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Targeting Macrophage Phenotype for Treating Heart Failure: A New Approach

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Abstract: Heart failure (HF) is a disease with high morbidity and mortality rates worldwide and significantly affects human health. Currently, the treatment options for HF are limited, and there is an urgent need to discover new therapeutic targets and strategies. Macrophages are innate immune cells involved in the development of HF. They play a crucial role in maintaining cardiac homeostasis and regulating cardiac stress. Recently, macrophages have received increasing attention as potential targets for treating HF. With the improvement of technological means, the study of macrophages in HF has made great progress. This article discusses the biological functions of macrophage phagocytosis, immune response, and tissue repair. The polarization, pyroptosis, autophagy, and apoptosis are of macrophages, deeply involved in the pathogenesis of HF. Modulation of the phenotypic changes of macrophages can improve immune-inflammation, myocardial fibrosis, energy metabolism, apoptosis, and angiogenesis in HF.

Keywords: heart failure, macrophage, polarization, pyroptosis, apoptosis, autophagy

Introduction

Heart failure (HF) is the final stage of various cardiovascular diseases, including cardiomyopathy, hypertension, ischemic heart disease, heart valve disease, myocarditis, and myocardial infarction. As a leading cause of hospitalization and mortality worldwide, HF seriously affects public health and increases socio-economic burdens.[1,2] Currently, the treatment of HF primarily relies on several types of medications, including angiotensin receptor enkephalinase inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEI), sodium-glucose cotransporter protein 2 inhibitors (SGLT2), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists. Additionally, iron and statins can also be used for treating HF.[3] Recently, despite the rapid progress of modern medicine in the diagnosis and treatment of HF, there are still challenges such as the high cost of examinations and side effects,[4,5] therefore, it is crucial to develop new therapeutic approaches with different treatment mechanisms to improve the prognosis of patients with HF.

Macrophages are crucial components of the human immune system. They can recognize, phagocytose, and destroy apoptotic cells and pathogens. They play a key role in the pathogenesis of HF,[6] help maintain cardiac homeostasis by protecting against eliminate inflammatory and cellular debris.[7] This study attempted to summarize the current understanding of the roles of macrophages in HF and explore related potential therapeutic targets.

Pathogenesis of HF

HF can be caused by various factors, with congenital cardiovascular disease, diabetes, obesity, smoking, myocarditis and cardiomyopathy, hypertension and coronary heart disease being the most common causes. It is not a single ailment, but rather a complex clinical condition. Under the joint action of various factors, cardiac preload and postload, return blood volume, and ventricular end-diastolic volume are all affected. As the compensatory mechanism of the heart is activated, it

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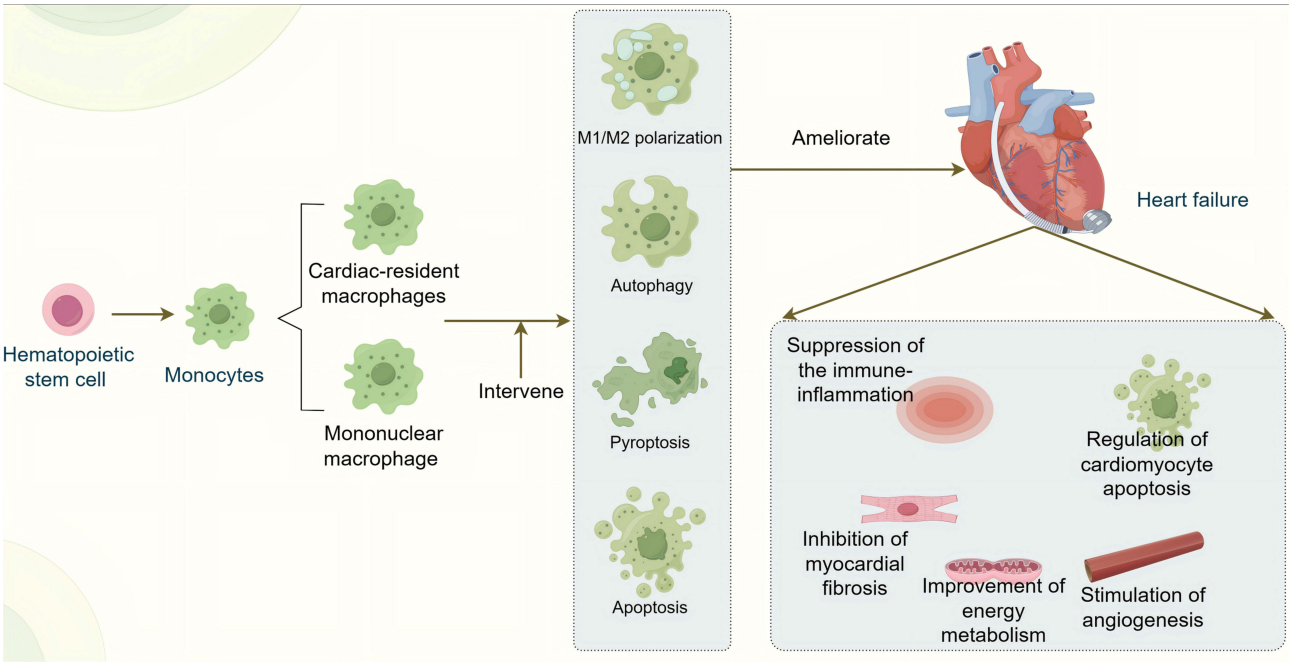
Graphical Abstract



promotes the progressive enlargement of the myocardium, and increases the need for oxygen during labor. Symptoms such as reduced exercise tolerance, dyspnea, and problems such as edema can occur after a sustained deterioration of cardiac function and myocardial compliance.[1]

Immune-inflammation response, myocardial fibrosis, abnormalities in energy metabolism, angiogenesis dysfunction, and cardiomyocyte death are the main pathogenetic mechanisms of HF, among which excessive inflammation is the key factor involved in its development and progression.[8] Myocardial fibrosis is a common pathological change of the myocardium, which usually leads to myocardial diastolic, conduction and metabolic abnormalities, resulting in HF.[9] Normal energy metabolism of myocardium is the basis of stable cardiac function, which can lead to a lack of energy supply to the myocardium when it is disrupted.[10] Microvascular insufficiency is an important factor leading to the development and deterioration of HF. Impaired angiogenesis caused by chronic ischemia can reduce myocardial perfusion and eventually lead to interstitial fibrosis, tissue damage and HF.[11] Cardiomyocyte apoptosis is the prelude of DNA cleavage and necrosis in cardiomyocytes, which can cause cardiomyocyte contractile dysfunction in heart diseases such as HF.[12]

Studies have indicated that macrophages are involved in various pathogenic processes and that they have non-negligible impacts on these processes.[13–16]

