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The different faces of the macrophage in asthma

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Purpose of review

Asthma is a chronic inflammatory disease in which changes in macrophage polarization have been shown to contribute to the pathogenesis. The present review discusses the contribution of changes in macrophage function to asthma related to polarization changes and elaborates on possible therapeutic strategies targeting macrophage function and polarization.

Recent findings

Macrophage function alterations were shown to contribute to asthma pathology in several ways. One is by impaired phagocytosis and efferocytosis. Another is by changing inflammation, by altered (anti)inflammatory cytokine production and induction of the inflammasome. Finally, macrophages can contribute to remodeling in asthma, although little evidence is present in humans yet.

Novel therapeutic strategies targeting macrophages include dampening inflammation by changing polarization or by inhibiting the NLRP3 inflammasome, and by targeting efferocytosis. However, many of these studies were performed in animal models leaving their translation to the clinic for future research.

Summary

The present review emphasizes the contribution of altered macrophage function to asthma, gives insight in possible new therapeutic strategies targeting macrophages, and indicates which knowledge gaps remain open.

Keywords

efferocytosis, inflammation, innate immunity, phagocytosis

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease of the lungs with many phenotypes that are all characterized by airway inflammation, reversible airflow obstruction, airway remodeling, and bronchial hyperresponsiveness. The precise characterization of these phenotypes is still evolving, but includes divisions based on the presence of allergy, increased numbers of eosinophils or neutrophils, time of disease onset, response to corticosteroids, and disease severity. In allergic asthma, allergens can trigger bronchoconstriction and this phenotype is associated with early-onset disease and increased eosinophil numbers in lung. Nonallergic asthma is associated with adult-onset disease and neutrophil infiltration. Patients with severe asthma can have a combination of characteristics and are usually corticosteroid resistant [1].

Although eosinophils and neutrophils are considered key determinants, the inflammatory profile in asthma is heterogeneous with various other cells involved. A role for macrophages in particular has long remained understudied, although it is now

known that they can polarize into many different phenotypes and that these differentially polarized phenotypes are changed in asthma [2,3]. In the past, a bimodal subdivision of macrophage polarization

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KEY POINTS

- New treatments should focus on macrophage function rather than identifying M1/M2 changes.
- Macrophages contribute to the pathology of asthma by altered cellular processes such as phagocytosis, efferocytosis, and (anti)inflammatory cytokine production.
- Asthma is associated with defective macrophage functions, although actual consequences may depend on disease severity and disease phenotypes.
- Studies pinpointing the actual consequences of macrophage (dys)function and macrophage-directed treatment in human asthma are needed.

was used, dividing macrophages in M1 and M2 macrophages in a similar fashion as used for T cells based on the expression of certain markers [4]. In this division M1 macrophages are associated with Th1 inflammation and considered pro-inflammatory and M2 macrophages are associated with Th2 inflammation and considered pro-repair and involved in wound healing. The bimodal subdivision has now been abandoned in favor of a model of a spectrum of polarization changes in macrophages that better illustrates the great variety in macrophage responses to stimuli [5]. A clear contribution of changes in macrophage polarization to asthma pathology has been shown by us and others [2,3,6,7^{*},8,9]. Both in humans and mice with (experimental) asthma, more M1 and M2 macrophages (old nomenclature was then used) were found in lung tissue. However, polarization markers are indicative of certain functions and therefore in this review we will focus on the contribution of alterations in macrophage function to asthma. In addition, we will elaborate on novel experimental asthma therapies that target macrophage function.

MACROPHAGES IN ASTHMA

Macrophages are abundantly present in lung tissue, but their contribution to asthma pathology seems to be through a change in function rather than number, as numbers of macrophages are unchanged in lung tissue of patients with asthma [2,9]. Similarly, no differences in macrophage percentages were found in bronchoalveolar lavage fluid of asthma and control subjects [8]. For sputum contradicting results have been found, with more [10], less [11], and similar [12] macrophage numbers in asthma versus controls. These differences may be because of asthma (pheno)type. In addition, location may

explain why differences were found in sputum and not in lung tissue. Alveolar macrophages, resident on the alveolar epithelial surface, can be demonstrated in sputum, but interstitial macrophages, located within lung tissue, are not present in sputum and can only be detected in tissue sections/biopsies. Therefore, (certain types of) asthma may be accompanied by changes in numbers of alveolar macrophages and not interstitial macrophages.

