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REVIEW

Reactive Oxygen Species in Asthma: Regulators of Macrophage Polarization and Therapeutic Implications: A Narrative Review

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Abstract: As a vital component of the immune system, macrophages play a critical role in the progression of asthma. The two classic polarization states of macrophages, M1 and M2, exhibit distinct functions. M1-polarized macrophages eliminate pathogens through the secretion of pro-inflammatory cytokines, while M2-polarized macrophages secrete anti-inflammatory factors to facilitate tissue repair. However, in asthma, the activation of M1 macrophages is often associated with excessive inflammatory responses, whereas M2 macrophages contribute to airway remodeling and chronic inflammation. These processes collectively exacerbate airway inflammation and remodeling, thereby aggravating asthma symptoms. Reactive oxygen species (ROS), as crucial signaling molecules, have been shown to regulate macrophage polarization and promote both M1 and M2 polarization states. This review summarizes the primary endogenous and exogenous sources of ROS in asthma and elaborates on the mechanisms by which ROS influence M1/M2 polarization of macrophages. Endogenous ROS arise chiefly from NOX2, xanthine oxidase, peroxisomes and mitochondria, whereas ozone and fine particulate matter are major exogenous sources. ROS activate MAPK, NF-κB and NLRP3 cascades, boosting IL-1β, IL-6 and IL-27 release by M1 cells, while low NOX2 flux or mitochondrial H_2O_2 supports STAT6-dependent ARG1 expression and drives an M2 program. Additionally, we discuss the impact of different macrophage polarization states on asthma pathophysiology and the potential applications of macrophage-modulating agents in asthma treatment, particularly those targeting ROS-mediated polarization pathways. ARG1 rich M2 cells convert L-arginine into proline, fostering collagen deposition; Ym1/2, Fizz1 and CD206 correlate with airway remodeling and declining lung function. Emerging antioxidant and macrophage-polarization strategies that selectively modulate ROS show promise in rebalancing M1/M2 responses and attenuating airway hyper-responsiveness. This review provides new insights into the interplay between ROS and macrophage polarization and highlights the potential for developing therapies aimed at modulating macrophage polarization via ROS regulation.

Keywords: asthma, macrophage polarization, reactive oxygen species

Introduction

Asthma is a chronic inflammatory airway disease characterized by recurrent wheezing, shortness of breath, chest tightness, and coughing.[1] In recent years, the prevalence of asthma has risen significantly, affecting nearly 250 million people worldwide and causing over 1000 deaths daily.[2] Despite significant advancements in asthma treatment over the past 15 years, which have allowed most patients to achieve effective disease control, the underlying etiology of asthma remains unclear.[3] Studies suggest that both environmental and genetic factors play critical roles in asthma pathogenesis. Genetic factors influence individual sensitivity to allergens, while environmental factors, such as allergen exposure, trigger allergic inflammation, a hallmark pathological feature of asthma.[4,5] In Indian rhesus macaques, macrophages make up about 70% of lung immune cells and play a pivotal role in airway inflammation induced by allergens.[6]

Pulmonary macrophages primarily consist of alveolar macrophages (AMs) and interstitial macrophages. AMs represent the majority (75–80%) and exhibit a low turnover rate, whereas interstitial macrophages display a higher turnover rate and share similarities with circulating monocytes, suggesting that monocytes might be a key source of interstitial macrophages.[6,7]

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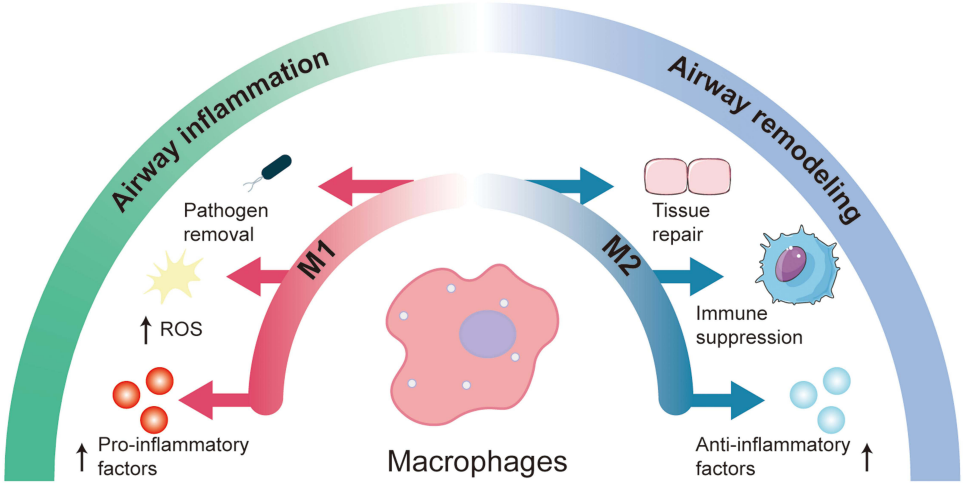

Figure 1 M1/M2 Polarization States of Macrophages and Their Functions. M1-polarized macrophages secrete pro-inflammatory cytokines and produce high levels of reactive oxygen species (ROS) to eliminate pathogens. In asthma, excessively activated M1 macrophages contribute to airway inflammation. M2-polarized macrophages, on the other hand, secrete anti-inflammatory cytokines, suppress immune activation, and promote tissue repair. Overactivation of M2 macrophages during early asthma leads to airway remodeling, which ultimately results in airway obstruction. Created in Adobe Illustrator.

The polarization state of macrophages is a crucial determinant of immune response. As shown in Figure 1, macrophages can polarize into two major phenotypes: classically activated (M1) and alternatively activated (M2). M1 macrophages typically exhibit pro-inflammatory functions, producing inflammatory cytokines and reactive oxygen species (ROS) to eliminate pathogens. In contrast, M2 macrophages are associated with anti-inflammatory responses, tissue repair, and immune suppression. A significant increase in M2 macrophages has been observed in asthma patients, where they contribute to airway remodeling and chronic inflammation through the secretion of cytokines such as IL-13, IL-6, and CCL2.[8] Therefore, dysregulated macrophage polarization is implicated in airway inflammation and exacerbation of asthma symptoms.

ROS, highly reactive oxygen-containing molecules, have been extensively studied for their role in promoting asthma progression.[9] In the asthmatic airway, inflammatory cells are recruited and produce various ROS, driving tissue damage and chronic airway inflammation.[10] Moreover, ROS actively participate in immune regulatory responses, including the modulation of macrophage polarization.[11] Understanding the sources of ROS in asthma and how ROS influence macrophage polarization not only sheds light on the immunopathology of asthma but also identifies potential therapeutic targets for disease management.

This review focuses on the role of ROS in asthma, particularly in regulating macrophage polarization. We will summarize how ROS influence immune cell functions, especially macrophage polarization, to modulate airway inflammation and immune responses. Furthermore, we will explore the potential therapeutic applications of ROS scavengers in asthma immunotherapy, offering new insights for future treatment strategies.

Sources of ROS in Asthma

ROS can be classified into endogenous and exogenous sources (Figure 2). Endogenous ROS are primarily generated by oxidases, including NADPH oxidase (NOX), xanthine oxidase, and peroxisomes, as well as by mitochondria. Exogenous ROS, on the other hand, are primarily derived from environmental pollutants.

