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Pathogenesis, diagnosis and treatment targeted macrophages in COPD

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Abstract. Chronic obstructive pulmonary disease (COPD) is a recurrent chronic lung disease. The macrophages, as an important type of innate immune cells, increased significantly in lung tissues and airspaces of COPD patients, suggesting a potential role of inducing inflammatory responses through activating innate and adaptive immune responses, accelerating disease progression. Recently, breakthrough achievements have been made in the diagnosis and treatment of COPD through targeting macrophages depending on high-throughput sequencing and analysis methods. In this review, the author summarizes the progress of macrophages in COPD in recent years, focuses on the new findings of high-throughput sequencing, revealing new directions and novel candidates in the pathogenesis, pathology, diagnosis and treatment targeting macrophages for COPD patients.

Keywords: Macrophage, Chronic obstructive pulmonary disease (COPD), High-throughput sequencing

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a recurrent chronic inflammatory lung disease stimulated by particulate matter (PM) and toxic gases like cigarette smoke (CS), which induce innate and adaptive immune responses, ultimately leading to emphysema, pulmonary fibrosis, airway remodeling, and respiratory dysfunction. Macrophages are an important innate immune cells that have the ability to recognize and phagocytose antigens, including CS and PM triggers for COPD, and can process and extract antigens for adaptive immune cells, ultimately leading to chronic and sustained activation of the immune system [1, 2]. The number of macrophages increased significantly within the pulmonary tissues and the airways of individuals with COPD, indicating a possible crucial function of inducing inflammatory responses through activating innate and adaptive immune responses, accelerating disease progression. Therefore, researchers have been focusing on exploring the function of macrophages in the development and advancement of COPD, as well as finding potential diagnostic and therapeutic targets and strategies. Breakthrough achievements have been made in this field with the progression of sophisticated sequencing techniques and analytical approaches, thus gain a rapidly developing age in the diagnosis and treatment of COPD through targeting macrophages [3, 4]. In this review, the author summarizes the progress regarding the roles of macrophages in disease development, pathology, diagnosis and treatment of COPD in recent years, focuses on the new findings of high-throughput sequencing, revealing new directions in macrophage research and providing new markers and candidates for diagnosis and treatment in COPD.

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2. Macrophages in COPD

In the past two decades, the role of macrophages in the occurrence and pathological progression of COPD has been made progress in the origins, functional properties continued to change in individuals with established COPD, and possible therapeutic interventions to modulate and restore the functional properties of macrophages, this implies the important roles of macrophages in the development of COPD. Consequently, treatments focused on macrophages might reduce inflammation and bolster their healing capabilities, exemplified by the prospective use of next-generation macrolides [1].

Macrophage is an bridge to link innate and adaptive immune, which play critical roles of autoimmune responses in maintaining persistent inflammation and has been focused on in COPD, although the specific nature of these mechanisms remains to be further clarified. Dong and colleagues have compiled data indicating that autoimmune activities may be present in COPD, and they investigate possible causes that could lead to the persistent inflammation defining the condition via autoimmune reactions [3]. For instance, research has shown that a significant portion, approximately one in three, of COPD patients who are non-smokers present with autoimmune diseases that affect specific organs, with thyroid disorders being especially common. Additionally, smoking, which is the most critical risk factor for developing COPD, has a well-established connection with the emergence of a range of autoimmune diseases in individuals. The generation of autoantibodies, coupled with decreased immune tolerance, is believed to contribute to the initiation and maintenance of autoimmune activities within the COPD framework [3]. Overall, macrophages, as specialized antigen-presenting cells, aggravate COPD through activating autoimmunity response from several aspects including pathological features, inflammatory phenotype, population susceptibility, sudden flare-ups and responsiveness to glucocorticoid treatment [3, 5].

