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The Role of Lung Macrophages in Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) as a common, preventable and treatable chronic respiratory disease in clinic, gets continuous deterioration and we can’t take effective intervention at present. Lung macrophages (LMs) are closely related to the occurrence and development of COPD, but the specific mechanism is not completely clear. In this review we will focus on the role of LMs and potential avenues for therapeutic targeting for LMs in COPD.

Keywords: Chronic obstructive pulmonary disease; Lung macrophages; Airway inflammation; Treatment targets
Introduction

COPD is a common preventable and treatable chronic inflammatory disease of the airway characterized by progressive airflow restriction and associated symptoms of the respiratory system. With the progression of COPD, it can cause respiratory failure, pulmonary hypertension, pulmonary heart disease, and recurrent exacerbations, which seriously affects living quality and lifespan of patients. Currently, COPD is the third leading cause of death in the world (1). In 2017, COPD caused 3.2 million deaths, accounting for 81.7% of the total deaths from chronic respiratory disease (2). It is predicted that over 5.4 million people may die from COPD-related diseases worldwide annually by 2060. The diagnosis and treatment of COPD will become a huge burden on social medical care. Risk factors for COPD include individual susceptibility and environmental factors. The pathogenesis of COPD involves in chronic airway inflammation, oxidative stress damage, and imbalance of protease/antiprotease etc. Immunomodulatory disorders are also involved in development of COPD. Some cells such as macrophages, neutrophils, dendritic cells (DCs), Tc1 and Th17 etc, mediate immunity function of COPD (3). In addition to their immune surveillance function, macrophages show plasticity according to their environment in different tissues; thus, they have tissue-specific roles in maintaining homeostasis and tight interactions with surrounding cell (4). Studies identified the numbers of macrophages increased in the lung of patients with COPD, which associated with disease severity and areas of lung destruction (5-7). Lung macrophages (LMs) possess multiple functions that chemotaxis, recruitment, phagocytosis, secreting cytokines, mediating apoptosis and immune outpost in COPD airway inflammation (8). Therefore, LMs play an indispensable role in the occurrence and progression of COPD.

1. Origin and Types of Macrophages

Macrophages, which were once considered to be supplied only by adult monocytes, are now known to have both bone marrow myeloid and embryonic origins (9-11). Macrophages are plastic under environmental influence and bring into play various functions through differentiating into diverse phenotypes. They are classified
as classical activated macrophages (M1) and alternative activated macrophages (M2) according to classic type (12), which is related to the mediating of different molecular signals. For example, M1 phenotype is induced by microbial products or pro-inflammatory cytokines including interferon-γ (IFN-γ), Toll-like receptors (TLRs) signaling pathway activated by lipopolysaccharide (LPS), tumor necrosis factor (TNF) etc (13). Meanwhile, M2 phenotype is driven predominantly by IL-4, IL-10, IL-13, MDC/CCL22 etc (14, 15). Macrophage differentiation is highly dynamic. Responding to micro-environmental clues macrophages can rapidly switch from one phenotype to the other (14).

Macrophages possess multiple functional properties as important organism innate immune cells. When antigens are not completely cleared, macrophages will perform the duties of presenting antigens, recognizing, and engulfing the invaded pathogens. In addition, macrophages can release multiple mediators and exert immune functions with other immune cells under environmental stimulation (16).

2. Origin and Subpopulations of LMs

LMs play important roles in the maintenance of homeostasis, pathogen clearance and immune regulation. LMs include alveolar macrophages (AMs) and interstitial macrophages (IMs). IMs, which are differentiated from AMs by their localization, remain less studied. AMs, including tissue-resident AMs (TR-AMs) and monocyte-derived AMs (Mo-AMs), as well as IMs are the major macrophage populations in the lung and have unique characteristics in both steady-state conditions and disease states (17). Previous studies showed TR-AMs seem to have lower responsiveness and limited plasticity, while Mo-AMs are more likely to be remodeled by the micro-environment (18, 19). The different characteristics of these two types of macrophages determine their distinct functions in lung diseases (20-22). Recent findings have revealed TR-AMs are long-lived cells shaped by the microenvironment and have immune-suppressive functions in the steady state and less plasticity in the defense state. Whether TR-AMs are truly self-renewing and whether TR-AMs have motility properties remain controversial. It is also unclear whether sustained pathogen and dust exposure leads to a predominantly monocytic origin of human LMs. Derived from
monocytes, Mo-AMs are more easily instructed by the environment than TR-AMs, and they are associated with cytokine storms and immune imbalance in severe infections (17). However, numerous studies in rodents (predominantly mice) showed that LMs are embryonic derived and originate from the yolk sac, the fetal liver and the bone marrow (23-25). The differences between mouse AMs and human AMs are unknown, and the origin of human TR-AMs and the composition of the human AM pool remain to be further discovered.

