and could not lower CRP, IL-1B, or IL-6 levels. On the contrary, anti-inflammatory agents for treating rheumatoid arthritis (RA), such as DMARDs and TNF-a antagonists, demonstrated therapeutic cardiovascular effects in patients with atherosclerosis and/or rheumatoid arthritis [66-67].

Chemokines are key regulators of immune cells. They work with their receptors in a complex system and orchestrate migration and differentiation of many immune cell types in atherogenesis and CVDs. Targeting chemokines and their receptors is a promising therapeutic area in immunotherapy to treat CVDs. CCR2, CCR5, CXCL12-CXCR4, and heterodimers of CCR5/CXCL4 are some chemokines under active investigation [28]. CCR2- deficiency or knockout in mice models and humans have shown less recruitment of classical monocyte to the MI

lesion sites, reduced left ventricular remodeling, alleviated ischemia injury, and decreased CRP levels [68]. CCL5 deficiency showed less arterial monocyte adhesion and smaller atherosclerotic lesion sizes. Plaque burden and macrophage plaque content were also reduced in mice models of CCL5-knockout (Reference). CCL5 antagonists, Maraviroc, which was proved to treat HIV significantly improved some biomarkers for CVDs, such as endothelial dysfunction, arterial stiffness, as well as early atherosclerosis [69].

Engineered cytokines and superkines

Various immune side effects and narrow therapeutic window are two big challenges of manipulating cytokines and their receptors due to their complex interaction with the immune system. As our understanding of the structural principles and functional signals governing cytokine-receptor interactions has advanced, it has become viable to artificially manipulate cytokine signaling through the application of protein engineering and synthetic immunology techniques [70]. There is progress in modifying cytokine receptors interface to enhance affinity with IL-2 “superkine” and IL-15 “super agonist”. The process of linking cytokines to larger carrier molecules, such as polyethylene glycol (PEG), albumin, or fusion with the Fc portion of immunoglobulins (Igs), is commonly employed [71].

Structural enhancement to generate “immune cytokines” with antibody-cytokine fusion properties to selectively target cells shown can improve efficacy. Following the modification, these immune cytokines gain the ability to selectively target particular

cell subtypes that exhibit higher local concentrations compared to normal tissues. One such example is CD64, which is abundantly expressed on the surface of macrophages, monocytes, and their precursor cells due to its high-affinity Fcγ receptor 1 characteristics. Consequently, immunotoxins designed to target CD64 have been evaluated in animal models of inflammation, including skin, rheumatoid arthritis, and ischemia-induced kidney injury. Notably, no adverse effects have been observed in relation to the presence of the antigen on other circulating leukocytes within the system [72].

Bi-specific immune cell ("engager cytokines"), and bispecific killer cell engagers (BiKEs) bring two major cytokine modifications [70]. The field of synthetic biology is actively exploring various non-natural engineered cytokines, fully synthetic analogs, as well as related functional domains or independent cytokine receptors, collectively referred to as "super cytokines". Super cytokines are designed with the purpose to avoid some intrinsic properties of natural cytokines that limit their therapeutic potentials, such as short half-life in circulation, off-target effects, and inherent pleiotropic functions.

GM-CSF-CCL2 fusokine, a fusion protein of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Chemokine Ligand 2 (CCL2), specifically targets C-C motif chemokine receptor 2 (CCR2). CCR2 is a chemokine receptor that is widely expressed on lymphocytes and plays a crucial role in various chronic inflammatory diseases, including CVD [73]. GMME1, a unique fusion protein consisting of GM-CSF and a truncated form of CCL2 (N-terminal truncation), is currently under investigation as a targeted immunosuppressant for CCR2. The extended plasma half-life of GM-CSF has significantly increased bioavailability of the C-terminal CCL2 fragment. By decreased CCR2-positive lymphocytes and monocytes which play key roles in the onset and advancement of autoimmune diseases [74], GMME1 has proved to significantly improve clinical symptoms of inflammatory arthritis in mice models and systemic proinflammatory cytokines [75]. ALX-0061, as a bi-specific, with two-domain Nanobody targeting interleukin-6 receptor (IL-6R) and HAS simultaneously, has completed phase IIb and phase II clinical trials to treat Rheumatoid Arthritis and Systemic Lupus Erythematous, respectively [76-77]. All these progresses made attempting to engineer cytokines may help overcome some key challenges researches were facing when targeting cytokines pathways to control atherogenesis and immune dysregulation in CVDs.

Specialized Pro-resolving Mediators in atherosclerosis

The other side of immunotherapy focus on inflammation resolution. Defective inflammation resolution causes persistent inflammation, dysregulation of tissue healing and tissue damage by necrosis. This defect in the resolution program underlines several chronic inflammatory diseases such as CVDs. A hallmark of inflammation resolution is the biosynthesis of active resolution mediators known as Specialized Pro-resolving Mediators (SPMs), which temper pro-inflammation and promote tissue homeostasis by activating tissue repair and regeneration pathways [78].