3. Pathogenesis and pathology of macrophages in COPD

In the pathogenesis of COPD, the macrophage-mediated apoptotic pathway is one of the key mechanisms leading to emphysema, in addition to the traditional factors of inducing inflammation, stress, and apoptosis [6, 7]. For example, the apoptosis inhibitor of macrophage (AIM) protein, which inhibits macrophage apoptosis, serves multiple roles and is released by macrophages. It circulates in the bloodstream, predominantly attached to IgM pentamers, and worsens emphysema symptoms by triggering the death of cells in the alveolar lining. Takimoto-Sato et al. found that patients with COPD exhibited up-regulation of AIM/IgM compared to healthy individuals who smoke, with a direct correlation between the AIM/IgM levels and the severity of the COPD condition. Additionally, patients with higher AIM/IgM levels experienced quicker onset of their first severe COPD episode and faced elevated mortality rates from all causes, as well as respiratory-related issues. These findings imply that AIM aggravates COPD progression by activating MMP-12, and that elevated AIM/IgM levels in the blood may indicate a grimmer outlook for those with COPD [8]. In addition, mTOR, targeting to rapamycin, is a serine/threonine kinase essential for regulating cell growth and metabolic functions. As stated by Dong et al., exposure to CS amplifies mTOR activity within alveolar macrophages in mice, while suppressing mTOR activity or its expression contributes to a rise in matrix metalloproteinases (MMP)-12 levels. The activation of mTOR in macrophages could play a role in diminishing MMP-12 levels and preventing lung inflammation and damage caused by CS. This provides a possible direction for the creation of novel pharmaceuticals for the treatment of COPD. In addition, the study points out that mTOR could have varying functions across diverse cellular varietie, which means that mTOR-related drugs may need to be designed for specific cell types in future therapeutic strategies [9].

Macrophages have many different subpopulations to play corresponding functions. It's another choice strategy to modulate macrophage polarisation and inflammatory responses, thereby alleviating the symptoms of COPD through increasing protective macrophages subpopulations [10]. Specifically, knockdown of RTEL1 promotes polarisation of M1-type macrophages and inhibits polarisation of M2-type macrophages, while reducing the expression of inflammatory factors [11]. In addition, Xu et al. noted that knockdown of RTEL1 reduced the number of inflammatory cells, improved cell alignment, reduced the count of cells undergoing proliferation (marked by ki67) and elevated the count of cells

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undergoing apoptosis (indicated by Caspase-3 positivity) in a mouse model for COPD, which further establishes the essential function of RTEL1 in COPD's progression and offers a novel approach for therapeutic interventions going forward [11]. In addition, Liu et al. found that M2-type macrophages, as a negative regulation of immune cell subsets, predominate within the pulmonary tissue of individuals with COPD and their numbers correlate corresponding to the intensity of COPD, and noted that an increase in M2-type macrophages and emphysema were also observed in a murine model subjected to CS exposure [12]. M2-type macrophages exaggerated the deterioration of lung function by discharging MMP-9/12, thereby advancing the progression of COPD, while CS treatment of human bronchial epithelial (HBE) cells induced M2-type macrophage polarisation and down-regulated the expression of the microRNA let-7. According to Liu et al., cigarette smoke extract (CSE)-treated HBE cells were able to induce macrophage polarisation towards the M2 via the IL-6/STAT3 signaling pathway, which decreases MMP-9/12 secretion, thus decelerates the advancement of COPD, a process that could be let-7 inhibition [13].

In addition, changes in cellular metabolism have been a hot research topic in recent years. The research group of Fujii et al. reveals a novel mechanism for altered lipid metabolism in alveolar macrophages (AMs) in COPD [14]. Transcriptomic and lipidomic analyses of AMs showed disease rank-dependent changes in response to AMs in COPD, particularly in cholesterol metabolism. As stated by Fujii et al., AMs in COPD exhibit alterations linked to interferon-α/γ responses and cholesterol metabolism that depend on the GOLD classification of the disease severity. These findings suggest that altered lipid metabolism in AMs in COPD may be a key factor in disease progression [14, 15].

4. Diagnosis and treatment of macrophages in COPD

Korean Red Ginseng (KRG) was shown to be effective in reducing emphysema caused by cigarette smoke condensate (CSC) [16]. KRG significantly decreased the quantity of macrophages present in bronchoalveolar lavage fluid and lessened the severity of emphysematous. In addition, KRG inhibited CSC-induced apoptosis, as shown by TUNEL staining and caspase 3 immunohistochemical staining. Further mechanistic studies demonstrated that KRG inhibited macrophage-mediated emphysema in vitro and in vivo by inhibiting the Bcl-2-associated X-protein/Caspase 3 signaling pathway and subsequently inducing the initiation of cellular survival pathways such as phosphoinositide 3-kinase, vascular endothelial growth factor, and protein kinase B. Therefore, KRG may become a candidate for COPD treatment with other classical medicines [16].