According to size and granularity, LMs are mainly divided into two subpopulations, AMs and IMs, both have subsets of small and large macrophages. AMs have similar numbers of small and large cells; IMs are mainly small. Small IMs and small AMs with more pro-inflammatory and phagocytic function respectively, large AMs with low pro-inflammatory and phagocytic ability (26).

3. LMs and COPD

3.1 The Subpopulations and Changes of LMs in COPD

Macrophage amounts are markedly increased (5-10-fold) in airways, lung parenchyma, BAL fluid and sputum of patients with COPD (27). In patients with COPD, AMs are replenished from local proliferation of some macrophages and recruitment of blood monocytes (6). More recently, studies on phenotyping of macrophages in COPD have identified four distinct phenotypes of macrophages (Table 1): a non-polarized macrophage (M0), a M1-type (iNOS+) more prone of inducing inflammation, a M2-type (arginase+) more prone of developing anti-inflammatory actions, and a dual positive-M1-M2-type macrophage, showing a mixed picture of M1-M2 related cytokines production (28, 29). Mathew Suji Eapen et al. found an increase in pro-inflammatory M1 compared to a relative decrease in anti-inflammatory M2 in COPD (30, 31), this suggests that M1 are dominant in the small airway. M2 (include M2a, M2b, M2c and M2d) possess anti-inflammatory properties and promote type Th2 immunity (12). However, more and more studies have shown that these subpopulations can sometimes overlap and their functions cannot be completely separated in COPD (32). Above suggest that there is a significant correlation between LMs and COPD-related chronic airway inflammation. Next, we
should focus on the distribution and a firm characterization of these four phenotypes of macrophages in the lung tissue of patients with COPD.

Table 1. The subpopulations of LMs

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Markers</th>
<th>Inducing differentiation substance</th>
<th>Secretions of LMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>M1 and M2 marker-negative</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M1</td>
<td>M1 marker-positive</td>
<td>LPS, INF-γ, TNF-α</td>
<td>IL-1β, IL-6, IL-12, TNF-α, iNOS</td>
</tr>
<tr>
<td>M2a</td>
<td>M2 marker-positive</td>
<td>IL-4, IL-13</td>
<td></td>
</tr>
<tr>
<td>M2b</td>
<td>M2 marker-positive</td>
<td>LPS and Immunocomplexes</td>
<td>IL-10 CCL18 CCL22</td>
</tr>
<tr>
<td>M2c</td>
<td>M2 marker-positive</td>
<td>IL-10, TGF-β, Glucocorticoid</td>
<td></td>
</tr>
<tr>
<td>M2d</td>
<td>M2 marker-positive</td>
<td>TNF-α</td>
<td></td>
</tr>
<tr>
<td>M1-M2</td>
<td>M1 and M2 marker-positive</td>
<td>M1 + M2</td>
<td>M1 + M2</td>
</tr>
</tbody>
</table>