Specialized pro-resolving mediators (SPMs) belong to a family of mediators existing in the local tissue microenvironment that counterbalance numerous proinflammatory signals. SPMs govern the extent and duration of inflammation by managing the movement of leukocyte and efferocytosis [79]. These SPMs include arachidonic acid-derived lipoxins, eicosatetraenoic acid-derived resolve's, docosahexaenoic acid-derived resolvins, protectins, and maresins [80]. Since SPMs promote tissue repair and regeneration, they play a protective role in specific diseases such as injury-induced neointimal hyperplasia, myocardial infarction, and atherosclerosis [81]. Additionally, they were found can potentially promote tissue regeneration and protect against atherosclerosis, aneurysms, and restenosis [81].

In human and murine models of atherosclerosis, the imbalance between specialized pro-resolving mediators and proinflammatory mediators is reported to be one of the drivers of atherosclerosis progression [82]. Biosynthetic enzymes such as 5-lipoxygenase and 12/15-lipoxygenase are involved in the generation of resolving SPMs and pro-inflammatory LTs. 12/15-lipoxygenase (12/15 LOX) has catalytic activities that lead to the generation of both pro- and anti-inflammatory metabolites [83]. 5-lipoxygenase (5-LOX), 5-LOX-activating protein and leukotriene A4 (LTA4) hydrolase are important enzymes for LT biosynthesis. There is evidence that gene variants that encode these enzymes cause CVDs [83]. When treated with a 5-LOX-activating protein inhibitor, C- reactive protein levels (a pro-inflammatory protein) were decreased in certain patients who had both MI and an enzyme gene variant [83]. In addition, when a diet rich in omega-3 fatty acids was given to people with the same 5- LOX variant, they developed less carotid atherosclerosis compared with the control group [84]. Although more studies are needed to determine the function of eicosatetraenoic acid (EPA) and the mechanism of these single- nucleotide polymorphisms in pro-resolving inflammation in CVDs [85], recent works have shown a connection between EPA and 5-LOX variant in decreasing CVD risk.

Another significant role of SPMs in promoting inflammatory resolution in atherosclerosis is its ability to enhance efferocytosis, a non-inflammatory clearance of apoptotic cells (ACs) in macrophages [85]. It has been shown that 12/15-LOX (an essential SPM biosynthetic enzyme), is significantly expressed on tissue-resident macrophages, which are specialized phagocytic cells, compared to monocyte-derived macrophages [83]. Also, metabolites from 12/15-LOX, such as lipoxins, enhance non-inflammatory phagocytosis of ACs by macrophages [86].

Another important endogenous lipid metabolite derived from polyunsaturated fatty acids, resolvins, were shown to have inflammation resolution properties. Resolvin D1 (RvD1) was especially found to regulate the NLR family pyrin domain containing 3 (NLRP3) inflammasome by degrading NLRP3 via autophagy [87], with a potential role in IL1B-driven atherosclerosis disease. In summary, pro-resolving mediators hold the potential in resolving inflammation-causing atherosclerosis and associated CVD complications.

Immune cell therapy

Targeting heart fibrosis for cardiac remodeling. Heart failure (HF) causes a significant burden on both families and society with an estimated economic cost of 346.17 billion USD globally each year [88-90]. By 2030, the prevalence of HF is expected to increase by 46% [91]. The five-year survival rate among symptomatic heart failure patients is less than 50%, with 2% to 17% dying each year [92]. Heart failure is mostly caused by persistent mechanical and/or neurohormonal stress to the myocardium that leads to cardiac remodeling. The stress- induced changes to cardiac function and structure leads to loss in normal ventricular constricting function and rhythms [88-93].

The current standard of pharmacological treatment of HF focuses on managing preload and afterload to keep hemodynamics stable, improve ejection fraction and cardiac output, and slow down and reverse remodeling [94]. However, heart transplantation is still the only final solution to cure heart failure.

Fibrotic cardiac remodeling from excessive and disordered fibrotic deposits is one of the primary reasons for myocardial stiffness, decreased diastolic relaxation, disrupted cardiac electrical conduction, increased lethal arrhythmias, and eventually heart failure. Understanding the mechanisms that block fibrotic remodeling of the heart represents a key question that may lead to a breakthrough in heart failure management.

The role of T cells in HF. Although medications used to treat pulmonary fibrosis, such as pirfenidone, show an ability to decrease cardiac fibrosis, they result in minimal improvement in diastolic function [95]. As a subset of lymphocytes, regulatory T cells (Tregs) have demonstrated remarkable anti-inflammatory and cardioprotective properties [5,96-97]. Many studies have shown its role as an immune regulator of unwanted immune responses as well as a regulator of pro-inflammatory T cells [98]. Immunotherapy with adoptive transfer of regulatory T cells (Tregs) in preclinical mouse models has demonstrated the ability to not only successfully block cardiac fibrosis, but also down-regulate pro-inflammatory cytokines and inflammatory cell infiltration [93].