Endogenous Sources

NADPH Oxidase

NADPH oxidase is a family of enzymes that utilize nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor to catalyze the reduction of O_2 into superoxide anion (O_2•−).[12] The NADPH oxidase family comprises several members, including NOX1 through NOX5.[13] Each member plays distinct roles in different cell types and physiological processes. Among these, NOX2 is primarily expressed in phagocytic cells such as eosinophils, neutrophils, macrophages, and dendritic cells.[14] NOX2 is a multi-subunit protein complex consisting of two transmembrane proteins,

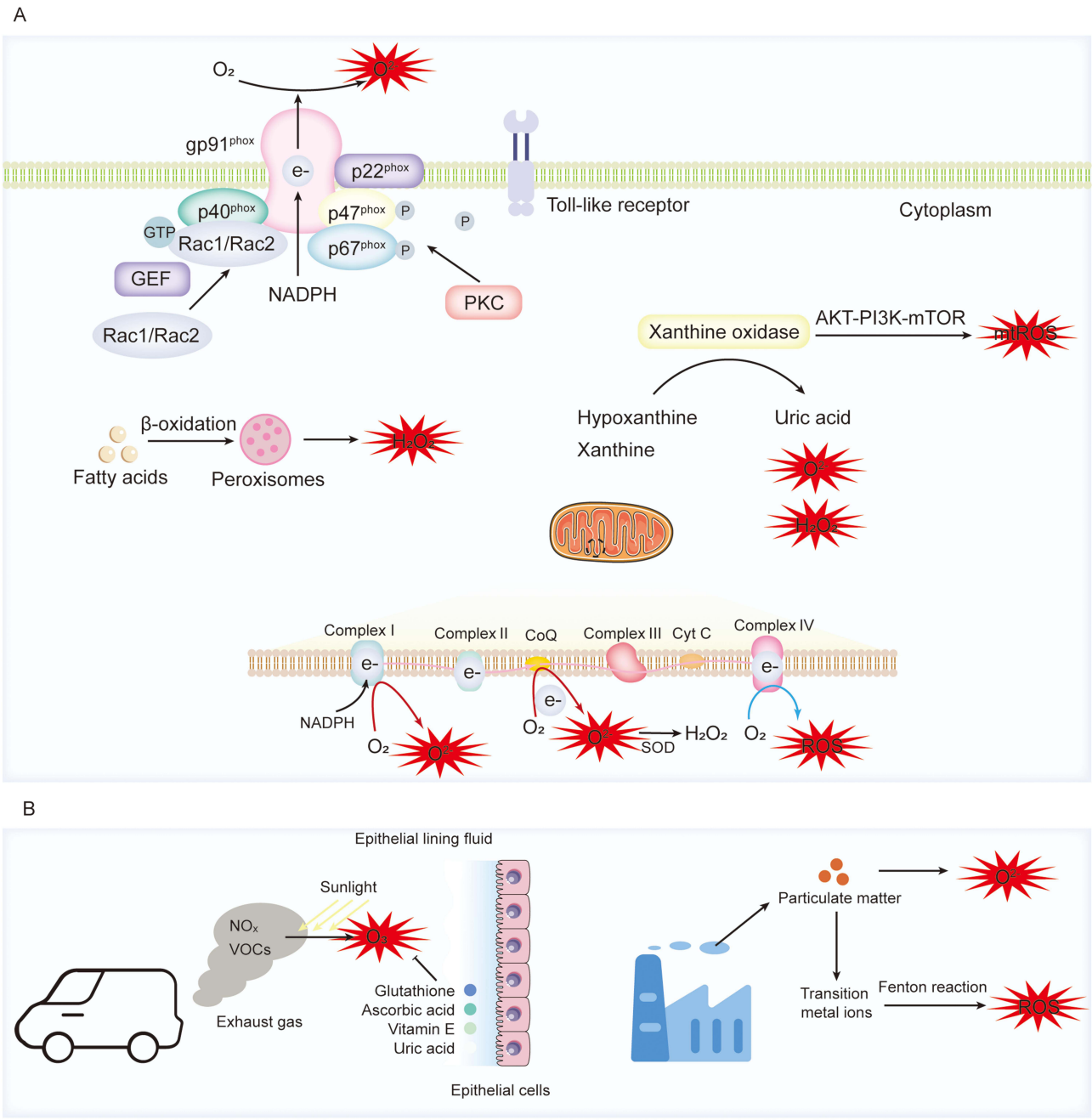

Figure 2 Sources of reactive oxygen species. ROS originate from endogenous (**A**) and exogenous (**B**) sources. (**A**) Endogenous ROS are produced mainly by oxidases, notably NADPH oxidase (NOX2), xanthine oxidase, and the peroxisomal β oxidation system, together with the mitochondrial electron transport chain. Within NOX2 the transmembrane subunits gp91^{phox} and p22^{phox} form its catalytic core. The cytosolic subunits p40^{phox}, p47^{phox}, and p67^{phox}, assisted by the small GTPases Rac1 and Rac2, move to the membrane after phosphorylation and guanine nucleotide exchange, stabilising the complex; electrons then flow from cytosolic NADPH to molecular oxygen and generate superoxide. Xanthine oxidase converts hypoxanthine and xanthine to uric acid while releasing superoxide and hydrogen peroxide and can further enhance mitochondrial ROS through the AKT PI3K mTOR pathway. Peroxisomes liberate H_2O_2 during fatty-acid β oxidation. In mitochondria electrons that leak from complex I and complex III, and under stress also from complex IV, reduce O_2 to superoxide, which is subsequently dismutated to H_2O_2. (**B**) Exogenous ROS arise mainly from air pollutants such as ozone and particulate matter. Tropospheric ozone is generated photochemically from nitrogen oxides and volatile organic compounds in vehicle exhaust. Although antioxidants in the epithelial lining fluid, including glutathione, ascorbic acid, vitamin E, and uric acid, react with ozone, high ozone concentrations can overwhelm this defence and promote ROS buildup. Particulate matter contains polycyclic aromatic hydrocarbons that undergo redox cycling to form superoxide, and fine particles rich in transition metal ions catalyse hydroxyl-radical formation through the Fenton reaction, thereby amplifying oxidative stress. Created in Adobe Illustrator.

gp91^{phox} and p22^{phox}, and three cytosolic components, p40^{phox}, p47^{phox}, and p67^{phox}.[13] The catalytic core of NOX2 is formed by gp91^{phox} and p22^{phox}, while p40^{phox}, p47^{phox}, and p67^{phox} assemble into a cytosolic trimer that binds to the catalytic core, forming the functional NOX2 complex.[15] This assembly process is regulated by the activation of