3.2 Regulation of Phenotype of LMs

Neutrophil and epithelial-derived antimicrobial peptides (AMPs), including β-defensin 2 (BD2), S100 calcium binding protein A8 (S100A8), S100 calcium binding protein A9 (S100A9) and S100A8/A9 heterodimer, as potent modulators of macrophage phenotype and metabolism, can improve the phagocytic function of macrophages (33, 34) through activating the phosphorylation of downstream protein such as JNK, c-JUN, AKT and p70S6 (35-37) and up-regulating the expression of receptors including CD32, CD64, MARCO and TLR-2 (38). In addition, S100A8/A9 causes the change of secretion profile (IL-1β, INF-γ, TNF-α, IL-6 and IL-10) and up-regulation of the surface markers (CD163, CD40, CD80 and CD38), this may be related to the polarization of the macrophages (39). Study showed that WNT/β-catenin signaling directly influenced AMPs expression and gave rise to changes in macrophage function (38). Further studies addressing the potential utility of WNT/β-catenin and S100A8/A9 signaling to improve the function of macrophages in COPD could therefore provide new therapeutic avenues for COPD.
TGF-β is a known inducer of metalloprotease disintegrins and described to be essential for macrophage homeostasis and differentiation (40, 41). Studies have shown that TGF-β signaling can induce expression down-regulation of macrophage surface MHC class I in COPD and cause disease progression. This effect has been associated with signaling via SMAD4 (6). Moreover, TGF-β can signal via the mTOR pathway, which was associated with cellular senescence in lung (42). Therefore, we speculate that the regulation of TGF-β signaling may be the key for COPD prevention and treatment.

4. The Functional Properties of LMs in COPD

To date, alveolar and interstitial resident macrophages as well as blood monocytes have been described in the lungs of patients with COPD, contributing to disease pathology by changes in their function. LMs have a critical important role as “janitors” in cleaning up or resolving the inflammatory reaction—for example, in removing neutrophils and their products such as elastase from the inflammatory niche. LMs are also key innate immune effector cells that identify, engulf, and destroy pathogens and process inhaled particles, including cigarette smoke (CS) and particulate matter (PM), the main environmental triggers for COPD (23). Moreover, LMs from patients with COPD present with alterations in the secretion of cytokines and chemokines, which process and regulate the chronic inflammatory response that underpins the progressive nature of COPD (23, 43).

4.1 The Changes of Phagocytosis in LMs

Compared to control subjects, AMs of COPD patients show impaired phagocytosis of H. influenzae, M. catarrhalis and S. pneumoniae (44). The defective phagocytosis of COPD macrophages is associated with altered mitochondrial function and an inability to regulate mROS production (45). Studies showed that CS caused the increase in endogenous reactive oxygen species (ROS), the exposure of ROS impaired the uptake of macrophages in H. influenzae and S. pneumoniae (46, 47), caused damage to the proteins that regulating the mitochondrial fission and fusion (48). Moreover, CS exposure weakened mitogen activated protein kinase (AMPK) phosphorylation, which in turn reduced the expression of the nuclear factor erythroid-
related factor 2 (Nrf2) with a parallel decrease in the antioxidant HO-1 (49), exacerbated oxidative stress damage and ultimately weakened the phagocytosis of LMs by impairing AMPK/Nrf2 and nuclear factor-κB (NF-κB) signaling pathways (50). Moreover, the maintenance of phagocytosis requires the participation of mediators, among, the 1-phosphosphingosine (S1P) system is an important signaling pathway. Hai B Tran et al. found that CS inhibited phagocytic function of airway macrophage were associated with disruption of epithelial-macrophage crosstalk via intercellular S1P signaling (51). CS and PM give rise to increased ROS which promotes airway epithelium to occur lipid oxidation and stimulates CD1b over-expression of AMs (52). Besides, the high amount of S1P receptors (S1PR2, S1PR5) and S1P degrading enzymes (SGPL1) weaken the phagocytosis of AMs (53, 54). Despite the large amount of molecular data emerged in the last few years, it is not clear if a genetic alteration predisposing AMs from COPD patients or the micro-environment milieu of the lung of diseased patients render AMs less efficient in the phagocytosis activity of these pathogens.

4.2 The Changes of Apoptosis and Autophagy in LMs

Apoptosis, a type of programmed cell death, is a physiologic mechanism for cell deletion without inflammation, which is necessary for the maintenance of homeostatic plasticity in the lung. Studies showed the cell type specific imbalance of positive and negative regulation of apoptosis has been proposed to be a critical determination of disease progression in COPD (55). LMs are key effector cells that identify, engulf, and destroy pathogens and process inhaled particles from CS and ambient PM exposure, the main environmental triggers for COPD. Studies showed the chronic exposure of LMs to inhaled PM and CS, as well as pathogens and their toxic products (such as LPSs) promotes apoptosis in macrophages themselves (23), reduced apoptosis through a lack of pro-apoptotic p53 expression (55), and an increase in anti-apoptotic Bcl and the cytoplasmic form of p21 has been reported in AMs from smokers in association with chronicity of inflammation in COPD pathogenesis (56).

