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REVIEW OPEN ACCESS

Contributions of Macrophages in the Disease Pathology of Myocardial Infarction and Atherosclerosis: A Literature Review

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Abstract

Introduction: Macrophages have been shown to play a role in the disease pathology of myocardial infarction and atherosclerosis, two prominent cardiovascular diseases. Understanding the mechanisms by which macrophages contribute to disease onset can serve as a valuable resource for the development of new therapeutics. This study specifically aims to identify the roles macrophages play in the regulation and progression of myocardial infarction and atherosclerosis in human and mice models, while highlighting current and developing treatments that target macrophages to prevent or delay these diseases.

Methods: This review examines studies and previous reviews in the last 20 years that report proinflammatory mediators secreted by pro-inflammatory (M1-like) macrophages in humans and mice that are affected by myocardial infarction or atherosclerosis or have undergone simulated conditions.

Discussion: Pro-inflammatory M1 macrophages influence both myocardial infarction and atherosclerosis via the secretion of proinflammatory mediators IL-1β, IL-1∝, IL-6, TNF-∝, VCAM-1, MMP-9, and MCP-1. These mediators are shown to promote adverse cardiac remodelling events in individuals with myocardial infarction including inflammation, increase in the infarcted area, and worsened left ventricular systolic function. For those with atherosclerosis, mediator release is correlated with lesion and plaque development due to increased leukocyte and lymphocyte migration. Mediators that directly influence either disease are also reported. As atherosclerosis is a risk factor for myocardial infarction, the overall promotion of atherosclerosis by both shared and specific inflammatory mediators therefore increases the likelihood an individual undergoes myocardial infarction. Current and developing treatments for myocardial infarction revolve around inhibiting mediator release and activity, whereas inducing macrophage polarization, inhibiting scavenger receptor activity, and inducing autophagy are the focus of therapeutic intervention for atherosclerosis.

Conclusion: Proinflammatory macrophages show a prominent role in the pathogenesis of myocardial infarction and atherosclerosis, including the body's ability to recover from these diseases. Further research in identifying macrophage phenotypes and improvements in drug delivery methods may serve as future avenues in improvement for macrophage-based medicines of common CVDs.

Keywords: cardiovascular disease; CVD; macrophage; myocardial infarction; MI; atherosclerosis; AS; M1; $CCR2^+$

Introduction

Cardiovascular disease (including atherosclerosis, myocardial infarction, coronary heart disease, and heart failure) remains as the leading cause of death worldwide [1]. As of 2020, approximately 19 million people globally have reportedly died from CVD, claiming more lives than cancer and chronic lower respiratory diseases combined [1]. Concerning economic cost, annual and direct cost of CVD in the US was estimated to be an average of $407.3 billion USD, with hospital inpatient stays taking up the highest cost at $111.4 billion USD [1]. Great effort has been made to understand the risk factors of CVD and develop relevant therapeutic approaches to combat it, including those that target gut microbes, miRNAs and therapeutic enzymes [2, 3, 4, 5]. Despite these efforts, the need to develop effective treatments to reduce CVD mortality still holds great importance. Macrophages play an important role in disease and injury response in the body. Their immune function ranges from eliminating necrotic cells or foreign pathogens at the site of damage or infection respectively, to secreting anti-inflammatory mediators that begin myofibroblast differentiation and tissue repair [6]. The inflammatory and anti-inflammatory roles of macrophages are correlated to their respective phenotype [6]. Expression of the C-C chemokine receptor (CCR2), which is heavily related to their ontogenetic origins that differentiates them

into one of two major populations, is used as a prominent marker for macrophage identification [6, 7, 8]. $CCR2^-$ macrophages originate from embryonic cells and enter tissues during tissue development, where they become tissue-resident macrophages [6, 7, 8]. Their population is maintained via self-renewal and self-proliferation, and they carry out the anti-inflammatory response during tissue injury [6, 7, 8]. In contrast, $CCR2^+$ macrophages start off as $CCR2^+$ monocytes that are derived from yolk-sac precursor cells and circulate in the blood [6, 7, 8]. They infiltrate tissue sites that have experienced injury and a reduction in tissue resident macrophages as a result [6, 7, 8] During infiltration, they differentiate into $CCR2^+$ macrophages and release inflammatory chemokines and cytokines, initiating the inflammatory response [6, 7, 8] Overall, recruited $CCR2^+$ macrophages that are present during the inflammatory phase are designated M1 macrophages, while $CCR2^-$ macrophages that reside in the tissue and are involved in the reparative phase following inflammation are M2 macrophages [9, 10]