The role of macrophages. The close relation between macrophage and fibroblasts directly influences the tissue microenvironment and disease outcomes [99]. However, the complexity of their distinct ontogenetic and transcriptional profiles in atherogenesis, tissue injury progression, cardiac disease, and pro-inflammatory versus inflammation resolution makes targeting them challenging [28,93]. There are several efforts to understand the individual contribution of tissue-resident versus circulating monocytes differentiated into macrophages to the fibrotic response. It has become evident that cardiac tissue-resident macrophages may drive the reduction of fibrosis activation, while macrophages recruited from pro-inflammatory circulating monocytes may promote pathogenic fibrosis formation [11,100].

Macrophages and other immune cells also directly participate in extracellular matrix (ECM) formation during cardiac injury and remodeling, such as macrophage-derived type IV collagens in the scar tissue formation in the heart [101]. Therapeutic modulation of macrophages beyond anti-inflammatory immunotherapies, such as targeting macrophage subsets to promote ECM remodeling, holds a promising future with expanding interests in cardiovascular immunology and technological advances [93].

Advancement in Heart Failure therapies

Engineering T cells- Immunotherapy for cardiac injury and repair. Engineering cytotoxic T cells to target specific antigens on cells by either modifying a T-cell receptor (TCR) or a chimeric antigen receptor (CAR) has proven very successful in immuno-oncology [102-104]. In cardiovascular diseases, especially heart failure, CAR-T therapy may bring novel immuno-therapeutic approaches to promote direct post-injury myocardium repair. Adoptive transfer of T cells that express a chimeric antigen receptor (CAR) targeting fibroblast activation protein (FAP) markedly diminished cardiac fibrosis and reinstated function following injury in a mouse model of heart disease. After treating experimental injured mice with FAP-CAR T cells, a reduction in fibrosis and partial restoration of both systolic and diastolic cardiac function was observed [19]. Notably, CAR-T cells targeting FAP are not new in cancer immunotherapy and have been used to treat mesothelioma in phase I clinical trial (NCT01722149) with a good safety profile [105-106]. Using CAR-T cells to target cardiac fibrosis did not further increase cytokine levels with self-limited partial cardiotoxicity, which resolved within 8 weeks [19]. In addition, only mild inflammation was seen when inflammatory and immune genes were examined.

Although more research is needed to understand CAR constructs for antigen affinities, efficacies, safety profiles, and alternative antigens expressed by pathogenic cardiac fibroblasts, CAR T-cell therapy might be a breakthrough in immunotherapy to treat cardiac injury and restore its function [19,102,107]. In a recent study, investigators injected CD5-targeted lipid nanoparticles (LNPs) containing the messenger RNA (mRNA) to reprogram

T lymphocytes. By using this method, therapeutic CART cells were generated in vivo. Antifibrotic CAR T (anti-FAP CAR T) cells also demonstrated evidence of trogocytosis and retained the target antigen which accumulated in the spleen [107]. Although the duration of reprogramming was transient, a potent reduction in heart fibrosis and heart size was observed, caused in part by an expanded T cell population. No persisting anti-fibroblast T cell activities were observed one week after treatment. This approach was manageable in dose and timing, adding extra safety features to its profile.

CAR T cell therapy has been approved by FDA since 2017 to treat certain leukemias and lymphoma. Also, LNP-mRNA technology was important in the development of mRNA COVID-19 vaccines, which holds promise for cardiac repair post-injury. Future studies will improve dosing strategies, LNP composition, and optimize targeting approaches to better manage therapeutic effects and toxicities [108].

Gene editing therapies and personalized diagnosis and treatment future in CVD. CRISPR gene editing technology is exciting because it enables the re-wiring of many gene-related chronic diseases. Verve Therapeutics has started its phase 1b clinical trial, VERVE-101, to use the CRISPR base editing technique to permanently turn off the proprotein convertase subtilisin/Kexin type 9 (PCSK9) gene in the liver of patients with heterozygous familial hypercholesterolemia (HeFH). The proprotein convertase subtilisin/Kexin type 9 (PCSK9) gene is found to interfere with and block the natural recycling of LDL receptors, which results in impaired LDL- C clearance from the plasma [109]. Gain-of-function PCSK9 mutation is one of the genetic causes of familial hypercholesterolemia and has become an important target in CVD treatment [110-112].