Physiology of Macrophages

Origin and Differentiation of Macrophages

Macrophages were initially identified as cellular sensors and healers of tissue damage in invertebrates in 1891 by Elias Metschnikoff[17] Macrophages are released into the peripheral blood after differentiation from bone marrow-derived hematopoietic stem cells, monocytes then further differentiate into tissue-settled macrophages. Macrophages control adaptive immune and innate immune responses.[18] Macrophages act as the“vacuum cleaners” in the lungs. Macrophages are also known as microglia in the brain tissue, osteoblasts in the bone tissue, sinus tissue cells, glomerular mesangial

cells, and other cells. Macrophages are known as Kupffer cells in the liver, adipose tissue macrophages in the adipose tissue, and Langerhans cells when in the skin.[19]

Tissue-Resident Macrophages

Originating from embryonic progenitor cells, tissue-resident macrophages (TRMs) originate from embryonic progenitor cells and differentiate from macrophages composed of fetal liver monocyte progenitor cells and yolk sac red myeloid progenitor cells. TRMs are found in nearly all tissues and perform various physiological roles.[20] TRMs mediate cell growth, remodeling, and homeostasis primarily through phagocytosis, antigen presentation, cytokine release, activating inflammatory and anti-inflammatory signaling, and producing growth factors and proteohydrolases. They are also crucial for immune defense, angiogenesis, tissue repair, and maintenance of homeostasis.[21,22]

Cardiac tissue-resident macrophages are a particular subset of macrophages with a spindle-shaped morphology that exists between cardiomyocytes, endothelial cells, and fibroblasts. The two subpopulations of cardiac tissue-resident macrophages, $CCR2^{-}$ and $CCR2^{+}$, enter the heart at distinct stages of development and are involved in several cardiac processes. $CCR2^{+}$ macrophages enter the endocardial trabeculae at 14.5d and sustain themselves mainly by attracting monocytes from the circulation and undergoing an autonomous process. $CCR2^{-}$ the macrophages enter the subepicardial chambers at 12.5d of embryonic days and remain in ventricular myocardium throughout the developmental process. They proliferate to maintain cell populations.[23]

The development of the cardiovascular system is closely linked to cardiac tissue-resident macrophages, which control the physiological and pathological processes of the cardiovascular system. These processes include sensing pathogens, presenting antigens, phagocytosing cellular debris, bacteria, and apoptotic cells, modulating inflammatory responses, and secreting various cytokines.[24] Additionally, cardiac tissue-resident macrophages play a significant role in cardiac growth development, homeostasis, and repair. They are also involved in myocardial remodeling after myocardial infarction, HF, and cardiac electrical conduction.[25,26]

Mononuclear Macrophages

In addition to theTRMs derived from embryogenesis, there are exist macrophages that differentiate from monocytes within the peripheral circulation, referred to as mononuclear macrophages.[27] Monocytes are circulating immune cells that originate from the bone marrow, myeloid progenitor cells or hematopoietic stem cells differentiate into mature monocytes and are released into the peripheral blood in response to certain cellular molecules. They migrate to different blood vessels and tissues where they can differentiate into dendritic cells or tissue-specific macrophages.[28]

Human monocytes are divided into three subpopulations based on the expression of CD14 and CD16. We refer to $CD14^{++}CD16^{-}$ classic monocytes as "inflammatory monocytes" because of their potent phagocytosis and pro-inflammatory capabilities. Non-classical monocytes $CD14^{+}CD16^{++}$ are known as "Patrol monocytes" because they are engaged in immune surveillance, tissue healing, and patrolling. Intermediate monocytes with $CD14^{++}CD16^{+}$ may present antigens and promote angiogenesis.[29] Monocyte-derived macrophages and pro-inflammatory monocytes continuously replace the macrophages in the myocardium when the heart is triggered by both internal and exterior insults. Monocyte-derived macrophages are involved in tissue healing and fibrosis in the late stage, autoimmune and inflammatory response in the intermediate stage, and early viral clearance of myocarditis.[30,31]

The Interaction Between Macrophages and Cardiomyocytes

In the heart, the interaction between macrophages and cardiomyocytes is crucial for cardiac function and disease progression. Macrophages can interact with cardiomyocytes through physical contact, thereby they can sense the rhythmic movement of cardiomyocytes, this interaction is beneficial in regulating the adaptive remodeling of the myocardium and promoting electrical conduction in cardiomyocytes.[32] It has been demonstrated that macrophages can release cytokines and growth factors, including TNF-α and Mydgf, which regulate the proliferation, hypertrophy, apoptosis, and electrical conduction of cardiomyocytes, thereby affecting cardiac repair and remodeling.[33] Concurrently, cardiomyocytes can also secrete cytokines, including interleukin-1β (IL-1β), interleukin-18 (IL-18), and Monocyte chemotactic protein-1 (MCP-1) to recruit macrophages and modulate their phagocytic functions.[34]

Macrophages can regulate cardiomyocyte death by producing exosomes.[35] Exosomes, such as MSC-Exos and CDC-Exos, can be secreted to regulate the polarization and phagocytic activity of macrophages. It has been demonstrated that exosomes released from hypoxic cardiomyocytes transfer miR-30a to resident cardiac macrophages, thereby promoting polarization toward pro-inflammatory M1 macrophages.[36] These interactions between macrophages and cardiomyocytes play a significant role in promoting cardiac health in those with HF.

Biological Functions of Macrophages

Phagocytosis

Macrophages, granulocytes (neutrophils, eosinophils, and basophils), and dendritic cells are all phagocytes. They are the first recognition of infection and play a key role in the recognition, phagocytosis, and degradation of pathogens and cellular debris in the human body as a "cleaner." Additionally, immunophagy is a key functional characteristic of macrophages.[37]

The whole process of phagocytosis can be divided into three interrelated processes: 1) recognition and attachment; 2) uptake; and 3) digestion and decomposition. After most pathogens enter the host through the respiratory system, intestinal mucosa, skin injury or genitourinary tract, macrophages infiltrate the lesion site by chemotaxis, synthesize, and secrete bioactive substances. Phagocyte receptors interact with the surface of pathogens, then the pseudopods of phagocytes extend and encircle bacteria, foreign particles, senescence cells, etc. Ingested components will be transferred into the cytoplasm to form phagolysosomes,[38] then phagolysosomes, swallowing vesicles and primary lysosomes fused to form secondary lysosomes,[39] and thereupon phagolysosomes and lysosomes fused to form phagolysosomes. Phagolysosomes are small vesicles containing enzymes and antimicrobial peptides. The acid hydrolases and other enzymes of the phagolysosomes break down pathogens into smaller molecules, which can be recycled by passing through the secondary lysosomal membrane. The residual body is made up of residual material, which can accumulate in intracellular space or transfer into extracellular space.[40]

Immune Response

Immune response is a series of biological events caused by the exposure of macrophages to "non-self" antigens. These effects mainly include immune defense, immune self-stabilization, immune surveillance and Immunomodulation.[41]