Other genetic markers used to classify macrophages and monocytes beyond CCR2 expression have been studied in both mice and humans. Lavine et al. identified two populations in neonatal mice hearts: one macrophage subset (MHC-$II^{low}CCR2^-$) and one monocyte subset (MHC-II^{low}CCR2+), and four populations in adult mice hearts: two resident-macrophage subsets (MHC-$II^{low}CCR2^-$, MHC-$II^{high}CCR2^-$), one monocyte-derived macrophage subset (MHC-$II^{high}CCR2^+$), and one monocyte subset (MHC-$II^{low}CCR2^+$) [11]. Ly6C expression is also used to differentiate monocytes in mice, as $Ly6C^{high}$ monocytes are shown to differentiate into M1 macrophages, while $Ly6C^{low}$ monocytes differentiate into the M2 phenotype [11]. In contrast, Bajai et al. identified two macrophage populations in humans ($CCR2^+$HLA-DR^{high} (MHC-II homologue), $CCR2^-$HLA-DR^{high}) and one monocyte population ($CCR2^+$HLA-DR^{low}) [7]. Expression of genes for, but not limited to, F4/80, CD14, CD16, Ifit3, Tnip3, Itgb7, Arg1, Cxc11/Ccrl2, Lyve1, il6, and *Mpo* are used to differentiate macrophages [10, 12, 13, 14]

In this review, we focus on how macrophages contribute to the development and regulation of myocardial infarction and atherosclerosis. We then present current and developing therapeutic approaches to these diseases that target macrophages. This review will serve as a resource for researchers and public health experts to use in better understanding the role of macrophages in cardiovascular pathology, as well as a tool to further develop CVD treatments.

Methods

This review examines peer reviewed studies and reviews from 2004-2024 discussing the involvement of macrophages in the regulation of myocardial infarction (MI) and development and progression of atherosclerosis (AS) in human and mice. The main measurement used to evaluate this is the level of inflammatory mediators released during injury response, and how it impacts certain cardiac events. Previous review papers on macrophage involvement in MI and AS were first consulted, and searched using the Web of Science database and the following operators: macrophage* AND atherosclerosis/"myocardial infarction". Relevant studies from those reviews with results that fulfill our criteria previously described are reported here, alongside studies searched on Web of Science using the following operators: "[mediator of interest]" AND atherosclerosis/"myocardial infarction". To validate if a journal is peer-reviewed, it is searched for on UlrichsWeb Global Serials Directory and checked for the referee icon. All mentions of clinical trials include their Nation Clinical Trial (NCT) ID number, alongside the original article that reports the results of the completed trial. For ongoing trials that lack a reporting paper, only their NCT ID number is referenced.