The limitations of the current standard of care treatment for HeFH includes rigorous patient adherence, regular healthcare access, and extensive healthcare infrastructure [113]. Using CRISPR gene editing to fundamentally turn off a disease-causing gene can be a game changer. This technique has been intensively studied in some other rare diseases such as Huntington's disease, sickle cell disease, transthyretin (ATTR) amyloidosis [114].

Personalized diagnosis and treatment for patients with cardiovascular diseases is the future. A standard measure to evaluate the pathogenic changes in damaged cells by employing single-nucleus RNA sequencing (snRNAseq) transcriptional analyses examines the cellular composition and molecular states of healthy human hearts [115-116]. From snRNAseq analyses of different kinds of cells involved in heart muscle and its function, it was observed that certain cell types are directly related to heart failure, with information about their locations, mutual relationships, and genetic expression variants. Single-cell RNA sequencing (scRNA-seq) on the other hand demonstrated high capacity to identify immunocytes [115]. Combining both sequencing tools may greatly facilitate finding any variants from healthy human hearts that can cause dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), as well as targeting immune cells involved in other disorders associated with heart failure via evaluating the influence of genotype in heart failure pathways and provide personalized diagnosis, and therapeutic targets for intervention guidance [116].

Conclusion

Despite our current understanding and the steady improvement in managing and treating CVD-related issues, it still remains a major cause of death worldwide. Our understanding of the etiology of the disease has evolved to appreciate the detrimental role of persistent inflammation in driving CVD progression. Multifactorial chronic as well as acute inflammation and immune dysregulations mechanisms are underlying the formation of atherosclerosis, cardiac remodeling, and various kinds of cardiovascular diseases. How to harness and manipulate our immune system that it can be used to do only right thing to our body is a long-standing goal for any researchers. Great advances made in cancer immunotherapy have proven that there is a great potential in the future of CVD immunotherapy. In this review, we summarized some new understandings about the inflammatory mechanisms causing atherosclerosis and some other cardiovascular diseases. We also highlighted some advances made in CVD therapies from immune responses and immune cells to tackle atherogenesis, inflammation resolution, and cardiac fibrosis and remodeling. Although several studies have demonstrated some form of efficacy in targeting inflammation for disease management, it is important to fully understand the associated side effects as seen in the CANTOS trial, suggesting that anti-inflammatory therapies have a potential to compromise host defenses against infections. Additionally, mechanistic studies are needed to fully understand how to better target the inflammatory aspect of CVD without compromising host immunity. Finally, using a big human genetic data and gene therapies can help identify specific targets to develop therapies, allowing for personalized individual specific treatment with greater therapeutic efficacy and safety.

References

1. Roth GA, Manseh GA, Johnson CO, Addolorato G, Ammirati E, *et al.* ((2020) Global Burden of Cardiovascular Diseases and Risk Factors; 1990–2019. J Am CollCardiol 76: 2982–3021.
2. GBD 2019 Diseases and Injuries Collaborators (2020) Global burden of 369 diseases and injuries in 204 countries and territories; 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 396:1204-1222.
3. Lopez, A. D. & Adair, T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. International Journal of Epidemiology 48,

1815– 1823 (2019).

4. World Health Organization. *World health statistics 2017: monitoring health for the SDGs; sustainable development goals*. (World Health Organization; 2017).

5. Roy P, Orecchioni M, Ley K (2022) How the immune system shapes atherosclerosis: roles of innate and adaptive immunity. Nat Rev Immunol 22: 251-265.

6. CDC. Heart Disease Facts | cdc.gov. *Centers for Disease Control and Prevention* (2022).

7. LaRosa JC, Hunninghake D, Bush D Criqui MH, Getz GS, et al. (1990) The cholesterol facts. A summary of the evidence relating dietary fats; serum cholesterol; and coronary heart disease. A joint statement by the American Heart Association and the National Heart; Lung; and Blood Institute. The Task Force on Cholesterol Issues; American Heart Association. Circulation 81: 1721-1733.

8. Ridker PM (2016) Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. Eur Heart J 37: 1720-1722.

9. Sampson UK, Fazio S, Linton MF (2012) Residual Cardiovascular Risk Despite Optimal LDL Cholesterol Reduction with Statins: The Evidence; Etiology; and Therapeutic Challenges. Curr Atheroscler Rep 14: 1-10.

10. Fiolet ATL, Opstal TSJ, Silvis MJM, Cornel JH, Mosterd A (2022) Targeting residual inflammatory risk in coronary disease: to catch a monkey by its tail. Neth Heart J 30: 25-37.

11. Rurik JG, Aghajanian H, Epstein JA (2021) Immune Cells and Immunotherapy for Cardiac Injury and Repair. Circ Res 128: 1766-1779.

12. Stemme S, Faber B, Holm O, Wiklund J, Witztum J L, et al. (1995) T lymphocytes from humanatherosclerotic plaques recognize oxidized low-density lipoprotein. Proc Natl Acad Sci U S A 92; 3893-3897.