Immune defense: When pathogenic microorganisms infiltrate the organism, specific antibodies are triggered. First, pathogens are coated with pathogen surface IgC and complement activation fragment C3, which can bind to FcR and CR1 on the macrophage surface to kill the bacteria through intracellular enzymes or reactive oxygen species. Then the pathogenic microorganisms are phagocytosed by the macrophage before inducing an immune response and subsequent elimination. This is an important part of the non-specific immune defense mechanism.[38]

Immune self-stabilization: The immune system is involved in self-stabilization, which is necessary to maintain the relative stability of the internal environment. During development, growth, and metabolism, the body continually produces a significant number of senescent, damaged, degenerated, and deceased cells. Macrophages identify phosphatidic acid molecules on surface of the apoptotic cells. This recognition allows macrophages to begin phagocytosis, preventing a series of harmful reactions triggered by dead cells.[42] In normal cells, PG molecules are only present on the inner surface of the membrane and are therefore not phagocytized or removed by macrophages.[43]

Immunosurveillance: The physiological defense mechanism of the immune system, known as immunosurveillance, enables the body to quickly identify and eliminate cells that are mutated, abnormal, or infected with viruses. Macrophages can kill tumor cells in different ways. They can directly phagocytize tumor cells, and produce specific enzymes and reactive oxygen molecules. They can also directly kill or inhibit the growth of tumor cells. A compromised immune surveillance function can result in cancer or chronic viral infection.[44]

Immunomodulation: Immunomodulation is biphasic, and macrophages play a key role in this process. By presenting antigens, macrophages trigger the immune response, release various physiologically active compounds that have immune-boosting properties, and promote T-cell and B-cell activation, proliferation, and differentiation. Sensitized lymphocytes induce humoral or cellular immune responses, or activate NK cells that directly kill target cells, thereby

performing a positive-phase regulatory function.[45] Overactivated macrophages can differentiate into inhibitory macrophages, which can secrete many soluble inhibitors, including prostaglandins and reactive oxygen molecules, to directly damage lymphocytes or inhibit lymphocyte proliferation. Activated macrophages cannot play a negative-phase regulatory role.[46,47]

Tissue Repair

After host tissue damage, the homeostasis of internal environment needs to be repaired and remodeled. In this process, collagen synthesis, angiogenesis, cell proliferation, and extracellular matrix remodeling are all facilitated by activated macrophages. By enhancing and inhibiting apoptosis, macrophages may regulate embryonic morphogenesis, particularly during structural molding and deformation of embryonic organs.[48]

A systemic inflammatory response syndrome characterized by an increased inflammatory response can arise from impaired macrophage phagocytosis after severe trauma. Furthermore, macrophages produce many cytokines and proteins that accelerate tissue repair during the proliferative, reconstructive, and inflammatory stages after trauma. M1-type macrophages kill pathogens, remove necrotic tissue, and secrete proinflammatory factors to promote inflammation in the wound surface. M2-type macrophage-derived anti-inflammatory factors promote the resolution of wound inflammation. Growth factors act on fibroblasts, vascular endothelial cells, and keratinocytes to promote wound granulation, tissue formation, and angiogenesis.[49] Successful wound healing depends on the prompt conversion of the M1-type macrophage phenotype to the M2 type. During this process, many cytokines secreted by macrophages regulate the proliferation of fibroblasts, the synthesis of collagen, and angiogenesis.[50]

Different Phenotypes of Macrophages in HF

Macrophages exhibit many phenotypes due to their widespread distribution and multitudinous functions in various tissues and organs, macrophages may differentiate into different phenotypes, affecting the progression of HF.

Macrophage Polarization

Macrophages exhibit great variability and heterogeneity, allowing them to differentiate into distinct cellular phenotypes in various microenvironments and physiopathological conditions. This process is referred to as macrophage polarization or phenotypic switching or recoding. Macrophages are categorized into two types: classically activated (M1-type) and alternatively activated (M2-type) based on their cell surface markers, cytokines, and metabolism-related genes.[51]

The M1 type is triggered by lipopolysaccharide (LPS), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), it generates pro-inflammatory cytokines, including IL-1β, interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-23 (IL-23), and induced nitric oxide synthase (iNOS). iNOS stimulates T cell immune responses, enhances Th1-type immune response, and stimulates the initial inflammatory response.[52] Alternative activation of macrophages results in four distinct subtypes: M2a, M2b, M2c, and M2d, each with unique immunological roles and markers.[53] The M2a subtype, induced by interleukins IL-4 and IL-13, highly expresses IL-10, TGF-β, and chemokines CCL17/18/22/24, this phenotype is implicated in anti-inflammatory processes and the maintenance of tissue homeostasis.[54] The M2b subtype, induced by immune complexes and toll-like receptor agonists, is characterized by high expression of IL-6, IL-1β, TNF-α, IL-10, IL-12, and TNFSF14, which plays an important role in immune regulation.[55] The M2c subtype, activated by IL-10, TGF-β, and glucocorticoids, secretes IL-10, TGF-β, CCL16, CCL18, MerTK, CD163, and CD206, and is involved in the inhibition of immune responses, recognition, clearance of apoptotic cells, tissue repair, and matrix remodeling.[56,57] Finally, the M2d subtype, activated by lipopolysaccharide (LPS), adenosine, and IL-6 highly expresses VEGF and IL-10 and can induce angiogenesis and promote tumor cell growth.[53]

In the recovery phase of inflammation, M1-type macrophages can switch into M2-type macrophages, which inhibit the inflammatory response and facilitate tissue repair.[58] In the early stages of inflammation, M1-type macrophages exacerbate the inflammatory response by releasing pro-inflammatory cytokines. The extent of inflamed tissues is determined by the balance of M1/M2 macrophages. In terms of function, receptor expression, cytokine production, and metabolism, the two phenotypes are different. Additionally, the polarization of the two types of macrophages allows them to flip between and exert distinct functions during the inflammatory responses. M1 and M2 macrophages can

change one another during the HF process at various times and in diverse ways. The development and incidence of HF are strongly correlated with the dynamic balance between the two types of macrophages. Heart function can be enhanced by promoting M1 macrophages to differentiate into M2 macrophages. Thus, encouraging the conversion of M1 to M2 type macrophages and maintaining the equilibrium between M1 and M2 type macrophages may be useful tactics for the treatment of HF.[59] (Figure 1).