Results

Role of Macrophages in Myocardial Infarction

Chen et al. reported the release of several inflammatory cytokines (IL-1β, IL-1∝, IL-6, TNF-∝), chemokine (MCP-1) and genes involved in adverse cardiac remodeling (MMP-9, TIMP1) by $CCR2^+$ macrophages [12]. Bajpai et al. reported high levels of expression of genes linked to adverse cardiac remodeling, including MMP-9, TIMP-1, PTX3, EREG and OSM, in human $CCR2^+$ macrophages [7]. RT-qPCR of these macrophages also showed an increase in mRNA expression of the proinflammatory mediators IL-1β, CCL7, TNF and IL-10 [7]. When comparing cohorts that possess high amounts of $CCR2^+$ macrophages to those with a lower percentage, cohorts with a lower percentage displayed improved left ventricular systolic function six months following LVAD implementation [7]. Lavine et al. reported decreased expression of MCP-1, IL-1β, IL-6, TNF, CXCL1 and Cyba1 mRNA in Rosa26-DTR mice hearts when CCR2 monocyte recruitment is inhibited, preventing the establishment of a $CCR2^+$ population and preserving the resident MHC-$II^{high}CCR2^-$ and MHC-$II^{low}CCR2^-$ populations via suppression of cell death [11]. Another study by Bajpai et al. reported depletion of tissue-resident $CCR2^+$ macrophages in mice before IR injury resulted in improved LV systolic function, smaller LV chamber dimensions and reduced akinetic myocardium, while $CCR2^-$ macrophage deletion has the opposite effect [13]. Depletion of $CCR2^+$ macrophages also showed a reduction in infarcts 28 days after IR injury, and a reduction in monocyte and neutrophil accumulation two days after injury [13]. $CCR2^+$ depleted before IR injury were shown to reduce cardiomyocyte hypertrophy compared to their controls, in addition to reduced inflammatory Ifit3+, and increased reparative Tnip3/Itgb7+ macrophages [13]. In contrast to $CCR2^+$ depletion, $CCR2^-$ macrophage depletion before MI altered the specialization of monocytes, augmented macrophage proliferation, increased the infarct

area, reduced LV systolic function and exaggerated LV remodeling [13]. Li et al. reported CCR2+ macrophages have also shown to promote extravasation of neutrophils into the heart during myocardial ischemia reperfusion injury, via production of CXCL2 and CXCL5 chemokines through TLR9/My88 signaling [15]. Lugrin et al. exhibited that IL-1∝ systemic and cardiomyocyte-specific knockout in mice resulted in reduced expression of il*6*, *Mpo*, IL-6, MCP-1 and VCAM-1 molecule, correlating to reduced cardiac inflammation [14]. Saxena et al. knocked-out IL-1R in reperfused and post-infarcted mice, resulting in reduced proinflammatory LyC6^{high} and reparative LyC6^{low} monocyte populations [16]. Inhibition of LyC6^{high} monocyte recruitment leads to reduction of the following activities by cardiac fibroblasts: reduction matrix-degrading protein synthesis and increased TGF-β induced myofibroblast transdifferentiation, events that lead to more favourable cardiac remodeling [16]. On the other hand, decreased LyC6^{low} monocyte recruitment leads to premature activation and differentiation of myofibroblasts during the inflammatory phase of cardiac repair, events that are unfavorable as the environment is hostile to reparative and contractile cells [16].

Table 1. Selected Papers Related to Either Macrophage or Their Mediators' Role in Myocardial Infarction Response, and Applied Interventions

Study	Model	Mediators Reported	Reported Effect of Mediators	Intervention Used and its Effect
Chen et al. (2024)	Human and mouse macrophages	IL-1β, IL-1∝, IL-6, TNF-∝, MCP-1, MMP-9, TIMP-1	Increased activity of inflammatory pathways, increased adverse cardiac remodelling	N/A
Bajpai et al. (2018)	Human CCR2$^+$ macrophages	IL-1β, MMP-9, TIMP-1, PTX3, EREG, OSM, CCL7, TNF, IL-10	Worsened left ventricular systolic function following LVAD implementation	Compared to a cohort with lower CCR2$^+$ percentage; observed improved left ventricular systolic function
Lavine et al. (2014)	Rosa26-DTR mice hearts CCR2 monocytes	IL-1β, IL-6, MCP-1, TNF, CXCL, Cyba1	Increased CCR2 monocyte recruitment, leading to an increased CCR2$^+$ population	Inhibited CCR2 monocyte recruitment; observed preservation of MHC-II$^{high/low}$CCR2$^-$ populations
Bajpai et al. (2018)	169-DTR and CCR2-DTR mice CCR2$^+$ macrophages	Researchers don't report specific mediators observed in their study.	N/A	Deleted CCR2$^+$ macrophages before IR injury; observed the following: 1) Improved LV systolic function, smaller chamber dimensions, and reduced akinetic myocardium. 2) Reduced infarcted area and reduced monocyte and neutrophil accumulation. 3) Reduced cardiomyocyte hypertrophy
Li et al. (2016)	B6 CCR2-DTR mice heart-resident CCR2$^+$ macrophages	Researchers don't report specific mediators observed in their study.	N/A	Depleted CCR2$^+$ macrophages using DTR; observed impaired extravasation, impeding their ability to reach injured myocardial tissue
Lugrin et al. (2023)	Male C57BL/6J *Il1a*$^{-/-}$ mice	il6, *Mpo*, IL-6, MCP-1, VCAM-1	Increased expression of pro-fibrotic and hypertrophic genes, leading to increased cardiac inflammation post MI	Performed systemic and cardiomyocyte-specific knockout of IL-1∝; observed reduced myocardial inflammation and long-term improvement of LV remodelling