Myeloid cell leukemia-1 (Mcl-1) is a key anti-apoptotic protein involved in the switch from cell viability to apoptosis in LMs (57). Mcl-1 forms heterodimers with
pro-apoptotic B-cell lymphoma-2 (Bcl-2) family members such as Bax to inhibit mitochondrial membrane permeability. Besides, reduced expression of Mcl-1 will cause increased ROS production, which further causes mitochondrial dysfunction and LMs apoptosis (58). Thus, it appears that Mcl-1 may be the key to reverse LMs apoptosis and prevent COPD aggravation.

Isthmin-1 (ISM1) is a lung resident anti-inflammatory protein that is critical for maintaining lung homeostasis. ISM1 may be related to the suppression of lung inflammation by specifically targeting csGRP78 (a receptor of AMs) AMs for apoptosis (59, 60). Studies showed that csGRP78 AMs produced predominantly MMP-12 and therefore exerted proinflammatory. By selectively inducing csGRP78 AMs apoptosis, recombinant ISM1 (rISM1) directly impeded damage by AMs-secreted proteinases such as MMP-12, MMP-9, and MMP-driven TNF-α (60). Accordingly, csGRP78 may be a potential target for developing COPD therapeutics and that rISM1 could be a useful drug for COPD.

Autophagy is a fundamental intracellular process responsible for regulation of LMs. Cigarette smoking induces autophagy of LMs, and excessive autophagy aggravates LM dysfunction (61). Dysfunction of LMs results in down-regulation of phagocytosis and bacterial clearance on one hand, and promotes release of inflammatory mediators and proteases on the other. Defective autophagy activity was reported in AMs of smokers (62). Autophagic activity is insufficient in the lungs of patients with COPD (63). Furthermore, CS-induced HMGB1 translocation and release contribute to migration and NF-κB activation through inducing autophagy in LMs, providing novel evidence for HMGB1 as a potential target of intervention in COPD (64). The mechanism and treatment of autophagy in LMs need to be further studied in COPD.

4.3 The Imbalance of Protease/anti-protease of LMs

The imbalance between protease and anti-protease is one of important pathogenesis in COPD. Under the activation of CS and PM, LMs produce and secrete a variety of elastolytic enzymes including MMP-2, MMP-9 and MMP-12 and cathepsins K, L and S, which contribute to the intra-cellular and extra-cellular killing
and processing of pathogens to affect the airway inflammation of patients with COPD (8, 23, 43). Studies showed MMP-1, 9 and 12 were produced by AMs (23). MMP-9 and 12 are associated with degradation of elastin in COPD airway (65), the expression of MMP-1 and 12 may play an important role in the pathogenesis of emphysema, and cathepsin L and MMP-9 may be involved in the development of airflow limitation (66). Another study showed that under IL-4 environment, mononuclear macrophages differentiated into the IMs induced by macrophage colony stimulating factor, which brought about an increase in generation of MMP-12 that resulted in the destruction of alveolar walls and emphysema development (67). Moreover, Pelin Uysal and co-workers found that concentrations of MMP-9 had a significant negative correlation with the severity of lung function in stable COPD patients (68). MMP-9 is inhibited by tissue metallo-proteinase-1 inhibitors (TIMP-1), the imbalance between the levels of MMP-9 and TIMP-1 might result in aberrant extracellular matrix (ECM) degradation or the accumulation of ECM proteins in alveolar and small airway walls, which could lead to COPD (69). Taken together, further studies are needed to clarify the pathogenesis of COPD considering protease and anti-protease.