Macrophage Pyroptosis

In 1992, Zychlinsky et al observed that macrophages harboring the gram-negative bacterial pathogen Shigella fowleri exhibited swift lysis.[60] Brennan and Cookson named this cellular phenomenon pyroptosis in 2001.[61] There are classical and non-classical methods of macrophage pyroptosis. Inflammasome activation, caspase regulation, and pigment (gasdermin) protein family are closely related. Gasdermin D (GSDMD) serves as a common substrate of inflammatory caspase in two different manners, it is crucial for membrane pore formation and pyroptosis. The classical pathway depends on the activation of Caspase-1, GSDMD can be cleaved by activated Caspase-1 to produce the N-terminal domain (GSDMD-N), which binds to phospholipoproteins on the cell membrane to form membrane pores and induce cell death. Meanwhile, activated Caspase-1 can stimulate the maturation and secretion of proinflammatory cytokines. For instance, it cleaves dormant IL-1β and IL-18 precursors into the corresponding mature cytokines, aggravating inflammation. In the non-classical pathway, inflammatory stimuli activate caspase-4/caspase-5 and caspase-11. Activated caspase-4/5/11 induces cellular pyroptosis by directly cleaving GSDMD proteins, but they can also indirectly activate caspase-1, which subsequently mediates the classical pathway of pyroptosis.[62–64]

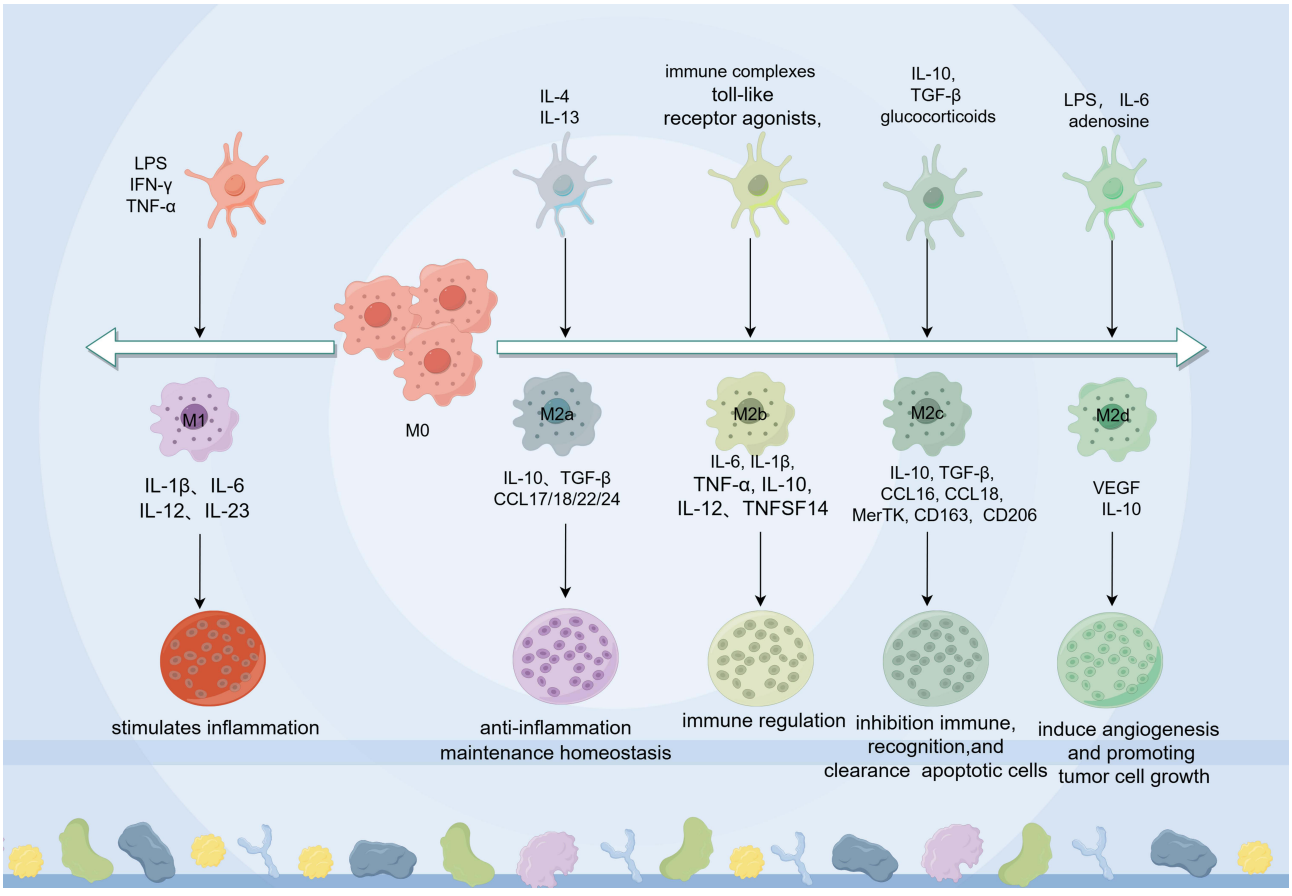


Figure 1 Macrophage polarization. Macrophages can be categorized into M1 and M2 types. M1 macrophages can be induced by LPS, IFN-γ and TNF-α. They produce IL-1β, IL-6, IL-12, IL-23 and iNOS and promote Th1 type immune response. M2 polarization has four subtypes—M2a, M2b, M2c, and M2d—defined by their inducing molecules and environmental responses. These subtypes play roles in tissue repair, immune regulation, angiogenesis, and tumor cell proliferation.

Macrophage pyroptosis plays a dual role for the host: it induces the inflammatory response and controls the infection, conversely, excessive pyroptosis may increase the risk of inflammatory diseases. Unlike apoptosis and necrosis, pyroptosis is a type of programmed cell death that can result in cardiac fibrosis, cardiac hypertrophy, myocardial dysfunction, excessive inflammation, and cardiac remodeling, all of which are linked to HF.[65] Numerous clinical characteristics of HF are intimately associated with macrophage pyroptosis, a significant loss of cardiomyocytes in HF may result from macrophage pyroptosis and the ensuing inflammatory response, which will worsen the condition of HF.[66] Research has discovered that the inhibition of pyroptosis in macrophages can ameliorate adverse cardiac remodeling and enhance cardiac function[67] (Figure 2).