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G protein-coupled receptors, Fc receptors, and integrin receptors, which phosphorylate $p47^{phox}$ and $p67^{phox}$ via protein kinase C (PKC). The phosphorylation of $p47^{phox}$ and $p67^{phox}$ induces conformational changes that promote their translocation to the membrane.[16,17] Toll-like receptors (TLRs) also contribute to NOX2 activation, although not directly. Instead, TLRs partially phosphorylate $p47^{phox}$, priming cells for heightened sensitivity to subsequent stimuli.[18] Additionally, the small GTPases Rac1 and Rac2 play crucial roles in NOX2 activation. Under the influence of guanine nucleotide exchange factors (GEFs), Rac1 and Rac2 bind to GTP and translocate from the cytosol to the membrane. There, they interact with the catalytic core of NOX2, stabilizing the complex and facilitating efficient electron transfer.[16,19] Within the catalytic core of the NOX2 complex, electrons are transferred from intracellular NADPH through the transmembrane region (formed by $gp91^{phox}$ and $p22^{phox}$). These electrons are ultimately delivered to extracellular oxygen molecules, producing O_2•−.[20]

Xanthine Oxidase

Xanthine oxidase (XO) is a member of the molybdenum-flavin enzyme family and contains molybdenum and flavin as cofactors.[21] XO typically exists as a homodimer, with each subunit comprising an Fe-S redox-active center, a flavin cofactor, and a substrate-binding domain.[22] Predominantly localized in the cytoplasm, XO catalyzes the oxidation of hypoxanthine and xanthine into uric acid, generating O_2•− and hydrogen peroxide (H_2O_2) as byproducts.[23] This property makes XO a potential source of ROS.[24] Studies have shown that the use of allopurinol, an XO inhibitor, in asthmatic mice suppresses airway inflammation and Th1, Th2, and Th17 immune responses, thereby mitigating airway damage.[9] ROS produced by XO can activate the p38 mitogen activated protein kinase (MAPK)- nuclear factor of activated T cells 5 (NFAT5) signaling pathway and promote the expression of the pro-inflammatory cytokine IL-6, a hallmark of M1 macrophages. This suggests that XO may contribute to the polarization of macrophages toward the M1 phenotype.[25] Research by Annette Ives et al has demonstrated that XO is a major source of ROS in macrophages. XO activates the AKT-PI3K-mTOR pathway, enhancing mitochondrial ROS (mtROS) production and simultaneously activating the NLRP3 inflammasome in mice. This dual mechanism drives macrophages toward a pro-inflammatory M1 phenotype.[26]

Peroxisomes

Peroxisomes are cytoplasmic organelles widely present in nearly all eukaryotic cells. They play a crucial role in the oxidative metabolism of amino acids and the β-oxidation of fatty acids, during which ROS are primarily generated in the form of H_2O_2 and O_2•−.[27,28] L-amino acid oxidase, D-amino acid oxidase, and polyamine oxidase catalyze the oxidation of amino acids, transferring electrons to O_2 and releasing H_2O_2 as a byproduct.[29,30] Fatty acids are broken down into acetyl-CoA via β-oxidation in peroxisomes and subsequently transferred to mitochondria to participate in the tricarboxylic acid (TCA) cycle. During this process, flavin adenine dinucleotide (FAD) in acyl-CoA oxidase accepts electrons from acyl-CoA and transfers them to O_2, resulting in the production of H_2O_2.[31] The H_2O_2 generated in peroxisomes can be degraded by catalase and glutathione peroxidase, enzymes contained within the organelle. However, an excessive influx of fatty acids into peroxisomes can lead to the accumulation of H_2O_2, causing elevated ROS levels and subsequent oxidative stress.[32]

Mitochondria

Mitochondria, as the primary energy suppliers of cells, generate mtROS during respiration, with O_2•− being the predominant form.[33] In mitochondria, NADH and reduced flavin adenine dinucleotide ($FADH_2$) transfer high-energy electrons to O_2 via the electron transport chain (ETC). This process produces ROS while simultaneously driving proton pumping from the mitochondrial matrix into the intermembrane space, creating a proton gradient that powers ATP synthesis through ATP synthase.[34] mtROS are primarily generated at Complexes I through IV of the ETC, with Complexes I and III being the major contributors.[35] Complex I serves as the entry point of electrons from NADH into the ETC.[36] The flavin mononucleotide (FMN) cofactor accepts electrons from NADH and transfers them to coenzyme Q (CoQ). During this transfer, FMN may leak electrons to O_2, producing O_2•−.[37] Complex III transfers electrons from CoQ to cytochrome c and features two CoQ binding sites: the Qi and Qo sites. At the Qo site, CoQ is oxidized, releasing electrons that are subsequently transferred to cytochrome c and the Qi site for CoQ reduction.[38] When the Qi site is inhibited, electrons accumulate at Complex III and are transferred to O_2 via the semiquinone intermediate at the Qo site, producing O_2•−.[39] These O_2•− are released to both sides of the mitochondrial inner membrane via Complex III[40] and are

subsequently converted into H_2O_2 by mitochondrial superoxide dismutase (SOD).[41] O_2•− in the intermembrane space can also reach the cytoplasm through voltage-dependent anion channels.[42] In addition to Complexes I and III, Complexes II and IV have also been implicated in mtROS production, though their mechanisms are less well understood.[43] The FAD cofactor in Complex II is thought to be a major site of mtROS generation.[43] Complex IV, as the terminal point of the ETC, rarely leaks electrons under normal conditions. However, under pathological conditions such as mitochondrial damage, partially reduced oxygen species may escape from Complex IV, forming ROS.[44]

Research suggests that the activation of innate immune signaling recruits mitochondria to macrophage phagosomes, enhancing mtROS production and increasing macrophage bactericidal activity in mice.[45] Lipopolysaccharide (LPS) stimulation induces metabolic reprogramming in macrophages, shifting from oxidative phosphorylation to glycolysis, which promotes mtROS production at Complex I and enhances the expression of M1 polarization markers such as IL-1β.[46] This may be attributed to mtROS-mediated oxidation of succinate dehydrogenase, stabilizing hypoxia-inducible factor 1-alpha (HIF-1α) and subsequently driving sustained IL-1β expression.[47] Furthermore, mtROS can activate the p38 MAPK signaling pathway, stimulating the expression of pro-inflammatory cytokines.[48]

Exogenous Sources: Air Pollutants as ROS Generators

Air pollutants significantly impact the onset of asthma and exacerbate its symptoms.[49] Traffic-related pollutants, such as ozone (O_3) and particulate matter (PM), are potent oxidants that contribute to ROS production.[50]

Ozone

O_3, a common air pollutant, is primarily formed through photochemical reactions involving nitrogen oxides and volatile organic compounds from vehicle exhaust.[51] Studies indicate that the airway epithelial lining fluid (ELF) serves as the first line of defense against O_3 exposure. Antioxidants present in ELF, such as glutathione (GSH), ascorbic acid, vitamin E, and uric acid, react with and neutralize most of the O_3.[52] However, high concentrations of O_3 can overwhelm the antioxidant capacity of the ELF, leading to excessive ROS generation and the release of inflammatory cytokines like IL-33.[53] In allergic asthma, epithelial-barrier integrity is frequently impaired, making airway epithelial cells particularly vulnerable to ROS released by infiltrating inflammatory cells. These ROS activate NF-κB and markedly amplify ozone-induced IL-8 production.[54] Neutrophils from asthmatic patients, in turn, display an exaggerated responsiveness to IL-8.[55] The chemokine also engages CXCR1/CXCR2 receptors on airway smooth-muscle cells, provoking bronchoconstriction[56] and further exacerbating asthma.[55]