Wang et al. mentioned a combination of active ingredients called ECC-BYF, which is derived from the traditional Chinese medicine and has been used clinically for the treatment of COPD [17]. ECC-BYF attenuates the inflammatory response of PM2.5-induced macrophages by enhancing autophagic flux. Studies have shown that ECC-BYF markedly suppressed the manufacture of inflammation-related cytokines induced by PM2.5, and this anti-inflammatory effect was accompanied by enhanced autophagic flux. In addition, ECC-BYF was able to promote autophagy by activating the transcription factor Foxo3, thereby reducing inflammation. In a PM2.5-induced COPD model, it also mitigated disruptions in autophagic processes and elevated Foxo3 concentrations in pulmonary tissue, ultimately leading to suppression of lung inflammation and enhanced lung function. These results offer a novel approach for managing COPD therapy by regulating the autophagy-lysosome system in macrophages to control the inflammatory response, in which ECC-BYF and the Foxo3 signaling pathway may be potential therapeutic targets [17].

Kim et al. explored the safeguarding influence of green tea extract (GTE) against CSC-induced emphysema and found that GTE significantly reduced macrophage-driven lesions associated with emphysema in pulmonary tissue [18]. The research showed that administering GTE resulted in decreased numbers of macrophages in the bronchoalveolar lavage fluid and diminished the emphysematous of mice exposed to CSC. Mechanistically, GTE suppressed the phosphorylation of extracellular signal-regulated kinase such as ERK caused by cigarette smoke condensate, which in turn lowered the expression of MMP-9, suggesting that the protective effect of GTE is tightly linked to the ERK/AP-1 signaling pathway, and subsequently reduces protease/antiprotease imbalance [18]. The

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findings of Kim et al. suggest that targeting the ERK/AP-1 signaling pathway and subsequently reducing MMP-9 expression represents a novel approach to treating emphysema [18, 19].

Explaining the mechanisms underlying the effectiveness of therapeutic drugs in COPD contributes to understand the progression of the disease. For example, The dual augmentation of cyclooxygenase-2 (COX-2) and soluble epoxide hydrolase (sEH) has been pinpointed as a new regulatory mechanism for macrophage activation in COPD, observed in macrophages from both COPD patients and murine models, as well as those exposed to CSE. Duan et al. showed that COX-2 and sEH could be pharmacologically reduced using4-(5-phenyl-3-{3-[3-(4-trifluoromethylphenyl)-ureido]-propyl}-pyrazol-1-yl)-benzenesulphonamide (PTUPB), which successfully inhibited the activation of macrophages, reduced the expression of genes linked to inflammation, and mitigated pulmonary damage, thereby ameliorating lung damage induced through tobacco smoke and lipopolysaccharide in respiratory performance in a murine model of COPD [20].

5. New discoveries using high-throughput sequencing in macrophages of COPD

According to inflammatory progression, Zhang et al. found that M0-type macrophages are elevated in individuals with COPD and exhibit a close relationship with modifications in the inflammatory surroundings [2]. Employing the CIBERSORT method along with the weighted gene co-expression network analysis technique, the researchers identified gene modules highly associated with M0-type macrophages and uncovered the biological roles of these potential genes by gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) enrichment analyses, including cytokine production, innate immune response, specific granuloma, phagolysis, lysosomes and iron death among other processes. These findings provide important clues for understanding the novel mechanisms of macrophages in COPD [2].

Indeed, excessive apoptosis of protective macrophage subpopulations caused COPD, but the mechanisms have not been fully elucidated. Fan et al. found that COPD is strongly associated with iron death in macrophages by integrating the data of RNA-seq and scRNA-seq [21]. They identified genes associated with iron death in macrophages and executed co-expression evaluation and anticipated potential therapeutics based on these genes. Two indicators, SOCS1 and HSPB1, were additionally selected and a model based on an artificial neural network (ANN) was constructed for diagnostic purposes. These findings highlight the important function of macrophage iron death in COPD and provide new ideas to treat COPD by inhibiting macrophage iron death [21].