Macrophage Autophagy

Autophagy is a lysosome-dependent biological self-protection mechanism that preserves the healthy intracellular environment by eliminating undesirable or hazardous materials and damaged organelles from various stress reactions. Autophagy is involved in defense, metabolism, and quality control.[68] After inducing autophagy in macrophages, the ULK1 complex binds to beclin-1 and VPS34 to generate hemispherical phagocytic bubbles or Phagophore, which encapsulate biological macromolecules and organelles that are old, damaged, or surplus. Autophagosome formation involves the continuous extension of misfolded proteins or damaged organelles into a closed ball, followed by lysosome fusion to form autolysosomes, Autophagosome "cargo" will be degraded by lysosomal enzymes, which recycle amino acids, fatty acids, and other products.[69,70]

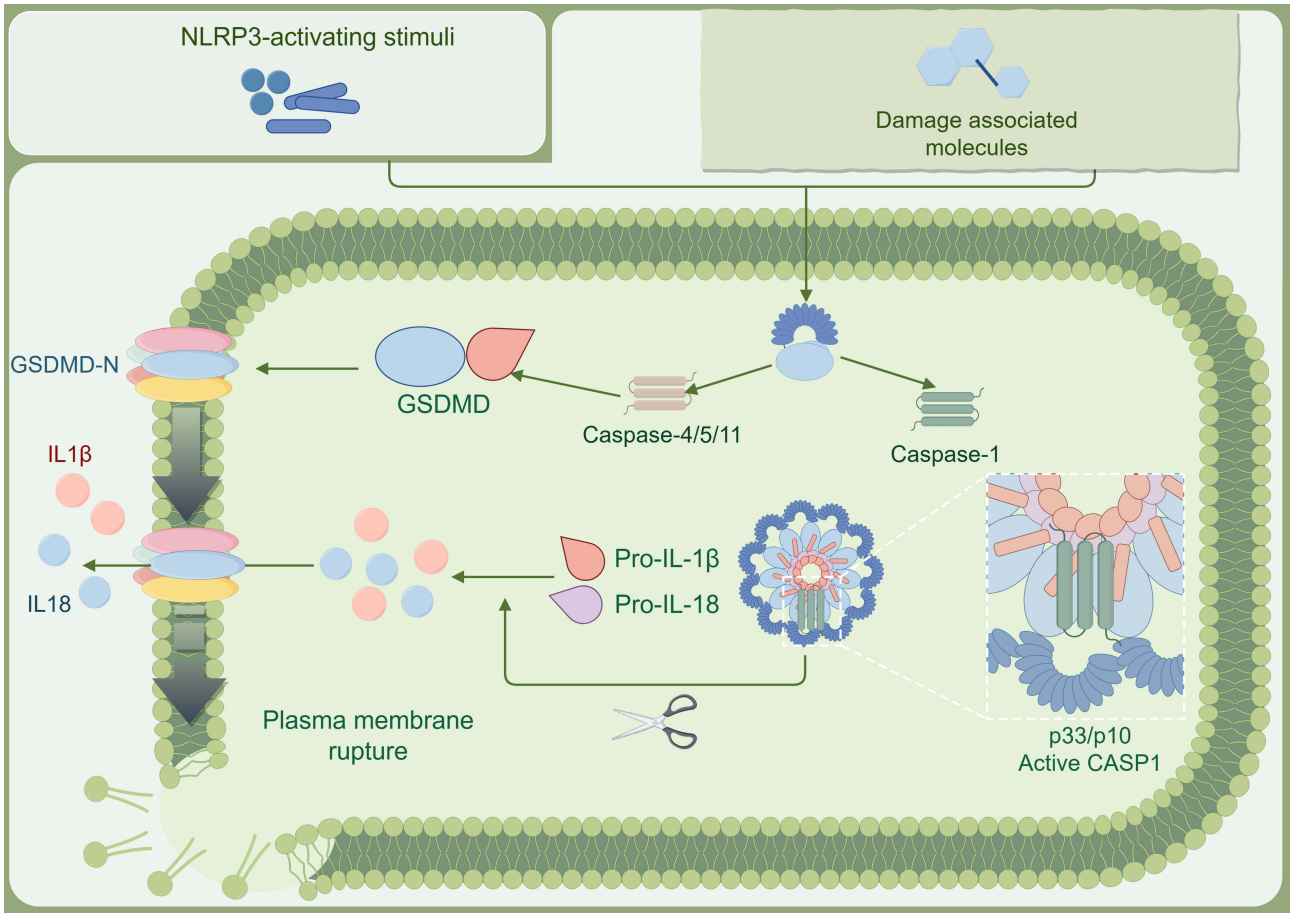


Figure 2 Macrophage pyroptosis. The process of macrophage pyroptosis primarily depends on inflammasomes and is triggered by different caspases. This leads to the polymerization and shearing of different members of the Gasdermin family, such as GSDMD. The released N-terminal domain of GSDMD binds to membrane lipids to form cell membrane holes, alters the osmotic pressure, and leads to cell swelling until the cell membrane ruptures.

Various cardiovascular disorders have been linked to dysregulated autophagy.[71] Cellular homeostasis depends on cellular autophagy, and macrophage autophagy is critical for the removal of damaged organelles and apoptotic cells.[72,73] Macrophage autophagy is pivotal in HF, whereas excessive autophagy promotes the buildup of pathologic products and the breakdown of healthy proteins and organelles. Basal autophagy preserves intracellular balance and organelle regeneration. Therefore, maintaining a moderate level of autophagy in macrophages is crucial to ensure the stability of the myocardium and halting the course of HF.[74] Cardiac remodeling represents a pivotal element in the deterioration of ventricular functionality and the clinical trajectory of HF. Studies have demonstrated that autophagy in macrophages may facilitate myocardial ischemic injury through the inflammatory response, thereby instigating cardiac remodeling. This process can subsequently deteriorate cardiac function, inducing the development of HF[75] (Figure 3).

Macrophage Apoptosis

Apoptosis, as a physiological form of programmed cell death, plays an important role in the development of biological systems, the stability of the internal environment, and the evolution of organisms.[76] Apoptosis is characterized by a series of well-defined morphological changes. Initially, the cell volume decreases, the nucleus solidifies, and chromatin condenses along the nuclear membrane. Then the nucleus collapses, producing small cellular fragments or apoptotic vesicles. Finally, intact apoptotic vesicles are phagocytosed, preventing the release of cellular contents into the surrounding area and blocking any inflammatory response.[77]

Numerous stimuli can induce macrophage apoptosis since they are extensively dispersed throughout the body and are engaged in various physiological and pathologic processes. Macrophage apoptosis can influence the process of cardiac remodeling by affecting the balance between pro-inflammatory and anti-inflammatory macrophages, thereby impacting the progression of HF. Macrophages possess the function of clearing necrotic cellular debris to prevent secondary necrosis, excessive macrophage apoptosis may lead to impaired phagocytic function and loss of cardiomyocytes, which are significant factors in the development of HF.[78,79]