Particulate Matter

PM, a major component of air pollution, primarily originates from vehicle emissions, industrial discharges, and construction activities. PM with a diameter of less than 10 micrometers (PM_{10}) is strongly associated with increased incidence and mortality of respiratory diseases.[57] Interestingly, the oxidative potential of PM, rather than PM itself, has shown a stronger correlation with adverse health effects.[58] PM contains high levels of polycyclic aromatic hydrocarbons (PAHs), which undergo metabolic activation by cytochrome P450 enzymes to form epoxides. These epoxides are converted into dihydrodiol intermediates by epoxide hydrolases, which are subsequently oxidized into quinones by dihydrodiol dehydrogenases.[59,60] Quinones are then reduced to semiquinone radicals by NADPH cytochrome P450 reductase. These semiquinone radicals are unstable and rapidly transfer electrons to oxygen, generating O_2•−.[61] Different PM sizes impose varying oxidative stress burdens. Smaller PM particles tend to contain higher levels of transition metal ions, such as nickel (Ni), chromium (Cr), and iron (Fe), which catalyze the production of hydroxyl radicals through Fenton reactions.[62] Once PM enters the airways, it is phagocytosed by macrophages, which subsequently promote inflammation and exacerbate disease progression.[59]

Regulation of Macrophage Polarization by ROS

The process by which macrophages exhibit distinct functional phenotypes in response to signals within their microenvironment is known as macrophage polarization.[63] Although recent studies suggest that macrophage polarization involves diverse and partially overlapping transcriptional programs, the classical M1/M2 paradigm remains widely used to reflect macrophage functional states.[64] Macrophages with a pro-inflammatory phenotype are categorized as M1 macrophages, while those with anti-inflammatory or immunosuppressive phenotypes are classified as M2

macrophages.[65] At the molecular level, M1 macrophages are characterized by the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-12, whereas M2 macrophages are associated with the expression of cytokines like TGF-β, CCL18, and IL-1Ra.[66] Different macrophage polarization states play distinct roles in asthma. As shown in Figure 3, recent research has shown that ROS act as regulatory factors capable of influencing and modulating the M1/M2 polarization of macrophages.[67,68]

ROS in Driving M1 Macrophage Polarization

ROS play a critical role in driving M1 polarization of macrophages. The surface receptor IFN-γR on macrophages recognizes IFN-γ secreted by immune cells, leading to the activation of Janus kinase (JAK).[69] Phosphorylated signal transducer and activator of transcription (STAT)1, activated by JAK, translocates into the nucleus and regulates the transcription of M1-related genes, such as TNF-α, inducible nitric oxide synthase (iNOS), and IL-12.[70] The LPS/TLR4 pathway is also crucial for M1 polarization.[71] Binding of LPS to TLR4 recruits myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF).[72] MyD88 activates the MAPK signaling pathway, promoting the expression of inflammatory cytokines and enzymes like iNOS.[73] MyD88 also triggers the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, a key event in M1 polarization, enabling NF-κB to translocate into the nucleus and drive the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[74] In addition, MyD88 has been reported to activate the STAT1 pathway, further promoting M1 polarization.[75,76] MyD88 also activates the transcription factor IRF5, which directly induces the genes encoding IL-12 subunits p40, IL-12p35, and IL-23p19, thereby enhancing M1 polarization.[77,78] The TRIF pathway, on the other hand, facilitates the production of type I interferons, amplifying M1-associated transcriptional programs.[79] Upon stimulation by IFN-γ and LPS, rapid activation of Phox and ROS release have been observed in microglia and astrocytes. The use of Phox inhibitors and catalase can suppress the activation of MAPK, NF-κB, and JAK/STAT pathways under IFN-γ and LPS stimulation,

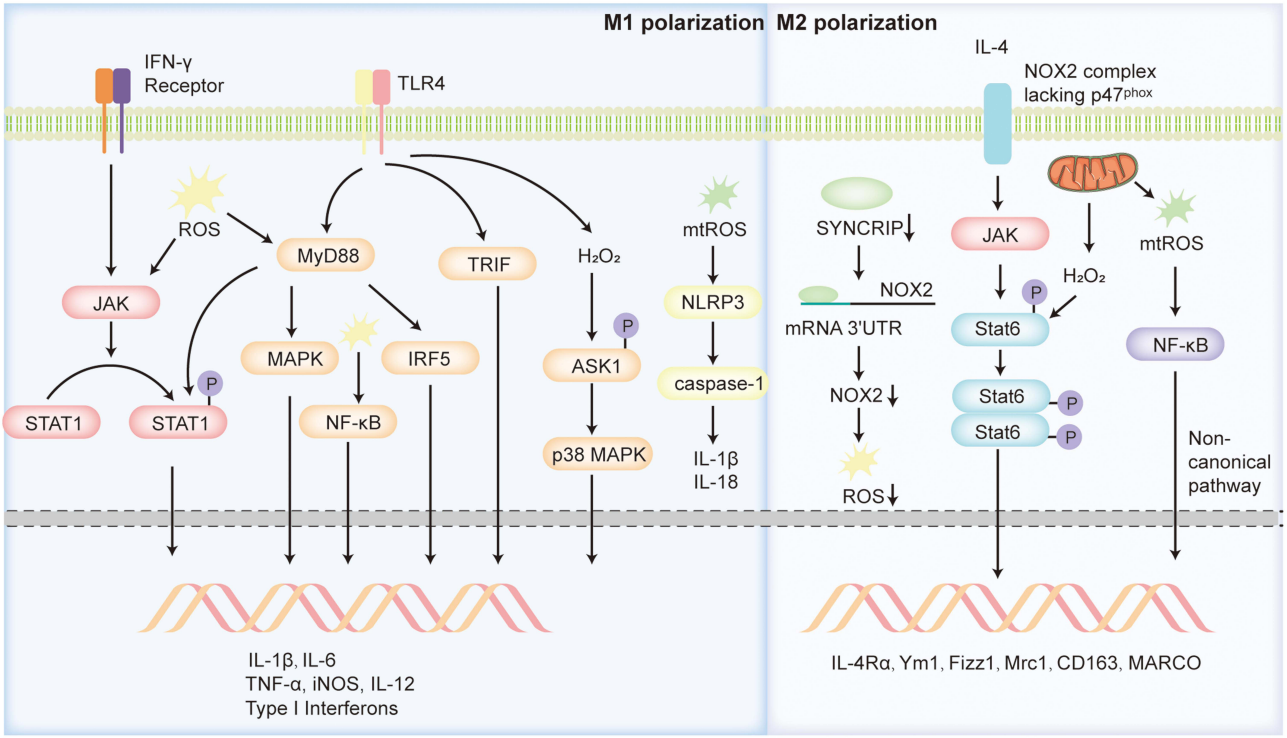

Figure 3 The Role of ROS in Macrophage Polarization. Under IFN-γ and LPS stimulation, corresponding receptors are activated, initiating the STAT1 and MAPK pathways to drive M1 macrophage polarization, a process that depends on ROS. ROS also facilitate M1 polarization by promoting ASK phosphorylation and activating NF-κB. Additionally, mtROS are essential for NLRP3 inflammasome-dependent M1 polarization. When macrophages engulf apoptotic materials, SYNCRIP expression is downregulated, leading to reduced stability of NOX2 mRNA, decreased NOX2 protein levels, and lower ROS production. The absence of the $p47^{phox}$ subunit in NOX2 has been shown to increase sensitivity to external stimuli, thereby enhancing Stat6 phosphorylation and promoting M2 polarization. Furthermore, mitochondrial ROS and H_2O_2 contribute to M2 macrophage polarization by activating non-canonical NF-κB and enhancing Stat6 phosphorylation, respectively. Created in Adobe Illustrator.