Finicelli et al. have revealed novel roles and regulatory mechanisms of macrophages using high-throughput sequencing techniques in COPD [1]. In particular, the effects of oxidative stress and extracellular vehicles (EVs) on macrophage function and polarisation have been the focus of research. Oxidative stress not only affects macrophage function, leading to its dysfunction in COPD, but is also strongly associated with macrophage polarisation, and these dysfunctional macrophages might play a part in the development of COPD by enhancing inflammatory responses and tissue damage [1]. Furthermore, the composition and cargo of EVs, an important mediator of intercellular communication, influenced COPD-associated inflammation, tissue remodelling and macrophage dysfunction, suggesting that macrophages are not only producers but also targets of EVs, engaged in the characteristic disease features of COPD, which include the destruction of alveolar walls and the development of emphysema [3]. These novel findings highlight the importance of high-throughput sequencing technology in gaining a deeper understanding of macrophages in COPD and provide potential targets for the development of new therapeutic strategies that may help to improve the advancement of the disease and the well-being of individuals with COPD [1].

Recent research advances suggest that new approaches to the diagnosis and treatment of COPD can be provided by targeting macrophages. Zhang et al. developed a model for diagnosis using data from the GSE20257 dataset comprising the trio of genes CLEC5A, FTL, and SLC2A3, which was validated by multivariate logistic regression analyses [2]. The model showed good predictive value in multiple datasets, indicating that these genes can be used as biomarkers for COPD diagnosis. In addition, through single-cell sequencing analysis of data and laboratory tests conducted in a controlled environment, the

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investigators verified that these three up-regulation of genes showed in the macrophages from individuals with COPD than in those from healthy subjects. These findings also provide new potential targets for immunotherapy of COPD, and CLEC5A, FTL, and SLC2A3 are anticipated to be potential candidates for immune-based treatments for COPD [2].

In addition, Fan et al. established a well-performing ANN diagnostic model (AUC = 0.816) by screening SOCS1 and HSPB1 as powerful diagnostic biomarkers using multiple machine learning techniques [21]. In addition, single-gene gene set enrichment analysis (GSEA) and gene set variant analysis (GSVA) were performed, suggesting that the HSPB1 expression was closely connected to the stimulin and glutathione metabolism signaling pathway; and SOCS1 was primarily engaged in the signaling pathway for folate biosynthesis among others. In addition, the study constructed a competitive endogenous RNA (ceRNA) network to further validate the expression changes of biomarkers in an in vitro COPD model. These results provide a new strategy for treating COPD by targeting SOCS1 and HSPB1 to inhibit macrophage iron death [21]. The functions of macrophages in COPD were list in table 1.

Table 1. The functions of macrophages in COPD.

Macrophages in COPD	Findings and Examples
Pathogenesis	AIM promotes development of COPD via MMP-12 upregulation [8].
	CS enhances mTOR activity in mouse AMs [7].
Pathology	Higher AIM/IgM ratios correlate with worse COPD prognosis [8].
	RTEL1 affects macrophage polarization and COPD development [11].
Treatment	KRG reduces macrophage number and emphysema [16].
	ECC-BYF treats COPD by enhancing autophagy [17].
	GTE reduces emphysematous lesions via ERK/AP-1 pathway [18].
	COX-2/sEH inhibition with PTUPB reduces macrophage activation and lung damage [20].

6. Conclusion and prospective

Macrophages contributes to the development of COPD, and targeted macrophages have made progress in the identification and management of COPD in recent years. Firstly, the researchers further understood the involvement of macrophages in the onset and development of COPD, especially with the discovery of many new subpopulations of macrophages using single-cell sequencing technology, such as tissue resident macrophages. Secondly, many target molecules were discovered through high-throughput sequencing, such as SOCS1, HSPB1, CLEC5A, FTL and SLC2A3. Finally, the mechanisms of traditional therapeutic drugs exert therapeutic effects were explored through affecting macrophage function. In the future, with the progression of comprehensive sequencing technologies and analysis methods, relevant prediction, diagnosis and treatment model algorithms will be established, providing new platforms for the diagnosis and prediction of COPD. There will also be a variety of target molecules pushed to the clinical transformation stage, providing new choices for the treatment of COPD.

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