Study	Model	Mediators Reported	Reported Effect of Mediators	Intervention Used and its Effect
Saxena et al. (2013)	C57BL/6 IL-1R$^{-/-}$ mice	IL-1β, IL-1∝	Increased recruitment of LyC6^{high} and LyC6 ^{low} leukocyte populations	Performed knockout of IL-1R in reperfused and post-infarcted mice; observed reduced LyC6^{high} and LyC6^{low} populations Reduced LyC6^{high} count leads to reduced matrix-degrading protein synthesis and increased myofibroblast trans differentiation. Reduced LyC6^{low} count causes premature myofibroblast differentiation during cardiac repair.

Role of Macrophages in Atherosclerosis

Blagov et al. and Fatkhullina et al. reported the release of several proinflammatory cytokines by M1 macrophages when exposed to inflammatory stimuli, including IL-1β, IL-1∝, IL-6, IL-8, IL-12, IL-18, and TNF-∝ [17,18]. Fatkhullina et al. reported that IL-6 increased the size of atherosclerotic regions two-fold in Apoe$^{-/-}$ mice, showing that it plays a proinflammatory role [18]. In a study by Luo et al., high-fat diet fed Apoe$^{-/-}$ mice were treated with carnosine and shown to undergo reduced plaque size alongside reduced expression levels of IL-6 [19]. IL-6 however has also shown to have an anti-inflammatory effect primarily through expressing IL-1R antagonist (IL-1RA) and releasing soluble TNF-∝ receptor, suppressing IL-1 and TNF-∝ activities respectively, showing that it is functional as both roles [19]. Studies by Yong et al. and Jaaskelainen et al. report high levels of IL-12 expressed in humans and Apoe$^{-/-}$ mice respectively [20, 21]. Hauer et al. reported similar results in LDRL$^{-/-}$ mice administered with recombinant IL-12, as atherosclerotic plaques sizes were shown to increase, and AS progression enhanced [22]. Consequently, blocking of IL-12 in these groups would reduce these outcomes [22]. Bhat et al. reported Apoe$^{-/-}$ mice administered with IL-18 exhibited increased progression of AS, and destabilization of atherosclerotic plaques, showing increased mRNA expression of CD36, NFkB, and MMP-9 [23]. Chi and Melendez reported TNF-∝ activity contributes to atherosclerosis via activating endothelial cells, upregulating the expression of adhesion proteins including VCAM-1, ICAM-1, and PECAM-, triggering leukocyte and lymphocyte migration from the blood into the arterial intima [24]. Ohta et al. exhibit this, reporting a reduction in plaque size in the aortic sinus in double knockout Tnf-∝$^{-/-}$ Apoe$^{-/-}$ mice compared to a single knockout Apoe$^{-/-}$ control group as a result of decreased expression of ICAM-1, VCAM-1, and MCP-1 [25]. Duewell et al. exhibit how knockout of genes related to the NLRP3 inflammasome (NLRP3$^{-/-}$, ASC$^{-/-}$, IL-1∝/IL-1β$^{-/-}$) in bone marrow cells transplanted into AS-prone, LDLR$^{-/-}$ mice result in decreased atherosclerotic lesion development [26].