Alpha-1 Antitrypsin (AAT) possesses anti-protease, anti-inflammatory, immunomodulation, anti-infective and tissue-repair functions (70). AAT deficiency (AATD) is one of the important pathogenesis of COPD (71). Experiment showed that AAT was able to inhibit the expression of the neutrophil chemotactic factors in macrophages, the ability of AMs to clear apoptotic neutrophils was impaired in AATD individuals (72), which was related to the development of COPD. Augmentation AAT therapy may slow progression of emphysema, the effect on lung function is less clear due to a lack of longitudinal studies, although observational studies suggest this to be the case (73). In the clinical setting, however, the introduction of substitution therapy with purified serum AAT protein for AATD-associated lung pathology has failed to reach therapeutic AAT levels (74). AAT-transgenic cell (such as macrophages) therapy for AATD-associated lung pathology are currently under investigation. All these approaches have failed to reach therapeutic AAT levels in the serum and/or the pulmonary the epithelial lining fluid, so far (75, 76).
4.4 Abnormal Metabolism in LMs

Aberrant metabolism of intracellular metals is already implicated in COPD pathogenesis. For instance, Menkes disease causes emphysema result from copper deficiency (77). Impaired phagocytosis and abnormal inflammatory response caused by disordered zinc homeostasis in macrophages (78). Maor Sauler et al. detected a high-metallothionein expressing macrophages subpopulation enriched in advanced COPD using single-cell RNA sequencing (79). Another study indicated metallothionein is induced by oxidative stress and inflammation, and protect against cellular injury by sequestering intracellular metals such as zinc and copper (80). Therefore, understanding the metallothionein regulation of zinc and copper in COPD may improve our understanding of disease pathogenesis.

Excess pulmonary iron has been implicated in the pathogenesis of lung disease. Specifically, IL-6 and hepcidin-related iron sequestration by LMs may result in immune cell dysfunction and ultimately lead to increased frequency of infective exacerbation (81). The mechanism that iron could cause susceptibility to COPD is not clear, but could be related to bacterial colonisation and infection of the airways (82). Nuclear receptor coactivator 4 (NCOA4) is a cargo receptor that mediates ferritinophagy and is important for the selective autophagy of ferritin (83-85). Studies showed that NCOA4 levels were increased in COPD (86, 87), NCOA4 promoted M2 polarization of macrophages through fenton reactions targeting ferroptosis, which increased the levels of MMP-9 and 12 by LMs and led to aggravation of COPD (88). Further researches are required to fully understand the mechanisms of pulmonary iron sequestration and ferroptosis in lung disease, and to determine if airway iron could be a target for COPD therapeutic intervention.

4.5 Oxidative Stress in LMs:

Increased oxidative stress drives the progression of COPD through several LMs-related mechanisms including mitochondria dysfunction, reduced activity of anti-proteases, increased release of transforming growth factor β (TGF-β) and nitric oxide (NO) (89). Reportedly, protein-protein interactions between Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) are associated with progression of COPD through
disturbing phagocytosis of LMs. Meanwhile, BTB and CNC homology 1 (Bach1) as a transcription factor that inhibits Nrf2 is increased in COPD (89). Thus, Bach1 inhibitors may be a potential novel target for anti-oxidize and promote phagocytosis of LMs via interfering interactions between Nrf2 and Keap1 in COPD.

4.6 Inflammatory Response

AMs from patients with COPD present with alterations in the secretion of cytokines and chemokines. These mediators are particular efficient in recruiting other innate immune cells such as neutrophils which process and remove pathogens/microorganisms from the inflammatory focus. Under activation of CS and PM, LMs secrete inflammatory mediators including CCR2, CCR5, TNF-α, IL-1β, IL-6, IL-10, IL-12, CCL2, CCL5, CCL7, CCL13, CCL22, CXCL1, CXCL6, CXCL-8, CXCL9, CXCL10, leukotriene B4 (LTB4), and reactive oxygen species (ROS) (23, 43).

CXCR-2 secreted by LMs involved in the development of COPD through inflammatory response (90). Study showed CXCR-2 inhibitor could significantly improve lung function of patients with COPD (91). Activated macrophages recruit neutrophils into lung tissues to participate in inflammatory response via secreting the chemokine CXCL-8. Simon Lea et al. (58) found that streptococcus pneumoniae caused greater macrophage apoptosis than the macrophages exposed to moraxella catarrhalis, which may be responsible for the reduced secretion of chemokine CXCL-8, this suggests that CXCL-8 may be another key signaling molecule in regulating COPD macrophage apoptosis and inflammatory response.