reducing the expression of M1 markers such as IL-1, IL-6, TNF-α, and iNOS.[80] This suggests that ROS may function as signaling molecules in the activation of the LPS/TLR4 pathway. Activation of the TLR4 pathway has also been shown to stimulate NOX and SOD, leading to the production of H_2O_2.[81] H_2O_2 can dissociate thioredoxin (Trx) from the apoptosis signal-regulating kinase 1 (ASK1)-Trx complex, inducing homodimerization and phosphorylation of ASK1. Phosphorylated ASK1 subsequently activates downstream p38 MAPK.[82] Moreover, ROS enhance the phosphorylation of IκB, marking it for ubiquitination and degradation, which releases and activates NF-κB dimers.[81] Recent studies have reported that checkpoint kinase 2 (CHK2) responds to ROS produced under LPS and IFN-γ stimulation by phosphorylating pyruvate kinase M2 (PKM2). Phosphorylated PKM2 promotes glycolysis, induces p21 accumulation, and triggers G1 cell cycle arrest, thereby facilitating M1 polarization.[68]

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome senses endogenous damage-associated molecular patterns (DAMPs) and exogenous pathogen-associated molecular patterns (PAMPs), initiating immune responses. It drives the caspase-1-dependent maturation and secretion of IL-1β and IL-18, promoting M1 polarization.[83] Numerous studies have indicated that ROS are involved in the activation of the NLRP3 inflammasome.[84,85] Targeting mitochondria with MitoQ to block mtROS production has been shown to effectively suppress NLRP3 inflammasome activation and reduce the maturation of IL-1β and IL-18.[86] However, cells lacking the $p22^{phox}$ subunit still produce normal levels of IL-1β, suggesting that NLRP3 activation depends on mtROS rather than NADPH oxidase-derived ROS.[87]

ROS in Promoting M2 Macrophage Polarization

ROS play a dual role in macrophage polarization, not only promoting M1 polarization but also critically regulating M2 polarization. Compared to M1 macrophages, M2 activation is often associated with reduced ROS production and increased arginase-1 (ARG1) activity. M2 macrophages improve phagolysosomal proteolytic activity, facilitating tissue remodeling by reducing NOX2 activity and increasing protease activity.[88] The decrease in NOX2 levels in M2 macrophages may result from macrophage interaction with apoptotic cell debris, which downregulates synaptotagmin-binding cytoplasmic RNA-interacting protein (SYNCRIP) expression. This reduces the binding of SYNCRIP to the 3′ UTR of NOX2 mRNA, ultimately lowering NOX2 mRNA abundance and expression, decreasing ROS generation, and promoting M2 polarization.[89] Similarly, Padgett et al demonstrated that NOX deficiency limits ROS production, leading to a significant increase in M2 macrophages along with reduced expression of TNF-α and IL-1β.[90] The absence of $p47^{phox}$, a cytosolic subunit of the NOX2 complex, biases macrophages toward M2 polarization. This is due to the heightened sensitivity of $p47^{phox}$-deficient macrophages to IL-4, resulting in significantly elevated phosphorylation of Stat6 upon IL-4 stimulation.[91] This finding suggests that $p47^{phox}$ not only participates in NOX2 complex assembly but also serves as a regulatory factor in the IL-4/Stat6 pathway. Similarly, microglia lacking $p47^{phox}$ exhibit enhanced M2 polarization and increased expression of M2 markers, such as IL-4Rα, chitinase 3-like protein 3 (Ym1), found in inflammatory zone 1 (Fizz1), mannose receptor c-type 1 (Mrc1), cluster of differentiation 163 (CD163), and macrophage receptor with collagenous structure (MARCO), under LPS stimulation. Treating macrophages with the NOX2 inhibitor apocynin produces similar effects.[92] Although these studies support the inhibitory role of NOX2-derived ROS in M2 polarization, Zhang et al demonstrated that ROS are essential during the early activation phase of biphasic ERK signaling. Using the NOX2 inhibitor BHA disrupts the differentiation of monocytes into M2 macrophages.[93] This suggests that ROS may have stage-specific effects on macrophage polarization, with NOX2-derived ROS being indispensable during the initial activation of M2 macrophages.

Beyond NOX, mtROS also play a critical role in regulating macrophage polarization. mtROS are indispensable for M2 polarization, as studies have shown that inhibiting mtROS in RAW 264.7 cells reduce the expression of the M2 marker ARG1.[94] Similar studies suggest that mtROS may activate NF-κB via non-canonical pathways, promoting an anti-inflammatory M2 phenotype.[67] The primary pathway for M2 polarization is the Stat6 pathway. Cytokines IL-4 and IL-13 bind to surface receptors, activating JAK, which phosphorylates the intracellular domain of the receptor. The phosphorylated receptor recruits Stat6, which is subsequently phosphorylated by JAK. Activated P-Stat6 forms dimers that translocate to the nucleus, initiating the transcription of M2-related genes.[95] Mitochondrial Cu, Zn-SOD converts $O_2\bullet-$ into H_2O_2, and studies have shown that increased Cu, Zn-SOD expression promotes M2 polarization by generating H_2O_2, which activates STAT6.[96]

Macrophage Polarization and Its Role in Asthma

In the early stages of asthma, monocyte-derived macrophages are activated and proliferate to facilitate pathogen clearance, initiate pulmonary inflammation, and contribute to the resolution of later-stage inflammation. Studies have shown that during the initial phase of lung injury, circulating Ly6C(hi) monocytes increase significantly, with their numbers positively correlated with the severity of pulmonary inflammation. Conversely, M2-like AMs become predominant in the later stages of the disease and are positively associated with the severity of lung fibrosis.[97] Based on the mechanisms of allergic responses, asthma is traditionally categorized into atopic and non-atopic asthma. Atopic asthma is associated with IgE-mediated allergic reactions, whereas non-atopic asthma does not involve IgE-mediated pathways.[98] In both atopic and non-atopic asthma, macrophage numbers are elevated. To determine the dominant macrophage phenotypes in these two asthma types, Robbe et al studied a house dust mite (HDM)-induced allergic mouse model and a farm dust extract (FDE)-induced non-allergic mouse model. Their findings revealed that in HDM-induced allergic asthma, macrophages predominantly exhibit M2 polarization, accompanied by a Th2 cell response. In contrast, macrophages in FDE-induced non-allergic asthma primarily display M1 polarization, alongside increased expression of Th1 and Th17 cells.[99]