Table 2. Selected Papers Related to Either Macrophage or Their Mediators' Role in Atherosclerosis Pathogenesis, and Applied Interventions

Study	Model	Mediators Reported	Reported Effect of Mediator's	Intervention Used and its Effect
Blavgov et al. (2023)	Human and mice macrophages	IL-1β, IL-1∝, IL-6, IL-8, IL-12, IL-18, TNF-∝	Accelerated development of atherogenesis (all), increased macrophage recruitment (IL-1β, IL-1∝, IL-12), increased expression of adhesion proteins (TNF-∝), increased production of additional proinflammatory cytokines (TNF-∝).	N/A
Fatkhullina et al. (2016)	Human and mice macrophages Apoe$^{-/-}$ mice (IL-6)	IL-1β, IL-1∝, IL-6, IL-12, IL-18, TNF-∝	Increased atherosclerosis progression (all), upregulation of macrophages (IL-1β, IL-1∝, IL-12), promoted fatty streaks (IL-6), increased signal uptake of oxLDL (IL-18), upregulated adhesion molecule expression (TNF-∝)	**IL-6:** Performed knockout of *Apoe* in mice; IL-6 observed to increase atherosclerotic regions two-fold in mice

Study	Model	Mediators Reported	Reported Effect of Mediator's	Intervention Used and its Effect
Luo et al. (2024)	Apoe$^{-/-}$ mice	IL-6	Increased size of atherosclerotic plaques	Treated mice with carnosine acid to reduce IL-6 expression; observed reduction in plaque size
Yong et al. (2013)	Humans	IL-12	Increased arterial stiffness	Used multivariate regression analysis to show a correlation between IL-12 and aortic pulse wave velocity, a surrogate marker for CVD-associated diseases
Jaaskelainen et al. (2013)	Apoe$^{-/-}$ mice	IL-12	Increased atherosclerotic lesion development and size	Feed mice a high cholesterol diet for 8 weeks observed increased lesion development associated with increased IL-12 production
Hauer et al. (2005)	LDRL$^{-/-}$ mice	IL-12	Increased atherosclerotic plaque size	Injected an anti IL-12 vaccine in mice, then initiated atherogenesis in both vaccinated mice and a control group; vaccinated mice showed reduced atherogenesis compared to control group
Bhat et al. (2015)	Apoe $^{-/-}$ mice	IL-18	Increased destabilization of atherosclerotic plaques via NFkB-mediated activation	Injected two groups of mice with IL-18: control group given no NFkB inhibitor, while the other group received an NFkB inhibitor; control group showed increases plaque development relative to inhibitor group
Chi and Melendez (2007)	Human and mice	TNF-∝	Promotes atherosclerotic development through endothelial cell activation, upregulation of adhesion proteins VCAM-1, ICAM-1, and PECAM-1	N/A
Ohta et al. (2005)	Tnf-∝$^{-/-}$ Apoe$^{-/-}$ mice	TNF-∝	Increased atherosclerotic plaque size via activation of adhesion proteins	Knocked out expression of TNF-∝ in mice, then administered cholesterol to both Tnf-∝$^{-/-}$ and control mice; Tnf-∝$^{-/-}$ mice exhibited reduced lesion size and development compared to control
Duewell et al. (2010)	LDLR$^{-/-}$ mice	NLRP3, ASC, IL-1β, IL-1∝,	Increased atherosclerotic lesion development via NLRP3 inflammasome activation	Fed NLRP3, ASC, IL-1β, and IL-1∝ deficient mice a high-cholesterol diet and compared it to a control group; gene deficient group showed markedly decreased atherosclerosis development compared to control

Discussion

MI occurs when blood flow to the heart is reduced or stopped, resulting in the death of cardiac tissue, including cardiomyocytes and macrophages. Necrotic cells release inflammatory triggers, referred to as danger associated molecular patterns (DAMPs) that are recognized by receptors located on dendritic cells and macrophages [9]. These signals recruit macrophages to the infarct region, where they release inflammatory cytokines and mediators that promote monocyte and neutrophil infiltration, resulting in removal of necrotic cells [10, 27]. After removal, macrophages polarize into an M2-like anti-inflammatory phenotype and release cytokines that terminate inflammation and begin the transition into the reparative phase [10, 27] during the reparative phase, anti-inflammatory cytokines released by macrophages aid in differentiation of fibroblasts to myofibroblasts, which secrete collagen and nonstructural matrix proteins to rebuild the extracellular matrix [10, 27].