Pyrin domain-containing 3 (NLRP3) can promote secretion of IL-1β and IL-18 by LMs (92), it is an important factor in the migratory aggregation of LMs and the generation of oxidative stress (93). Experiments demonstrated that NLRP3 knockdown significantly alleviated lung inflammation in mice, inhibition of NLRP3 inflammasome indirectly blocks the inflammatory effects of IL-1β and IL-18, which may be regarded as an ideal target for COPD treatment (90, 94).

Maude and co-workers proved that pro-inflammatory monocyte-derived macrophages was significantly enriched in COPD, which expressed elevated amounts of C-type lectin receptor (CLEC5A) (95). Indeed, CLEC5A has been shown to be up-
regulated in LMs from smoking mice or humans and can mediate features of COPD pathology (96), that may be related to macrophages activation such as cytokine elaboration, MMPs and adhesion molecule expression. The specific mechanism remains to be further studied.

Current studies show that activation of TLR-2, TLR-4, and TLR-9 are implicated in the pathogenesis of COPD (97, 98). TLRs induce the secretion of cytokines by LMs through the MAPK and NF-κB signaling pathways (99), which may be related to the development of COPD. Further researches are needed to identify the role and the mechanism of specific type of TLRs in macrophage of COPD models and patients.

5. LMs-related Treatment Targets and Drugs in COPD

At present, Bronchodilation, anti-inflammatories drugs are generally used as treatment strategies for stable COPD in clinical practice, but the clinical benefits are limited and do not reverse the disease process or cure the disease. The development of new therapeutic agents for COPD is urgently needed. Changing the behavior of key cells or pathways involved in the pathogenesis of COPD has the potential to attenuate the chronic inflammatory response of lung tissues and preventing rapid decline in lung function over time. Recent studies showed that targeted drugs for abnormal LMs function can fight against airway inflammatory and weaken lung tissue damage by regulating the LMs-related signaling (30, 67). Those drugs are shown in Table 2.

Corticosteroids: Inhaled corticosteroids (ICSs) are used for management of COPD and have been shown to reduce acute exacerbations of COPD, but are also associated with increased occurrence of pneumonia (100). Studies have shown that long-term use of ICSs may have negative influences on TLR2 expression in LMs of COPD patients, which will increase the susceptibility to pulmonary infection in severe COPD patients (101), but the specific mechanism remains ill defined. ICSs are currently only recommended in patients with elevated eosinophil and overlap syndrome according to the gold guidelines (102). We should balance the advantages and the disadvantages of corticosteroids and then determine the optimal treatment plan for COPD individuals.

Phosphodiesterase (PDE) Inhibitors: The phosphodiesterases (PDEs) are a
group of 11 families of metallo-phosphohydrolases that hydrolyse adenosine 3′5′-cyclic monophosphate (cAMP) and guanosine 3′5′-cyclic monophosphate (cGMP) to their inactive 5′-monophosphate (103). PDE inhibitors can cause a variety of cellular effects and influence inflammatory cell activation, immune cell activation and smooth muscle contractile responses (104). Among, the PDE4 inhibitors (roflumilast, cilomilast) can attenuate inflammatory response and tissue destruction by reducing the production of TNF-α as well as specific MMPs from LMs (105). Similarly, PDE5 inhibitors (tadalafil, sildenafil) have already significantly attenuated pulmonary vascular remodelling and chronic inflammation by down-regulating the generation of MMP-2 and MMP-9 by LMs (106, 107), which may be useful in intervening COPD progression. Some studies indicated low concentrations of theophylline can increase histone deacetylase activity and restore impaired AMs efferocytosis (108-110). However, the therapeutic usefulness of some oral PDE inhibitors is limited by their side effects, including nausea and vomiting etc (111). So, experts recommend that PDE inhibitors only for the Group D population of COPD according to current GOLD guidelines (102).