M1 Polarization: Inflammation and Pathogenesis in Asthma

M1 macrophages play a vital role in host defense against pathogens by releasing large amounts of pro-inflammatory cytokines and chemokines through phagocytosis.[100] However, some studies suggest that bacterial and viral pathogens observed in the airways of atopic asthma patients are insufficient to be effectively controlled by M1-activated macrophages.[100,101] Despite this, pro-inflammatory mediators released by M1 macrophages have been shown to exacerbate lung damage and accelerate airway remodeling. For example, elevated levels of nitric oxide (NO) in the exhaled breath of asthma patients are primarily derived from macrophages. High concentrations of NO can induce oxidative DNA damage, trigger inflammation, and enhance mucus secretion in allergen-induced asthma mouse models.[102,103] Additionally, M1 macrophages secrete pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, and TNF-α, which activate $CD4^+$ T cells and enhance IL-5 secretion.[104] IL-5 is a major activator of eosinophils, promoting their proliferation, migration, and degranulation, thereby exacerbating airway inflammation and hyperresponsiveness in asthma patients.[105] Moreover, IL-6 contributes to pulmonary fibrosis by promoting fibroblast proliferation, activating the MAPK signaling pathway, and synergizing with TGF-β to drive fibrotic progression.[106] Animal studies have shown that high levels of LPS can induce type 1 asthma, characterized by non-eosinophilic inflammation, airway hyperresponsiveness, and increased IL-12 expression.[107] Administering LPS to the lungs of asthmatic mice increases inflammatory macrophage subtypes ($CD11b^{high}F4/80^{high}CD11c^{var}$) and enhances the expression of inflammatory cytokine IL-27.[107] Elevated levels of IL-27 and IFN-γ have been observed in steroid-resistant asthma patients. Their synergistic action inhibits glucocorticoid receptor (GR) nuclear translocation via the MyD88-dependent signaling pathway, contributing to glucocorticoid resistance.[108] IL-27 has been reported to activate IFN-inducible gene expression in monocyte-derived cells[109] and induce pro-inflammatory gene expression through STAT1-dependent pathways. Additionally, IL-27 amplifies inflammation by enhancing monocyte responses to TLR stimulation and suppressing IL-10 signaling and production.[110] These findings suggest that IL-27 promotes M1 macrophage development and contributes to inflammatory damage in asthma. Interestingly, Th2-related factors such as IL-4 have been shown to enhance the expression of inflammatory cytokines, including IL-6, TNF-α, and IL-12, in macrophages challenged with *Neisseria meningitidis* through the MyD88 pathway.[111] This indicates that IL-4 not only regulates the anti-inflammatory functions of macrophages but also promotes M1-associated cytokine expression under specific conditions. Similarly, IL-33, a Th2 cytokine, can promote the expression of M2 macrophage markers such as arginase, Ym1, and mannose receptor in M1 or M2 polarized macrophages. However, in unpolarized macrophages, IL-33 enhances the expression of M1-associated chemokine CCL3.[112] This dual effect suggests that IL-33 may play a critical role in balancing inflammation and repair, though its precise mechanisms require further investigation.

M2 Polarization: Remodeling and Fibrosis in Asthma

While M1 macrophages are typically highly expressed in non-atopic asthma and are associated with severe asthma,[66] M2 macrophages are considered closely related to atopic asthma and are the predominant macrophage type in this condition.[63] In NM-induced lung injury mice model, macrophage polarization exhibits a time-dependent pattern: M1 macrophages are most prominent 1–3 days after NM exposure, whereas M2 macrophages peak during the later stages, particularly on day 28, contributing to lung fibrosis.[113] In asthma animal models, M2 macrophages are characterized by the high expression of ARG1, chitinase-like proteins Ym1/2, Fizz1, and macrophage mannose receptor 206 (CD206).[63]

Arginase-1

Arginase-1 (ARG1) is one of the most representative markers of alternatively activated macrophages. It hydrolyzes L-arginine into L-ornithine and urea, facilitating nitrogen excretion.[114] In macrophages, the expression of ARG1 is typically silenced but can be induced more than four orders of magnitude upon receiving Th2 cytokine signals.[115] Apart from being metabolized via the ARG1 pathway, L-arginine can also be catalyzed by iNOS to produce NO and L-citrulline.[116] Consequently, ARG1 in M2 macrophages competes with iNOS for the substrate L-arginine. Elevated ARG1 expression reduces the availability of L-arginine for iNOS, thereby inhibiting NO synthesis.[117] NO relaxes airway smooth muscle cells, leading to bronchodilation,[118] and its inhibition in asthma mouse models has been shown to induce airway hyperresponsiveness.[119] As a product of the ARG1 reaction, L-ornithine is converted into polyamines, which contribute to airway hyperresponsiveness in allergen-induced asthma models. This effect can be alleviated by inhibiting ornithine decarboxylase.[119] Polyamines, particularly spermine and spermidine, also stimulate smooth muscle relaxation by reducing intracellular calcium concentrations.[120] Additionally, L-ornithine can be converted into proline by ornithine δ-aminotransferase.[121] Proline, a critical precursor for collagen synthesis, promotes collagen deposition, leading to airway remodeling and fibrosis in asthma patients.[122] These findings suggest that ARG1 regulates NO levels by competing with iNOS for L-arginine and contributes to bronchial contraction and airway remodeling through its metabolic products. As such, ARG1 plays a significant role in promoting asthma pathogenesis.

Chitinase-Like Proteins

Chitinase-like proteins (CLPs) are a group of proteins that lack traditional chitinase enzymatic activity but retain structural domains similar to chitinases. These domains allow CLPs to bind with high affinity to chitin and participate in recognizing PAMPs.[123] Although the chitinase-like proteins Ym1 and Ym2 are expressed only in mice, they are functionally analogous to human galectin-10, which contributes to the formation of Charcot-Leyden crystals. Understanding the immunoregulatory roles of Ym1 and Ym2 may provide insights into asthma mechanisms in humans.[124] Elevated expression of Ym1 and Ym2 has been observed in the bronchoalveolar lavage fluid (BALF) of allergic asthma mouse models, and this upregulation correlates significantly with airway inflammation.[125] The expression of Ym1 and Ym2 is driven by Th2 cells and their cytokines, IL-4 and IL-13, with Ym2 particularly showing marked upregulation in the BALF of lungs affected by allergic asthma. This suggests that Ym2 may play a critical role in allergic pulmonary inflammation.[126] Ym1 and Ym2 have been shown to bind to heparan sulfate and glucosamine (GlcN) oligosaccharides, such as chitobiose, chitotriose, and chitotetraose.[126] Considering that heparan sulfate and GlcN oligosaccharides can bind and activate cellular responses to transforming growth factor-β (TGF-β), promoting cell proliferation and fibrotic responses,[127] and that carbohydrate molecules mediate cell-matrix interactions and facilitate immune cell and fibroblast migration and localization,[128] Ym1 and Ym2 may play key roles in these processes. For example, Ym1 has been identified as a chemotactic factor for eosinophils, promoting their recruitment and thus contributing to the progression of inflammation.[129] These findings suggest that Ym1 and Ym2 may exert significant roles in allergic airway remodeling by interacting with carbohydrate molecules, contributing to inflammation and tissue remodeling in asthma.