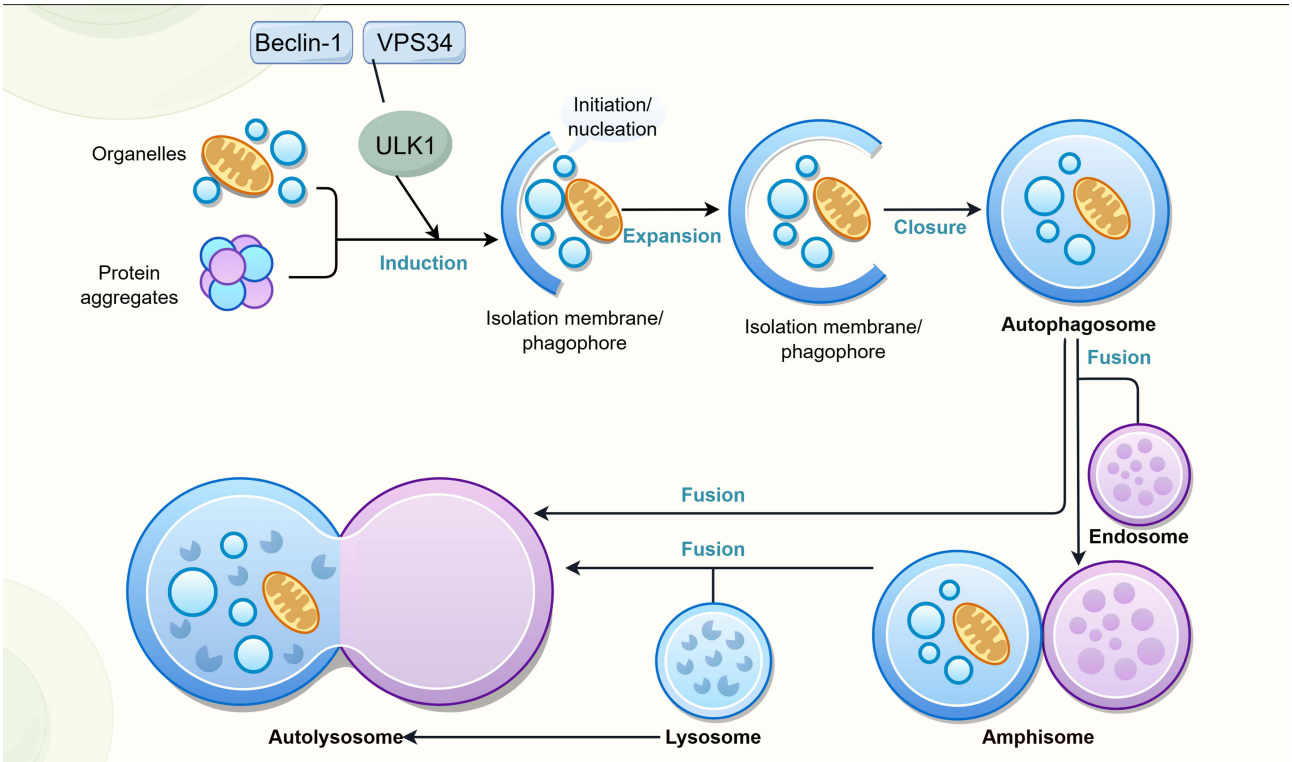


Figure 3 Macrophage autophagy. Macrophages sensing autophagy-inducing signals form intracellular spherical double-membrane autophagosomes, which fuse with lysosomes to form monolipid membrane-coated autolysosomes. Then, misfolded proteins or damaged organelles are degraded by lysosomal hydrolysis enzymes.

In the presence of iNOS, endogenous or exogenous NO can lead to macrophage apoptosis. Stimuli, like LPS, also enhance the production of NO by activating iNOS and using L-arginine and other molecules as substrates, this in turn influences gene expression and causes apoptosis.[80] Cardiomyocyte apoptosis is correlated with every stage of HF development. A study reported that the expression level of macrophage apoptosis inhibitor CD5L on epicardial adipose tissue is associated with the development of HF.[81] Gajawada P[82] indicated that the activation of PI3 kinase and Akt may lead to macrophage apoptosis, which in turn can induce cardiac remodeling and trigger the progression of HF (Figure 4).

The Role of Macrophages in HF

The immune-inflammation, myocardial fibrosis, poor energy metabolism, impaired angiogenesis, and cardiomyocyte apoptosis are important pathogenetic mechanism in HF. Previous studies have demonstrated that macrophages are involved in these pathological processes.[14] The survival and adaptive cardiac remodeling of HF patients are controlled by cardiac macrophages, which significantly infiltrate into HF hearts.

Suppression of the Immune-Inflammation

HF can be triggered by a variety of pathological changes, such as myocardial ischemia and pressure or volume overload. HF is closely related to the local and systemic activation of inflammatory signaling cascades, and innate and adaptive immune systems.[83] By mediating inflammatory/repair pathways, pro-inflammatory macrophage modulate all stages of HF.[84] Monocytosis and macrophages can be seen in the early injury and late repair phases of the disease process, such as inflammation, they are the main causes of inflammation in HF.[85] There was a one-fold increase in the abundance of macrophages in myocardial biopsies of individuals with HF who had preserved ejection fraction. Additionally, there was increased expression of cardiac ICAM-1 and plasma IL-684. Macrophages are both innate and adaptive immune cells that play a key role in the remodeling, healing, and inflammatory processes associated with cardiac damage. M1 macrophages promote inflammation, whereas M2 macrophages promote healing and tissue repair.[86] In response to chemokines, peripheral blood monocytes infiltrate into damaged tissues in the early and intermediate phases of HF, they can differentiate into M1 macrophages. M1 macrophages secrete pro-inflammatory cytokines (IL-6,IL-1β, etc).,that

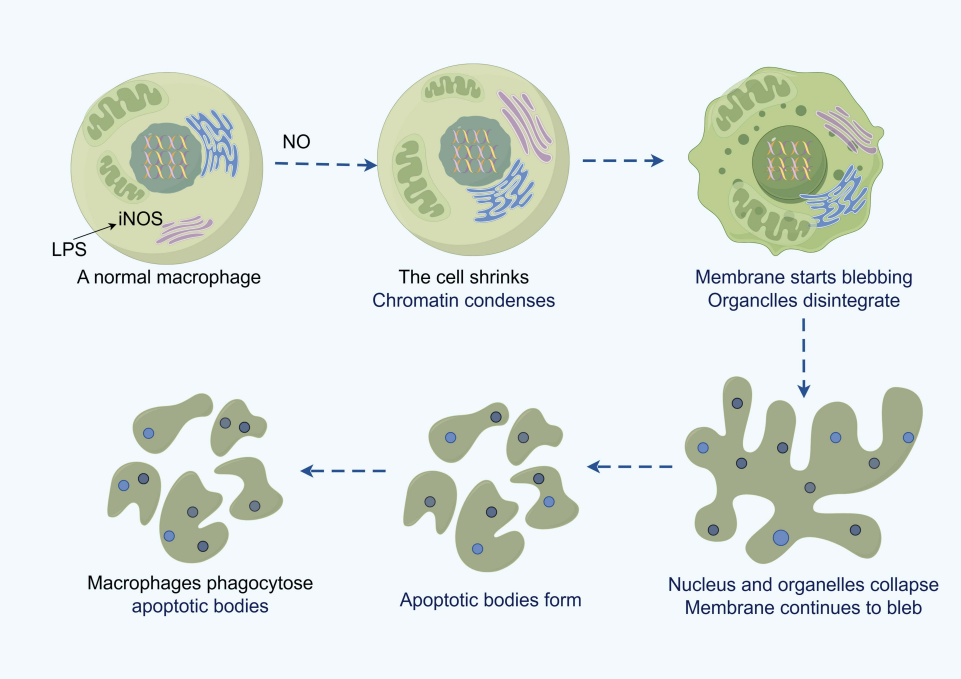


Figure 4 Macrophage apoptosis. Stimuli, such as LPS, activate iNOS in macrophages, reducing cell volume, and inducing nuclear sequestration, and chromatin condensation along the nuclear membrane. Then, the nucleus collapses to produce small cell debris or apoptotic bodies.