**Macrolides:** Macrolides exert immune-modulatory effects in chronic airway inflammation. They can reduce the production of pro-inflammatory mediators such as IL-1, IL-6, IL-8, and TNF-α by LMs in COPD patients through suppressing activator protein 1 and the NF-κB mediated cascade (112). In addition, azithromycin improved COPD LMs phagocytic ability, which was related to an increase in CD206 expression and involved the PS pathway (113). Studies demonstrated that Clarithromycin can prevent emphysema by modulating lung inflammation (114). Sandra Hodge et al. Concluded that two novel nonantibiotic macrolides, macrolides-2′-desoxy-9-(S)-erythromycylamine (GS-459755) and azithromycin-based 2′-desoxy molecule (GS-560660) can improved AMs phagocytosis and associated with the reduction in IL-1β and NLRP3 of AMs (115).

**Table 2.** LMs related drugs in COPD
**Drugs** | **The target or mechanism of drugs** | **Clinical application**
--- | --- | ---
Corticosteroids (ICS) | Anti-inflammation, influences on TLR2 expression | Increase in occurrence of pneumonia, only used for patients with high blood eosinophilic or overlap syndrome (ACOS)
PDE inhibitors | Inhibition of PDEs degradation and inflammation response | PDE4 inhibitors (roflumilast, cilomilast), only used for Group D population of COPD
Macrolides | Anti-inflammation by suppressing activator protein 1 and NF-κB, improving LMs phagocytic ability | Azithromycin and Clarithromycin have been used in clinical practice, (GS-459755) and (GS-560660) are in investigation.
Simvastatin | Anti-inflammation, efferocytosis and antioxidant capacity, | Simvastatin prolonged time to first COPD exacerbation and reduced exacerbation rate. (a single-centre RCT)
Atorvastatin | | |
Vitamin D | It is not clearly | Vitamin D intake improve COPD exacerbations and FEV1 in the patients with severe and very severe COPD (RCT study)
MK-7123 | CXCR-2 inhibitor | MK-7123 has been applied to clinical study, and it can significantly improve lung function
Infliximab | TNF-α inhibitor | In the treatment of COPD, infliximab has a higher probability of causing lung malignancy
Mepolizumab | IL-5 inhibitor | Only suitable for COPD patients with higher eosinophils
Benralizumab | IL-5 inhibitor | Addition of benralizumab does not reduce annual exacerbation rates in patients with moderate or severe COPD with a history of frequent exacerbations Clinical trials
MitoQ, SkQ1 | Mitochondria-targeted antioxidant | Oral mitoQ treatment reduces airway hyper-responsiveness, neutrophilic inflammation (all drugs are in laboratory research stage)
Mito-TEMPO | | |
Glutathione peroxidase | Antioxidant mimetics | preclinical research and clinical trials
Setanaxib | NOX inhibitor | preclinical research and clinical trials.
Dimethyl fumarate and sulforaphane | Nrf 2 activators | dimethyl fumarate and sulforaphane have been stopped because of side effects and cytotoxicity
ECC | Anti-inflammation by activation of MAPK/Nrf2 and NF-kB | Laboratory research
Gardenia essential oils | Anti-inflammation by reducing NO release and production of TNF-α and PGE2 | Laboratory research

**Statins:** Studies revealed the beneficial effect of statins in COPD are their anti-inflammatory properties (15, 116), their antioxidant capacity (117), and their potentiation of efferocytosis in LMs (118). Accumulated evidence suggests that statins enhance COPD LMs efferocytosis via increasing the production of peroxisome proliferator-activated receptor gamma (119) and inhibiting RAS homolog gene family member A (118). Simvastatin can suppress the generation of MMP-9 from rat AMs.
and human monocyte-derived macrophages and exert antiinflammatory effect, which may be related to RAS activation and subsequently Raf-MEK, ERK or PI3K-Akt activation, activator protein 1 as well as NF-κB stimulation (120). Peter Schenk et al. found that simvastatin at a dose of 40 mg daily significantly prolonged time to first COPD exacerbation and reduced exacerbation rate (121). Reportedly, inhaled atorvastatin is able to improve pulmonary emphysema in mice through reducing Nrf2 and MMP-12 (122).