13. Libby P (2021) The changing landscape of atherosclerosis. Nature 592: 524-533.

14. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997) Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. N Engl J Med 336: 973-979.

15. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, et al. (1994) The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med 331: 417-424.

16. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, et al. (1996) Elevated Levels of Interleukin-6 in Unstable Angina. Circulation 94: 874-877.

17. Leibundgut G, Witztum JL, Tsimikas S (2013) Oxidation-specific epitopes and immunological responses: Translational biotheranostic implications for atherosclerosis. Current Opinion in Pharmacology 13: 168-179.

18. Binder CJ, Papac-Milicevic N, Witztum JL (2016) Innate sensing of oxidation-specific epitopes in health and disease. Nat Rev Immunol 16: 485-497.

19. Aghajanian H, Toru Kimura 4, Rurik JG, Hancock AS, Leibowitz MS, Li Li, et al. (2019) Targeting cardiac fibrosis with engineered T cells. Nature 573, 430–433.

20. Patel, SH, Christodoulou C, Weinre C, QiYU, da Rocha EL et al. (2022) Lifelong multilineage contribution by embryonic-born blood progenitors. Nature 606: 747-753.

21. Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, et al. (2017) Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science 355: 842-847.

22. Ribeiro R, Macedo JC, Costa M, Ustiyan V, Shindyapina AV, et al. (2022) In vivo cyclic induction of the FOXM1 transcription factor delays natural and progeroid aging phenotypes and extends healthspan. Nat Aging 2: 397-411.

23. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P et al. (2004) Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. New England Journal of Medicine 351: 2611-2618.

24. Warren-Gash C, Blackburn R, Whitaker H, McMenamin J, Hayward AC (2018) Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. Eur Respir J 51: c1701794.

25. Davidson JA, Banerjee A, Smeeth L, McDonald HI, Grint D,Herrett E, et al. (2021) Risk of acute respiratory infection and acute cardiovascular events following acute respiratory infection among adults with increased cardiovascular risk in England between 2008 and 2018: a retrospective, population-based cohort study. Lancet Digit Health 3: e773-e783.

26. Brown AO, Mann B, Gao G, Hankins JS, Humann J, et al. (2014) Streptococcus pneumoniae Translocates into the Myocardium and Forms Unique Microlesions That Disrupt Cardiac Function. PLOS Pathogens 10: e1004383.

27. Bazaz R, Marriott HM, Francis SE, Dockrell DH (2013) Mechanistic links between acute respiratory tract infections and acute coronary syndromes. J Infect 66: 1-17.

28. Lutgens, E. et al. (2019) Immunotherapy for cardiovascular disease. European Heart Journal 40: 3937-3946.

29. Vosko I, Zirlik A, Bugger H (2023) Impact of COVID-19 on cardiovascular disease. Viruses 15: 508.

30. Levi M, van der Poll T, Büller HR (2004) Bidirectional Relation Between Inflammation and Coagulation. Circulation 109: 2698-2704.

31. Schouten M, Wiersinga WJ, Levi M, van der Poll T (2008) Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 83: 536-545.

32. Shorr AF, Bernard GR, Dhainaut JF, Russell JR, Macias WL, et al. (2006) Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome. Crit Care 10: R92.

33. van der Poll T, Levi M, Büller HR, van Deventer SJ, de Boer JP, et al. (1991) Fibrinolytic response to tumor necrosis factor in healthy subjects. J Exp Med 174: 729-732.

34. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, et al. (2021) Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 38: 101019.

35. Taquet M, Husain M, Geddes JR, Luciano S, Harrison,PJ (2021) Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 COVID-19 cases. EClinicalMedicine 39: 101061.

36. Chang WT, Toh HS, Liao CT, Yu WL (2021) Cardiac Involvement of COVID-19: A Comprehensive Review. Am J Med Sci 361: 14-22.

37. Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, et al. (2021) Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ 373: n1098.

38. Sidik SM (2022) Heart disease after COVID: what the data say. Nature 608: 26-28.

39. Srinivasan A, Wong F, Couch LS, Wang BX (2022) Cardiac

Complications of COVID-19 in Low-Risk Patients. Viruses 14: 1322.

40. Xie Y, Xu E, Bowe B, Al-Aly Z (2022) Long-term cardiovascular outcomes of COVID-19. Nat Med 28: 583-590.

41. Mitra S, Drautz-Moses DI, Alhede M, Maw MT, Liu Y, et al. (2015) In silico analyses of metagenomes from human atherosclerotic plaque samples. Microbiome 3: 38.

42. Ionescu RF, Enache RM, Cretoiu SM, Cretoiu D (2022) The Interplay Between Gut Microbiota and miRNAs in cardiovascular diseases. Front Cardiovasc Med 9: 856901.