might worsen cardiac tissue injury.[87] In the late stages of HF, macrophages are mainly M2 type, which can release anti-inflammatory molecules (IL-4, IL-10, etc.) and participate in tissue repair.[88]

It was shown that Remimazolam can treat cardiac ischemia-reperfusion damage by inhibiting M1 polarization of macrophages.[89] By activating the Src/PI3K/Akt pathway, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) enhances the M2 polarization of macrophages. This alteration decreases pro-inflammatory factor production by macrophages to heal sepsis-induced cardiac damage and increase cardiomyocyte activity.[90] Wang et al[91] demonstrated that the CCL24 antibody might prevent Ang II–induced HF by inhibiting cardiac fibroblast activation and M2 polarization of macrophages. Zhang X's findings indicated that Astragaloside IV could suppress ROS/Caspase-1/GSDMD signaling pathway to reduce macrophage pyroptosis, and alleviate MI-induced cardiac dysfunction and the inflammatory response.[92] Zhang et al indicated that latifolin can stop DOX-induced cardiac failure in mice by lowering the proportion of macrophages that are M1/M2 polarized.[93] The study[94] found that Nuanxinkang can regulate the polarization of macrophages through the IKKβ/IκBα/NF-κB pathway, thereby inhibiting inflammatory responses and alleviating cardiac damage caused by ischemia-reperfusion (IR).

Inhibition of Myocardial Fibrosis

Activation of myocardial fibroblasts and collagen accumulation are the main characteristics of myocardial fibrosis. Collagen fibers are a crucial component in myocardial contractility, and their abnormal deposition can result in pathological remodeling and HF. Macrophage pyroptosis and its pathological byproducts can promote myocardial fibrosis, destabilize vascular wall plaques, impair coronary angiogenesis, harm vascular endothelial cells, and even directly cause cardiomyocyte mortality, all of which can worsen HF over time.[95] Polarizing macrophages can stimulate the expression of collagen and α-smooth muscle actin in cardiac fibroblasts. Additionally, receptor for advanced glycation end products (RAGE) plays a critical role in recruiting and activating specific macrophages through autophagy, which subsequently reduces myocardial fibrosis.[96] Dagliflozin was found to exert its anti-fibrotic and cardioprotective effects by inhibiting the pro-inflammatory progression of macrophages.[97] QiShenYiQi pills were found to ameliorate cardiac fibrosis after pressure overload-induced cardiac hypertrophy by modulating the RPS19/TGF-β1 signaling pathway in macrophages.[98] Gong ZT's study suggests that MSCNIC-exo may significantly facilitate post-infarction cardiac repair by promoting macrophage M2 polarisation through upregulation of miR-125a-5p targeting the TRAF6/IRF5 pathway, which has great potential for clinical translation.[99] Combining tanshinone IIA with puerarin at a 1:1 dose has been demonstrated to alleviate cardiac dysfunction caused by myocardial infarction, decrease collagen production and fibroblast release, increase M2 macrophage expression, and prevent myocardial fibrosis and ventricular remodeling.[100]

Improvement of Energy Metabolism

The ATP required for myocardial metabolism in healthy adults is mainly supplied by mitochondrial oxidative phosphorylation and glycolysis. Mitochondrial oxidative phosphorylation supplies approximately 95% of the myocardial ATP, and glycolysis provides the remaining 5%. At the early stages of HF, myocardial energy metabolism can be maintained relatively normally, but disease progression progressively impairs the dynamic balance between aerobic oxidation, fatty acid oxidation, and glycolysis.[101]

Feng[102] et al reported that patients with dilated cardiomyopathy (DCM) have a higher abundance of $CCR2^+$ macrophages, which was closely linked to the development of HF. Additionally, genes related to glycolysis were upregulated in blood-derived CCR2 monocytes of patients with DCM, these macrophages also showed increased glucose uptake. These findings suggest that cardiac $CCR2^+$ monocytes and macrophages rely on metabolic reprogramming to initiate inflammatory responses that cause myocardial injury. Dimethyl fumarate (DMF) was shown to enhance macrophage glycolysis and mitochondrial oxidative phosphorylation in infarcted hearts, it promotes post-infarction remodeling by altering the metabolism of macrophages and fibroblasts.[103]

The heart is an organ with a high energy demand, mitochondria are the primary organelles responsible for energy metabolism, and the maintenance of mitochondrial homeostasis is essential for normal energy metabolism in the heart. Bartelt[104] et al indicated that to preserve normal cardiac function, cardiomyocytes expel defective mitochondria via exocytosis vesicles, which must be then removed by specific macrophages. It was shown that Xinmaikang may preserve

the arterial vasculature by facilitating the PINK1/Parkin signaling pathway-mediated mitophagy in macrophages.[105] Niclosamideattenuated HF in mice possibly by enhancing mitochondrial respiration in myocardial macrophages, suppressing collagen release in cardiac fibroblasts, and decreasing the serum level of IL-6.[106] The study revealed that Nuanxinkang can prevent cardiac remodeling subsequent to myocardial infarction (MI), enhance cardiac function, and avert the progression to HF by regulating the HIF-1α/PDK1 axis, thereby inducing metabolic reprogramming and phenotypic differentiation of macrophages.[107]

Stimulation of Angiogenesis

Stressful stimuli, like pressure overload, ischemia, and hypoxia, promote angiogenesis to maintain cardiac function. However, repeated stimulation induces myocardial hypertrophy, leading to fibrosis, vascular thinning, and finally HF.[108]

Using a pressure-loaded hypertensive mouse model of cardiac hypertrophy, Liao et al found that early resident macrophages proliferate and promote angiogenesis in a Kruppel-like factor 4 (KLF4)-dependent manner.[109] Revelo et al observed that a reduced abundance of cardiac-resident macrophages suppressed angiogenesis in mice hearts, indicating that cardiac-resident macrophages promote angiogenesis.[110] Wong[26] et al found that a low abundance of cardiac CCR2-negative macrophages may hinder coronary neovascularization and increase the mortality rate in a mice model of dilated cardiomyopathy, CCR2-negative macrophages can be employed to dilate the coronary artery and preserve cardiac output. Shexiang Baoxin Pills activated macrophages to release pro-angiogenic factors, such as VEGF-a, through the PI3K/Akt and MAPK/Erk1/2 signaling pathways.[111]

Regulation of Cardiomyocyte Apoptosis

Cardiomyocyte apoptosis is a key process leading to cardiac decompensation and HF after myocardial infarction. Several studies have suggested that inhibiting cardiomyocyte apoptosis is a useful treatment for HF.[112] Zou et al reported that Hmgcs2 can directly bind to PPAR α, which is activated by Src activity,[90] Activation of the Src/PI3K/Akt pathway promotes macrophage M2 polarization, reduces apoptosis, and restores cardiomyocyte viability.