In comparison, AS is characterized by the accumulation of fatty lesions in major arteries in the body. A major risk factor for atherosclerosis is low-

density lipoprotein (LDL), a non-productive lipoprotein that promotes the creation of atherosclerotic plaques that can be oxidized to oxLDL, and in individuals with atherosclerosis, it can be found in high levels in the bloodstream [28, 29]. M1 macrophages such as $LyC6^{high}$ monocytes are recruited to metabolize accumulated oxLDL where they release inflammatory cytokines and factors to promote leukocyte invasion, leading to a buildup of macrophages within the arterial wall (foam cells) [29, 30, 31]. When foam cells become trapped in the arterial wall, high levels of stressors are activated within the macrophages, leading to necrotic cell death within the plaque that leads to instability, and eventual plaque rupture [29, 31]. In contrast to M1 macrophages, M2 macrophages are responsible for reducing inflammation at atherosclerotic sites, removing cellular debris, and facilitating tissue repair [32].

Both MI and AS regulation and progression in human and mice models are the result of identical pro-inflammatory mediators, including but not limited to IL-1β, IL-1∝, IL-6, TNF-∝, VCAM-1, MMP-9, and MCP-1, all of which are released by M1 (primarily $CCR2^{+}$) macrophages during the inflammatory phase. This demonstrates that inflammatory M1-like macrophages do not exclusively contribute to advancing one disease or the other, rather it plays a crucial role in both. As the buildup of plaques in the coronary arteries can obstruct the flow of blood to the heart and cause MI, promotion of AS by M1 macrophages directly influences the likelihood an individual will undergo MI [33]. Therefore, preventing the development of AS by M1 macrophage activity can reduce the occurrence of MI, preventing the opportunity for those same macrophages to secrete inflammatory mediators that result in adverse cardiac remodeling and function. Several proinflammatory mediators are also reported to directly affect regulation of MI or AS. CXCL1, CXCL2, CXCL5, CCL7, IL-10, PTX3, EREG, and OSM are reported here to affect MI specifically, with CD36, NLRP3, IL-8, IL-12, and IL-18 for AS. Considering the dynamic between AS and MI discussed earlier, mediators that affect the development of AS can indirectly impact the MI occurrence.

Current treatments for MI focus on inhibiting inflammatory cytokines and chemokines, including IL-1, IL-6, TNF-∝, and CCL2. Canakinumab is an IL-1β neutralizing antibody shown in clinical trials to successfully lower the rate of recurrent cardiovascular events in individuals who previously had MI (NCT01327846) [34]. Similarly, colchicine inhibits production of IL-1β via the NLRP3 inflammasome, in addition to inhibiting TNF-∝/NfkB signaling, resulting in reduced occurrence of ischemic cardiovascular events in those with MI (NCT02551094) [35]. Tocilizumab is an IL-6 antibody reported to increase myocardial salvage in patients with acute ST segment elevation myocardial infarction (STEMI) (NCT03004703), attenuate inflammatory response and reduce TnT release in nSTEMI patients (NCT01491074) and reduce systemic inflammation and myocardial injury (NCT03863015) [36,37,38]. Treatments for MI in ongoing clinical trials such as one for hydroxychloroquine (NCT02648464), a broad immunosuppressive, uses incidence of major cardiovascular events (MACE) as a primary endpoint, with no focus on blocking or inhibiting a certain inflammatory mediator or pathway. MEDI6570 is an anti-LOX 1 receptor antibody in clinical trials being tested for non-calcified plaque volume in patients previously inflicted by MI (NCT04610892). Finally, etanercept is a TNF-∝ inhibitor currently being tested in STEMI patients (NCT04610892).