43. Ziganshina EE, Sharifullina DM, Lozhkin AP, Khayrullin RN, Ignatyev IM, et al. (2016) Bacterial Communities Associated with Atherosclerotic Plaques from Russian Individuals with Atherosclerosis. PLoS One 11: e0164836.

44. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, et al. (2022) Pathophysiology of Atherosclerosis. Int J Mol Sci 23: 3346.

45. Gou W, Fu Y, Yue L, Chen GD, Cai X, et al. (2021) Gut microbiota, inflammation, and molecular signatures of host response to infection. J Genet Genomics 48: 792-802.

46. Ji L, Chen S, Gu G, Zhou J, Wang W, et al. (2021) Exploration of Crucial Mediators for Carotid Atherosclerosis Pathogenesis Through Integration of Microbiome, Metabolome, and Transcriptome. Front Physiol 12: 645212.

47. Choi H, Dey AK, Priyamvara A, Aksentijevich M, Bandyopadhyay D, et al. (2021) Role of Periodontal Infection, Inflammation and Immunity in Atherosclerosis. Curr Probl Cardiol 46: 100638.

48. Ling MR, Chapple ILC, Matthews JB (2016) Neutrophil superoxide release and plasma C-reactive protein levels pre- and post-periodontal therapy. J Clin Periodontol 43: 652-658.

49. Kaiser F, Donos N, Henderson B, Alagarswamy R, Pelekos G, et al. (2018) Association between circulating levels of heat-shock protein 27 and aggressive periodontitis. Cell Stress and Chaperones 23: 847-856.

50. Hardy R, Lawlor DA Kuh D (2015) A life course approach to cardiovascular aging. Future Cardiol 11: 101-111-113.

51. Newman AB, Arnold AM, Naydeck BL, Fried LP, Burke GL, et al. (2003) 'Successful Aging': Effect of Subclinical Cardiovascular Disease. Arch Intern Med 163: 2315-2322.

52. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, et al. (2014) Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes. N Engl J Med 371: 2488-2498.

53. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, et al. (2014) Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med 20: 1472-1478.

54. Fujino T, Asada S, Goyama S, Kitamura T (2022) Mechanisms involved in hematopoietic stem cell aging. Cell Mol Life Sci 79: 473.

55. Zhang Q, Zhao K, Shen Q, Han Y, Gu Y, et al. (2015) Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature 525: 389-393.

56. Guembe MJ, Fernandez-Lazaro CI, Sayon-Orea C, Toledo E, Moreno-Iribas C, et al. (2020) Risk for cardiovascular disease associated with metabolic syndrome and its components: a 13-year prospective study in the RIVANA cohort. Cardiovasc Diabetol 19: 195.

57. Grundy SM (2008) Metabolic Syndrome Pandemic. Arterioscler Thromb Vasc Biol 28: 629-636.

58. NHLBI, N. Metabolic Syndrome - What Is Metabolic Syndrome? | NHLBI, NIH. National Heart, Lung, and Blood Institute.

59. Vatashchuk MV, Bayliak MM, Hurza VV, Storey KB, Lushchak VI (2022) Metabolic Syndrome: Lessons from Rodent and Drosophila Models. Biomed Res Int 2022: 5850507.

60. Dziegielewska-Gesiak S (2021) Metabolic Syndrome in an Aging Society – Role of Oxidant-Antioxidant Imbalance and Inflammation Markers in Disentangling Atherosclerosis. Clin Interv Aging 16: 1057-1070.

61. Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP (2019) Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol 70.

62. Namdarimoghaddam P, Fowokan A, Humphries KH, Mancini GBJ, Lear S (2021) Association of "hypertriglyceridemic waist" with increased 5-year risk of subclinical atherosclerosis in a multi-ethnic population: a prospective cohort study. BMC Cardiovasc Disord 21: 63.

63. Márquez AB, van der Vorst EPC, Maas SL (2021) Key Chemokine Pathways in Atherosclerosis and Their Therapeutic Potential. J Clin Med 10: 3825.

64. Tuñón J, Badimón L, Bochaton-Piallat ML, Cariou B, Daemen MJ, et al. (2019) Identifying the anti-inflammatory response to lipid lowering therapy: a position paper from the working group on atherosclerosis and vascular biology of the European Society of Cardiology. Cardiovasc Res 115: 10-19.

65. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, et al. (2017) Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 377: 1119-1131.

66. Bathon JM, Giles JT, Solomon DH (2018) Editorial: Tumor Necrosis Factor Antagonists: Killing Two Birds with One Biologic Stone. Arthritis Rheumatol 70: 326-329.

67. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, et al. (2011) Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis 70: 576-582.

68. Zhang H, Yang K, Chen F, Liu Q, Ni Jet al. (2022) Role of the CCL2-CCR2 axis in cardiovascular disease: Pathogenesis and clinical implications. Front Immunol 13.