Found in Inflammatory Zone 1

Fizz1, a cysteine-rich secretory protein, is predominantly expressed in immune cells, particularly macrophages.[130] It is recognized as a marker of alternatively activated macrophages in mice.[131] As a marker of oxidative stress, Fizz1 expression is significantly upregulated in the BALF of ovalbumin-sensitized mice.[132] In airway epithelial cell brushings

from mice challenged with the fungal allergen *Alternaria*, Fizz1 expression increased over 20-fold, an effect absents in STAT6-deficient mice, indicating that Fizz1 activation is STAT6-dependent.[133] The study also revealed that Fizz1 binds to collagen-producing fibroblasts, promoting the expression of type I collagen and α-SMA in fibroblasts. This interaction contributes to peribronchial fibrosis, airway epithelial thickening, and airway remodeling.[134] Similarly, Fizz1 knockout mice in a bleomycin-induced pulmonary fibrosis model exhibited impaired activation of lung fibroblasts and reduced chemotactic activity of bone marrow-derived dendritic cells, whereas Fizz1 overexpression exacerbated pulmonary fibrosis.[135]

Macrophage Mannose Receptor

CD206, a C-type lectin receptor expressed on the surface of macrophages, participates in immune responses by recognizing sugars such as mannose, galactose, glucose, and certain glycoproteins.[136] Studies have demonstrated that CD206 expression is significantly upregulated in RAW264.7 macrophages polarized toward the M2 phenotype.[137] In CD206-deficient mice, the uptake of cockroach allergens by macrophages was markedly reduced. Additionally, macrophages from CD206-/- mice exhibited significantly decreased levels of miR-511-3p and displayed an M1-like phenotype. CD206-/- mice in a cockroach allergen-induced asthma model showed exacerbated lung inflammation. Overexpression of miR-511-3p in macrophages restored an M2-like phenotype, suggesting that CD206 promotes M2 macrophage polarization by upregulating miR-511-3p.[138] Further studies have shown that CD206 expression is higher in female asthma patients compared to males. This is likely due to the effects of IL-4 and IL-13, as estrogen enhances IL-4 secretion, potentially explaining the sex-related differences in CD206 expression.[136] Additionally, a higher number of $CD206^+$ M2 macrophages is associated with greater asthma severity. These macrophages are resistant to inhaled corticosteroid therapy. However, after depleting $IL\text{-}10^+$ M2-like macrophages, the number of $CD206^+$ macrophages decreased following corticosteroid treatment in patients with asthma. This highlights the importance of considering polarization states and the heterogeneity of macrophage populations in therapeutic strategies for asthma.[136]

Therapeutic Strategies Targeting Macrophage Polarization in Asthma

Macrophages perform essential immune functions in the lungs, but these functions are dysregulated in asthma.[139] In recent years, the complexity and plasticity of macrophage phenotypes have been redefined, highlighting gaps in our understanding of their role in asthma pathogenesis.[140] In this review, we discussed the sources of ROS and how ROS regulate macrophage polarization states. Despite the evident impact of macrophage polarization on asthma, current therapeutic strategies have largely overlooked this aspect, especially the potential of modulating macrophage polarization through ROS. Table 1 summarizes the roles of drugs targeting macrophage polarization in asthma therapy, with increasing evidence suggesting that such drugs exert therapeutic effects at least partially by modulating ROS production.

Studies have shown that AMs in children with poorly controlled asthma exhibit significantly reduced phagocytic capacity.[149] Fitzpatrick et al reported elevated oxidative stress markers, including glutathione disulfide (GSSG), oxidative DNA byproducts, and inflammatory levels, in the ELF of children with severe asthma. This was accompanied by diminished phagocytic ability, which could be ameliorated by the antioxidant reduced glutathione (GSH). GSH restored phagocytic function, reduced airway hyperresponsiveness, and mitigated Th2 imbalance.[141] Since M2 macrophages generally have lower phagocytic capacity than M1 macrophages,[139] ROS may influence asthma progression by modulating macrophage polarization states. Soluble epoxide hydrolase (sEH), which converts antioxidant epoxyeicosatrienoic acids into diols, contributes to oxidative stress. Atorvastatin has been reported to decrease MDA levels while elevating SOD activity in mice, concurrently suppressing M1 macrophage polarization and favoring the M2 phenotype.[150] In an OVA murine asthma model, atorvastatin also activated the Nrf2 pathway and mitigated airway inflammation.[142] Given that Nrf2 activation lowers ROS production, restrains M1 polarization, and alleviates pulmonary inflammation,[151] it is plausible that atorvastatin exerts anti-asthmatic effects by attenuating ROS and thereby limiting M1-driven responses. Nonetheless, dedicated studies are still required to verify atorvastatin's macrophage-modulating actions in asthma. Beyond statins, IL-25—a prototypical Th2 cytokine—has been shown to enhance mitochondrial respiratory-chain complex activity, elevate ROS, activate AMPK, and ultimately drive M2 polarization of monocyte-derived macrophages.[143] Notably, N-acetyl-l-cysteine suppresses IL-25-induced ROS generation and consequently blocks this

Table 1 Therapeutic Agents Targeting Macrophage Polarization for Asthma Treatment

Therapeutic Agent	Macrophage Polarization State	Model	Stage	Effect on Asthma Treatment	Mechanism of Action	References
GSH	–	Patients with asthma	Pre-clinical	Reduce airway hyperresponsiveness	Inhibit Nrf2 and alleviate Th2 imbalance.	[141]
Atorvastatin	Promote M2 Polarization	BALB/c mice	Pre-clinical	Alleviates airway inflammation	Activate Nrf2, reduce ROS.	[142]
N-acetylcysteine	Inhibit IL-25–induced M2 macrophage polarization	Human monocyte cell line	Pre-clinical	–	Inhibit IL-25–mediated mitochondrial ROS production and M2 macrophage polarization.	[143]
Celastrol	Promote M2 Polarization	Diet-induced obesity mice	Pre-clinical	Alleviates airway hyperresponsiveness and inflammation	Promote M1-to-M2 macrophage polarization via the PI3K/AKT pathway, reducing M1 markers (iNOS, IL-1β, TNF-α) and increasing M2 markers (Arg-1, IL-10).	[144]
Calycosin	Inhibit M2 Polarization	BALB/C mice	Pre-clinical	Inhibit OVA-induced airway inflammation and remodeling.	Inhibit the elevation of ARG1, IL-10, YM1, and MRC1 levels in the lung tissue of OVA-induced asthmatic mice.	[145]
Quercetin	Inhibit M1 Polarization	C57BL/6 mice	Pre-clinical	Improve airway inflammation in neutrophilic asthma.	Inhibit the pro-inflammatory M1 phenotype of macrophages and reduce inflammatory cytokine and MDA levels.	[146]
AUDA	Promote M2 Polarization	Obese asthmatic mice	Pre-clinical	Alleviates airway hyperresponsiveness and inflammation	Reduce the elevation of IL-1β, IL-6, and TNF-α in RAW264.7 macrophages stimulated by LPS.	[147]
Ruxolitinib	Suppress M2 macrophage polarization	C57BL/6 mice	Pre-clinical	Inhibit OVA-induced allergic asthma	Inhibit mitochondrial ROS-dependent STAT6 activation, thereby weakening DMM-induced M2 macrophage activation.	[148]

Abbreviations: AKT, Protein kinase B; Arg-1, Arginase-1; AUDA, 12-(3-Adamantan-1-yl-ureido)-dodecanoic acid; DMM, Dimethyl malonate; GSH, Reduced glutathione; iNOS, Inducible nitric oxide synthase; LPS, Lipopolysaccharide; MDA, Malondialdehyde; MRC1, Mannose receptor C type 1; Nrf2, Nuclear factor erythroid 2 related factor 2; PI3K, Phosphatidylinositol 3 kinase; STAT6, Signal transducer and activator of transcription 6; YM1, Chitinase like protein 3.