Recent treatments for AS revolve around the approach of inducing macrophage polarization to an atheroprotective phenotype, inhibition of scavenger receptor (SR) activity, and induction of autophagy. Macrophages can polarize towards different phenotypes based on microenvironment stimuli [39]. Therefore, introduction of anti-inflammatory factors including HDL and anti-inflammatory cytokines such as IL-4, IL-13, and IL-19 in atherosclerotic regions are able to promote M1 to M2 macrophage polarization, leading to reduced lesion and plaque progression [17, 39]. Natural medicines such as curcumin and ginsenoside Rb1 and Rg3, as well as synthetic drugs including sitagliptin, liraglutide, and metformin are all treatments for atherosclerosis that involve polarizing macrophages to its anti-inflammatory, atheroprotective phenotype [40,41,42,43,44,45]. Binding of LDL to scavenger receptors on macrophages serves as a main trigger for inflammation. Therefore, developing ligands with a high affinity for SRs such as CD36 and MSR1 are able to significantly reduce inflammatory activation. Marleau et al. demonstrated this with their ligand EP80317, a growth hormone-releasing peptide, which binds to CD36 and reduces uptake of oxLDL in $Apoe^{-/-}$ mice, exerting preventative and therapeutic effects on atherosclerotic lesion development [46]. Autophagy is a cellular process where damaged organelles like mitochondria are degraded and removed [47]. It prevents the formation of ROS by damaged mitochondria and inhibits NLRP3 inflamma some activity via ubiquitination of the complex [48, 49]. Compounds including rapamycin, everolimus, resveratrol, berberine, and ursolic acid have all been reported to prevent or treat atherosclerotic plaque progression via enhancing the cellular autophagy response [49, 50, 51, 52].

Conclusion

There is substantial evidence proving that increased activation of M1 inflammatory macrophages will lead to adverse cardiovascular events, and minimization of their activity, production, and polarization can minimize and even prevent these events. Many inflammatory mediators and pathways involved in both MI and AS are identical, emphasizing the similarity in the pathogenesis of these

diseases. Going forward, improved phenotyping of macrophage populations can lead to increased specificity of therapeutic targets, allowing more specialized medicines to be created. This can be further improved upon with novel drug delivery methods involving nanoparticles, viral vectors, and small molecule agents, allowing these treatments to reach their desired target more effectively [53]. Overall, macrophages play a critical role in our body's response to a wide variety of diseases, and greater understanding of their physiology - specifically in the context of CVDs - can greatly improve efforts in alleviating a condition that affects millions worldwide.

List of Abbreviations
AS: atherosclerosis
CCL: C-C chemokine ligands
CCR: C-C chemokine receptor
CD: cluster of differentiation
CVD: cardiovascular disease
DAMPs: danger associated molecular patterns
DTR: transgenic diphtheria toxin receptor
EREG: epiregulin
ICAM: intercellular adhesion molecule
IL: interleukin
LV: left ventricular
LDL: low-density lipoprotein
LOX: lipoxygenases
MACE: major cardiovascular events
MCP: monocyte chemoattractant protein
MHC: major histocompatibility complex
MMP: matrix metalloproteinases
MI: myocardial infarction
NFkB: nuclear factor-kappa B
NLRP3: NOD-like receptor pyrin domain-containing 3
PECAM: platelet endothelial cell adhesion molecule
RT-qPCR: reverse transcriptase quantitative polymerase chain reaction
STEMI: ST-segment elevation myocardial infarction
TIMP: tissue inhibitor of metalloproteinase
TNF: tumor necrosis factor
VCAM: vascular cell adhesion molecule

Conflicts of Interest
The author declares that they have no conflicts of interest

Ethics Approval and/or Participant
The work was a literature review that examined previous studies and articles. Therefore, no approval or participant consent was required.

Authors' Contributions
CNC: collected all the studies, articles and reviews, analyzed the data and interpreted it, and gave final approval of the version to be published.

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