69. Francisci D, Pirro M, Schiaroli E, Mannarino MR, Cipriani S, et al. (2019) Maraviroc Intensification Modulates Atherosclerotic Progression in HIV-Suppressed Patients at High Cardiovascular Risk. A Randomized, Crossover Pilot Study. Open Forum Infect Dis 6: ofz112.

70. Zheng X, Wu Y, Bi J, Huang Y, Cheng Y, Yangyang Li, et al. (2022) The use of supercytokines, immunocytokines, engager cytokines, and other synthetic cytokines in immunotherapy. Cell Mol Immunol 19: 192-209.

71. Abbas AK, Trotta ER, Simeonov D, Marson A, Bluestone JA (2018) Revisiting IL-2: Biology and therapeuticrospects. Sci Immunol 3: eaat1482.

72. Murer P, Neri D (2019) Antibody-cytokine fusion proteins: a novel class of biopharmaceuticals for the therapy of cancer and of chronic inflammation. N Biotechnol 52: 42-53.

73. Nahrendorf M, Swirski FK, (2017). Cholesterol, CCR2, and monocyte phenotypes in atherosclerosis. European Heart Journal 38: 1594-159.

74. Lotfi N, et al. (2019) Roles of GM-CSF in the Pathogenesis of Autoimmune Diseases: An Update. Frontiers in Immunol 10: 1265.

75. Rafei M, Berchiche YA, Birman E, Boivin MN, Young YK, et al. (2009) An engineered GM-CSF-CCL2 fusokine is a potent inhibitor

of CCR2-driven inflammation as demonstrated in a murine model of inflammatory arthritis. J Immunol 183: 1759-1766.

76. Yip RML, Yim CW (2021) Role of Interleukin 6 Inhibitors in the Management of Rheumatoid Arthritis. J Clin Rheumatol 27: e516-e524.

77. Ablynx. (2019) A Phase II Multicenter, Randomized, Double-blind, Placebo Controlled, Dose-range Finding Study to Evaluate the Safety and Efficacy of ALX-0061 Administered Subcutaneously in Subjects With Moderate to Severe Active Systemic Lupus Erythematosus.

78. Serhan CN, Chiang N , Dalli J (2018) New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. Molecular Aspects of Medicine 64: 1-17.

79. Doran AC, Yurdagul A, Tabas I (2020) Efferocytosis in health and disease. Nat Rev Immunol 20: 254-267.

80. Chiang N, Serhan CN (2020) Specialized pro-resolving mediator network: an update on production and actions. Essays Biochem 64: 443-462.

81. Díaz Del Campo LS, Rodrigues-Díez R, Salaices M, Briones AM, García-Redondo AB (2022) Specialized Pro-Resolving Lipid Mediators: New Therapeutic Approaches for Vascular Remodeling. Int J Mol Sci 23: 3592.

82. Bäck M, Yurdagul A, Tabas I, Öörni K, Kovanen PT (2019) Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. Nat Rev Cardiol 16: 389-406.

83. Singh NK, Rao GN (2019) Emerging role of 12/15-Lipoxygenase (ALOX15) in human pathologies. Prog Lipid Res 73: 28-45.

84. Khan SU, Lone AN, Shahzeb Khan M, Virani SS, Blumenthal RS, et al. (2021) Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. EClinicalMedicine 38: 100997.

85. Fredman G, Tabas I (2017) Boosting Inflammation Resolution in Atherosclerosis. Am J Pathol 187: 1211-1221.

86. Snodgrass RG, Brüne, B (2019) Regulation and Functions of 15-Lipoxygenases in Human Macrophages. Front Pharmacol 10:719.

87. Cao L, Wang Y, Wang Y, Lv F, Liu L, et al. Resolvin D2 suppresses NLRP3 inflammasome by promoting autophagy in macrophages. Exp Ther Med 22, 1222 (2021).

88. Lippi G, Sanchis-Gomar, F (2020) Global epidemiology and future trends of heart failure. AME Medical Journal 5.

89. Ni H, Xu J (2015) Recent Trends in Heart Failure-related Mortality: United States, 2000-2014. NCHS Data Brief 1-8.

90. Savarese G, Lund LH (2017) Global Public Health Burden of Heart Failure. Card Fail Rev 3: 7-11.

91. Zhai M, Du, Liu, C. & Xu H, (2021) The Effects of Dapagliflozin in Patients With Heart Failure Complicated With Type 2 Diabetes: A Meta-Analysis of Placebo-Controlled Randomized Trials. Front Clin Diabetes Healthc.

92. McKinsey TA, Foo R, Anene-Nzelu CG, Travers JG, Vagnozzi RJ, et al. (2022) Emerging epigenetic therapies of cardiac fibrosis and remodeling in heart failure: from basic mechanisms to early clinical development. Cardiovasc Res 118: 3482-3498.

93. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, et al. (2022) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 145: e895-e1032.

94. Lewis GA, Dodd S, Clayton D, Bedson E, Eccleson H, (2021) et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med 27: 1477-1482.

95. Nevers T, Salvador AM, Grodecki-Pena A, Knapp A, Velázquez F, et al. (2015) Left Ventricular T-Cell Recruitment Contributes to the Pathogenesis of Heart Failure. Circ Heart Fail 8: 776-787.

96. Theall B, Alcaide P (2022) The heart under pressure: immune cells in fibrotic remodeling. Curr Opin Physiol 25: 100484.

97. Martini E, Stirparo GG, Kallikourdis M (2018) Immunotherapy for cardiovascular disease. J Leukoc Biol 103: 493-500.

98. Buechler MB, Fu W, Turley SJ (2021) Fibroblast-macrophage reciprocal interactions in health, fibrosis, and cancer. Immunity 54: 903-915.

99. Kim AJ, Xu Na, Umeyama K, Hulin A, Ponny SR, et al. (2020) Deficiency of Circulating Monocytes Ameliorates the Progression of Myxomatous Valve Degeneration in Marfan Syndrome. Circulation 141: 132-146.

100. Bevan L, Lim ZW, Venkatesh B, Riley PR, Martin P, et al. (2020) Specific macrophage populations promote both cardiac scar deposition and subsequent resolution in adult zebrafish. Cardiovasc Res 116: 1357-1371.

101. Maldini C, Ellis G, Riley JL (2018) CAR T cells for infection, autoimmunity and allotransplantation. Nat Rev Immunol 18: 605-616.

102. Moreno-Cortes E, Forero-Forero JV, Lengerke-Diaz PA, Castro JE (2021) Chimeric antigen receptor T cell therapy in oncology - Pipeline at a glance: Analysis of the ClinicalTrials.gov database. Crit Rev Oncol Hematol 159: 103239.

103. June CH, Sadelain M (2018) Chimeric Antigen Receptor Therapy. N Engl J Med 379: 64-73.

104. Curioni A, Britschgi C, Hiltbrunner S, Bankel L, Gulati P, et al. (2021) A phase I clinical trial of malignant pleural mesothelioma treated with locally delivered autologus anti-FAP-targeted CAR T-cells. Annals of Oncology 30: v501.

105. Bughda R, Dimou P, D'Souza RR, Klampatsa A (2021) Fibroblast Activation Protein (FAP)- Targeted CAR-T Cells: Launching an Attack on Tumor Stroma. Immunotargets Ther 10: 313-323.

106. Rurik JG, Tombácz I, Yadegari A, O Méndez Fernández P, Shewale SV, et al. (2022) CAR T cells produced in vivo to treat cardiac injury. Science 375: 91-96.

107. 1Ktori S (2022) CAR T Cells Generated In Vivo Reverse Fibrosis, Restore Cardiac Function in Mice with Heart Failure. GEN - Genetic Engineering and Biotechnology News.

108. Spolitu S, Dai W, Zadroga JA, Ozcan, L (2019) PCSK9 and Lipid Metabolism. Curr Opin Lipidol 30: 186-191.

109. Abifadel M, Guerin M, Benjannet S, Rabès JP, Le Goff W, et al. (2012) Identification and characterization of new gain-of-function mutations in the PCSK9 gene responsible for autosomal dominant hypercholesterolemia. Atherosclerosis 223: 394-400.

110. Bayona A, Arrieta F, Rodríguez-Jiménez C, Cerrato F, Rodríguez-Nóvoa S, et al. (2020) Loss-of-function mutation of PCSK9 as a protective factor in the clinical expression of familial hypercholesterolemia. Medicine (Baltimore) 99: e21754.

111. Guo Q, Feng X, Zhou Y (2020) PCSK9 Variants in Familial Hypercholesterolemia: A Comprehensive Synopsis. Front Genetic 11: 1020.

112. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB (2019) Diagnosis and Treatment of Heterozyous Familial

Hypercholesterolemia. J Am Heart Assoc 8: e013225.

113. CRISPR infusion eliminates swelling in those with rare genetic disease | Science | AAAS.

114. Chaudhry F, Isherwood J, Bawa T, Patel D, Gurdziel K, et al. (2019) Single-Cell RNA Sequencing of the Cardiovascular System: New Looks for Old Diseases. Front Cardiovasc Med 6: 173.

115. Reichart D, Lindberg EL, Maatz H, A Miranda AM, Viveiros A, et al. (2022) Pathogenic variants damage cell composition and single cell transcription in cardiomyopathies. Science 377: eabo1984.

116. Wen F, Tang X, Xu L, Qu H (2022) Comparison of single-nucleus and single-cell transcriptomes in hepatocellular carcinoma tissue. Mol Med Rep 26: 339.