M2-skewing effect.[143] Collectively, these findings underscore the therapeutic potential of targeting mitochondrial ROS and redox signaling to control macrophage polarization and airway inflammation in asthma.

Some plant extracts with strong antioxidant properties have shown potential in regulating macrophage polarization and improving asthma outcomes. Celastrol, derived from the roots of *Tripterygium wilfordii*, enhances the expression of heme oxygenase-1 (HO-1) to exert antioxidant effects.[152] Celastrol suppresses M1 polarization of AMs, promotes M2 polarization, and reduces airway inflammatory cell infiltration and goblet cell hyperplasia in diet-induced obesity asthma mice.[144] Calycosin, a flavonoid extracted from *Astragalus membranaceus*, inhibits mtROS production by increasing levels of SOD and GSH and reducing malondialdehyde levels.[153] Calycosin has been reported to suppress elevated levels of ARG1, IL-10, CLP, and Mrc1 in the lung tissues of OVA-induced asthma mouse models, thereby mitigating airway inflammation and remodeling.[145] The natural flavonoid quercetin inhibits NOX2, thereby reducing LPS-induced intracellular ROS levels.[154] Quercetin also suppresses the pro-inflammatory M1 phenotype of macrophages, alleviating airway inflammation in LPS/OVA-induced asthma mouse models.[146] These findings highlight the therapeutic potential of targeting macrophage polarization and ROS regulation in asthma management. Further exploration of these strategies may provide more effective treatments for different asthma phenotypes.

Beyond plant-derived extracts, studies have shown that sEH inhibitors, such as 12-(3-Adamantan-1-yl-ureido)-dodecanoic acid (AUDA), can shift macrophages from an M1 to an M2 phenotype, reducing airway inflammation and hyperresponsiveness in obese asthma mouse models.[147] Dimethyl malonate, an inhibitor of succinate dehydrogenase, suppresses dehydrogenase activity and, through mitochondrial ROS–dependent STAT6 activation, up-regulates M2-signature genes Arg1, Ym1, and Mrc1, thereby aggravating OVA-induced allergic asthma in vivo. Scavenging mitochondrial ROS with mitoTEMPO or blocking STAT6 activation with ruxolitinib mitigates the pro-M2 effect of DMM.[148] Collectively, these data identify dehydrogenase as a mitochondrial ROS gated brake on M2 polarization and underscore its potential as a therapeutic target in M2-driven asthma, although further work is needed to translate dehydrogenase centered interventions into clinical practice.

Conclusion and Future Perspectives

An increasing body of research highlights the critical role of macrophages in the progression of asthma, with ROS acting as key signaling molecules that promote macrophage activation. ROS are derived from both endogenous and exogenous sources. Endogenous ROS primarily include intracellular oxidase systems (mainly NOX, XO, and peroxisomes) and mtROS, while exogenous ROS are predominantly generated by air pollutants. ROS regulate macrophage polarization states through intracellular signaling pathways. Although ROS have been shown to influence macrophage polarization, the specific inclination of ROS toward particular polarization states remains unclear. Given that ROS from different sources exhibit distinct roles across various stages of M2 polarization, future research should focus on understanding the regulatory effects of ROS from diverse origins at different macrophage developmental stages to clarify the directional influence of ROS on polarization.

In summary, ROS and macrophage polarization constitute a central pathogenic axis that drives airway inflammation and remodeling in asthma. Broad-spectrum antioxidants can attenuate airway hyperresponsiveness, but their lack of cellular specificity prevents precise control of the M1 to M2 transition. Future work should map the pathways of ROS production and clearance within macrophage subsets and design redox-modulating agents, for example nanoparticle-based delivery systems, that selectively target macrophages and steer their polarization. Combining ROS modulation with metabolic reprogramming, cytokine blockade, or signaling pathway inhibition is likely to generate multitarget strategies that suppress inflammation while bypassing the limitations of single antioxidant interventions. Research should also move beyond indiscriminate ROS scavenging toward preservation of redox homeostasis, which restrains excessive inflammation without sacrificing macrophage functional diversity. Biomarkers that dynamically report macrophage polarization and ROS levels will facilitate patient stratification and assessment of therapeutic efficacy, accelerating clinical translation of lead compounds. A more detailed mechanistic and temporal portrait of macrophage-derived ROS should deliver refined, multifaceted therapeutic options and ultimately improve outcomes in refractory asthma.

Abbreviations

AMs, alveolar macrophages; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; PKC, protein kinase C; TLRs, Toll-like receptors; GEFs, guanine nucleotide exchange factors; mtROS, mitochondrial ROS; MAPK, mitogen activated protein kinase; NFAT5, nuclear factor of activated T cells 5; FAD, flavin adenine dinucleotide; TCA, tricarboxylic acid; $FADH_2$, reduced flavin adenine dinucleotide; FMN, flavin mononucleotide; CoQ, coenzyme Q; SOD, superoxide dismutase; LPS, lipopolysaccharide; HIF-1α, hypoxia-inducible factor 1-alpha; O_3, ozone; PM, particulate matter; ELF, epithelial lining fluid; PM_{10}, PM with a diameter of less than 10 micrometers; PAHs, polycyclic aromatic hydrocarbons; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TRIF, TIR-domain-containing adapter-inducing interferon-β; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Trx, thioredoxin; ASK1, apoptosis signal-regulating kinase 1; CHK2, checkpoint kinase 2; PKM2, pyruvate kinase M2; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; NLRP3, NOD-like receptor family pyrin domain containing 3; ARG1, arginase-1; SYNCRIP, synaptotagmin-binding cytoplasmic RNA-interacting protein; Ym1, chitinase 3-like protein 3; Fizz1, found in inflammatory zone 1; Mrc1, mannose receptor c-type 1; HDM, house dust mite; FDE, farm dust extract; NO, nitric oxide; GR, glucocorticoid receptor; CD206, mannose receptor 206; ARG1, Arginase-1; CLPs, Chitinase-like proteins; BALF, bronchoalveolar lavage fluid; GlcN, glucosamine; TGF-β, transforming growth factor-β; sEH, Soluble epoxide hydrolase; AUDA, 12-(3-Adamantan-1-yl-ureido)-dodecanoic acid; HO-1, heme oxygenase-1.

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

The authors declare that they have no competing interests.

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