**Vitamin D:** Increasing evidences suggest that vitamin D (VitD) deficiency aggravates the development of COPD-like characteristics (lung function changes, emphysema and pulmonary inflammation) in the lungs of CS-exposed mice (123), this may be related to the imbalance in protease/antiprotease expression caused by the increased MMP-2, MMP-9, and MMP-12 (124) as well as the inhibition in TGF-b1 signaling pathway responsible for fibrosis in COPD (125). There was clinical study showed that vitamin D supplementation improved lung function in VitD deficient COPD Patients (126, 127). Hence, the supplementation of vitamin D in VitD deficiency COPD may be one of the potent interventions to prevent the disease progression. Currently, the application of vitamin D in COPD patients has been tried in randomized controlled trial (128). Large preventive trials assessing the effect of vitamin D supplementation on COPD onset need to be established to provide more insights into the treatment of COPD with VitD deficiency.

**Cytokine-Targeted Drugs:** CXCR-2 secreted by LMs involved in the development of COPD through inflammatory response (90). Currently, MK-7123 (CXCR-2 inhibitor) (129) has been applied to clinical study, and it can significantly improve lung function of patients with COPD. As for other Cytokine-Targeted drugs, there are some limitations, infliximab (TNF-α inhibitor) (130) has a higher probability of causing lung malignancy, mepolizumab (IL-5 inhibitor) (131) is only suitable for COPD patients with higher eosinophils, and benralizumab (132, 133) shows little efficacy in patients with severe COPD.

**Agents of Antioxidative Stress:** Currently, mitochondria-targeted antioxidant
(mitoQ, mito-TEMPO, pyrroloquinoline quinone, and SkQ1) (134, 135), antioxidant mimetics (catalase, and glutathione peroxidase) (136) and novel NOX inhibitor (Setanaxib) (137) has been used in preclinical research and clinical trials. Traditional Nrf 2 activators (dimethyl fumarate and sulforaphane) (138) have been stopped because of its transient activity, side effects as well as cytotoxicity.

**Chinese Herbal Medicines:** The effects of AMPK/Nrf2 and NF-κB signaling pathways in LMs inflammation response have already been identified (50). Studies have shown that IL-17 can activate the MAPK and NF-κB pathways, further regulated the expression of pro-inflammatory cytokines in COPD (139). Li et al. proposed that five Chinese Herbal Medicines compound (ECC) play an important role in inhibiting the IL-17-related inflammatory response by regulating the activation of MAPK/Nrf2 and NF-κB signaling (140). Upon activation by harmful stimuli, AMs release inflammatory mediators including NO, prostaglandin E2 (PGE2), and TNF-α to destroy the lung tissue and lead to respiratory dysfunction (141). Studies showed that gardenia essential oils inhibited the NO release and reduced the production of TNF-α and PGE2 in the murine AMs (142). However, whether these Chinese herbal medicines and their active ingredients used for COPD therapy are needed further research.

6. Conclusion and prospects

COPD is a common disease in respiratory system, which seriously damages human health and causes a huge economic burden to our society. Currently, the disease is incurable and the pathogenesis is not completely clear, but the role of macrophages in the development of COPD has been established, LMs play a key part in orchestrating the chronic inflammatory response in lung tissue and airspaces in patients with COPD, parafunctional LMs are involved in the development of COPD through multiple pathways. In summary, further studies on LMs related signaling pathway and treatment targets are needed to provide more new evidence for precise treatment strategies of COPD.

CRediT authorship contribution statement
J.W and X.Z: wrote the manuscript. X.D and W.Y: supervised and reviewed the writing of the manuscript. C.X, G.X, X.Y, L.L, Y.F and H.C: assisted in collecting, processing, and analyzing relevant data. All authors had read and agreed to the published version of the manuscript.

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Declaration of interest

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Highlights

1. Different subpopulations of lung macrophages have different functional properties.
2. In patients with chronic obstructive pulmonary disease, alveolar macrophages, which have identified into four phenotypes: M0, M1, M2 and dual positive-M1-M2, are elevated in alveolar space and replenished from local proliferation of some macrophages and recruitment of blood monocytes.
4. Macrophages-related potential treatment targets for chronic obstructive pulmonary disease.
Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.