The mechanisms of intervention in macrophage treatment of HF as shown in Table 1.

Conclusion and Perspective

HF seriously affects people's health due to its high morbidity, mortality, and recurrence rates. Macrophages are important components of the cardiac innate immunity. In recent years, numerous research have been carried out on the production, differentiation, and recruitment of macrophages (including tissue-resident macrophages and monocyte macrophages), as well as the biological functions of phagocytosis, immunological response, and tissue healing. Regulating the function of macrophages can help delay HF progression, and has the potential to serve as a new target for the prevention and treatment of HF. When HF occurs, distinct phenotypes of macrophage pyroptosis, autophagy, apoptosis, and polarization are often observed. Pathological alterations such as myocardial fibrosis, aberrant cardiomyocyte apoptosis, cardiac inflammatory response, and problems related to energy metabolism are among the ailments that might result from these characteristics. Cardiac immune-inflammation, myocardial fibrosis, energy metabolism, angiogenesis, and cardiomyocyte apoptosis can be improved by regulating macrophage polarization, pyroptosis, autophagy, and apoptosis.

So far, a substantial body of research has confirmed the involvement of macrophages in the pathogenesis of HF. However, the mechanisms for specific targeting and manipulation of macrophages to ameliorate HF have not been well defined. Subsequent studies should consider exploring the following avenues: (1) The phenotypic plasticity of macrophages across diverse physiological conditions and the potential for modulating these phenotypes to improve therapeutic efficacy for HF; (2) Identification of targeted pharmacological agents capable of selectively engaging macrophages to enhance myocardial performance and prevent the progression of HF; (3) Conducting clinical trials to assess the safety and efficacy of macrophage-targeted therapies; and (4) Highlight the significance of interdisciplinary research and the integration of emerging technologies to advance the understanding of macrophages in the context of HF, and translate these insights into therapeutic strategies for its treatment.

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Table 1 Mechanisms of Intervention in Macrophage Treatment of HF

Intervention Method	Model	Macrophage Phenotype	The Mechanism of Improve HF	References
Remimazolam	Ischemia/reperfusion mice model induced by ligating the left anterior descending coronary artery	Inhibition of M1 polarization	Inhibition of the inflammatory response	Xu[89]
Hmgcs2	Sepsis mice model induced by cecal ligament and puncture	Promoting M2 polarization	Inhibition of the inflammatory response	Zou[90]
CCL24 antibody	HF patients	Inhibition of M2 polarization	Inhibition of myocardial fibrosis	Wang[91]
AS-IV	MI mice model induced by ligating the left anterior descending coronary artery	Inhibition of macrophage pyroptosis	Inhibition of inflammatory response	Zhang[92]
Latifolin	Cardiotoxic mice induced by DOX	Lower macrophage M1 / M2, polarization percentage	Inhibition of the inflammatory response	Zhang[93]
Nuanxinkang	HF mice model induced by ligating the left anterior descending coronary artery	Lower macrophage M1 / M2, polarization percentage	Inhibition of the inflammatory response	Dong[94]
Macrophage RAGE deficiency	MF mice induced by transverse aortic constriction	Inhibiting autophagy	Inhibition of myocardial fibrosis	He[96]
Dagliflozin	Mice model of cardiac hypertrophy induced by ascending aortic stenosis	Inhibition inflammatory response in macrophages	Inhibition of myocardial fibrosis	Wu[97]
QiShenYiQi Pill	Rat model of cardiac hypertrophy by inducing ascending aortic stenosis	Inhibition of macrophage polarization	Inhibition of myocardial fibrosis	Anwaier[98]
MSCNIC-exo	MI rat model induced by ligating the left anterior descending coronary artery	Promoting M2 polarization	Inhibition of inflammatory response	Gong[99]
Tanshinone IIA and puerarin	HF mice model induced by ligating the left anterior descending coronary artery	Inhibition of M1 polarization,Promoting M2 polarization	Inhibition of myocardial fibrosis	Gao[100]
Dimethyl fumarate	Mice model of myocardial infarction induced by ligation of the left coronary artery	Enhanced glycolysis and mitochondrial oxidative phosphorylation in macrophages	Improving energy metabolism	Mouton[103]
Xinmaikang	Mice model of AS induced by high-fat diet	Increases mitophagy in macrophages	Improving energy metabolism	Cao[105]
Niclosamide	Mice model of HF induced by transverse aortic constriction	Enhancing mitochondrial respiration in myocardial macrophages	Improving energy metabolism	Fu[106]
Nuanxinkang	MI mice model mice model induced by ligating the left anterior descending coronary artery	Lower macrophage M1 / M2, polarization percentage	Regulating metabolic reprogramming	Lin[107]
CCR2- macrophages depletion	Mice model of CCR2- macrophage depletion was induced by diphtheria toxin	Macrophages expand the coronary artery system	Stimulating angiogenesis	Wong[26]
Shexiang Baoxin Pills	Mouse model of inflammatory angiogenesis induced by Polyvinyl alcohol sponge implantation	Macrophage release VEGF-a	Stimulating angiogenesis	Zhang[111]
Hmgcs2	Mice model of sepsis induced by cecal ligation and puncture	Promoting the M2 polarization of macrophages	Regulation of cardiomyocyte apoptosis	Zou[90]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ARNI, including angiotensin receptor enkephalinase; CHF, chronic heart failure; DCM, dilated cardiomyopathy; DMF, dimethyl fumarate; GSDMD, Gasdermin D; HF, heart failure; HMGCS2, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase 2; IFN-γ, interferon gamma; IL-1β, including interleukin-1β; IL-10, including interleukin-10; IL-12, including interleukin-12; IL-13, interleukin-13; IL-4, interleukin-4; IL-6, including interleukin-6; IL-23, including interleukin-23; iNOS, induced nitric oxide synthase; KLF4, Kruppel-like factor 4; LPS, lipopolysaccharide; MI, myocardial infarction; RAGE, receptor for advanced glycation end products; SGLT2, sodium–glucose cotransporter protein 2 inhibitors; TRM, tissue-resident macrophages; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor alpha.

In conclusion, the significant role of macrophages in the context of HF warrants more studies. Future studies should develop tailored treatment protocols that address the heterogeneity of the disease, its various manifestations, to refine therapeutic results, thus enhancing treatment efficacy and promoting the life quality of patients with HF.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no known conflicts of interests or personal relationships that could have appeared to influence the work reported in this paper.

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