CHANGES IN MACROPHAGE FUNCTION IN ASTHMA

Phagocytosis

As professional phagocytes, macrophages have the ability to recognize and eliminate pathogens and other foreign material, thereby playing an important role in innate immunity. In addition, several of the markers used to denote differentially polarized macrophages (e.g. CD64, CD163, CD206) are receptors important for phagocytosis. Therefore, changes in phagocytic behavior appear to be linked to asthma. Several studies have reported impaired phagocytosis of bacteria, yeasts, and particulate matter by airway macrophages and monocyte-derived macrophages from patients with asthma compared to controls (reviewed by Fricker *et al.* [13]). Recent findings also demonstrated less phagocytosis of *Staphylococcus aureus* by airway macrophages in children with neutrophil-predominant severe asthma as compared to severe asthma with few neutrophils [14]. Similarly, airway macrophages from patients with noneosinophilic asthma displayed lower phagocytic capacity of IgG-opsonized yeast than airway macrophages from patients with eosinophilic asthma [15].

However, studies appear to be inconsistent because sulfur colloid particle uptake by airway macrophages was higher in patients with mild asthma compared to healthy volunteers [16]. Furthermore, Kulkarni *et al.* [17^{*}] recently demonstrated that phagocytosis of *S. aureus* by alveolar macrophages from children with mild-to-moderate asthma was similar between patients with eosinophilic and noneosinophilic asthma and lower after allergen avoidance for 3 weeks.

These inconsistent findings for phagocytosis are also seen for CD163, a high-affinity scavenger receptor for hemoglobin that has been investigated in the context of asthma. More CD163⁺ macrophages were found in lungs of patients with asthma with fatal disease compared to control patients [18] and soluble CD163 in sputum was also higher in asthma compared to controls [19]. Moreover, in a mouse model of ovalbumin-induced experimental asthma,

airway hyperresponsiveness and eosinophil counts were significantly lower in CD163-deficient mice compared to wild-type mice [18]. On the other hand, loss of CD163 expression in house dust mite-exposed mice was associated with enhanced eosinophilic inflammation, possibly through higher production of CCL24 by macrophages resulting in more recruitment of eosinophils [20]. The same investigators showed that CD163 can suppress CCL24 secretion by binding of the major house dust mite allergen, Derp1 [20].

Thus, although most studies suggest that asthma is associated with defective macrophage phagocytosis, contradicting results indicate that this may not be a general phenomenon of the disease. The phagocytic capacity may depend on the type of material that is being phagocytosed and dysfunctional phagocytosis is likely more pronounced during more severe forms of asthma, but exact mechanisms remain poorly understood. Further characterization of phagocytosis by macrophages and its effects on asthma symptoms is therefore warranted.

Efferocytosis

The phagocytic clearance of apoptotic cells is named efferocytosis. In contrast to phagocytosis, this process triggers anti-inflammatory behavior, mediated by receptors like Mer tyrosine kinase and executed by interleukin-10 (IL-10) production [21]. There are fewer IL-10⁺ macrophages in asthma, suggesting that efferocytosis may be impaired [2]. Indeed, Huynh *et al.* [22] described lower efferocytosis of apoptotic T cells by alveolar macrophages from patients with severe (but not mild-to-moderate) asthma compared to healthy volunteers. Findings from Simpson *et al.* [23] also showed that efferocytosis of apoptotic bronchial epithelial cells by sputum macrophages was impaired in patients with noneosinophilic asthma compared to eosinophilic asthma, suggesting this feature may be phenotype-specific. In contrast, recent work by Erriah *et al.* [24[■]] demonstrated that efferocytosis of apoptotic granulocytes by monocyte-derived macrophages from patients with asthma was similar compared to healthy controls and also did not differ between noneosinophilic and eosinophilic asthma. This may be explained by the different origins of cells, as in contrast to monocyte-derived macrophages, lung macrophages are of fetal origin and more representative of niche effects [25–27].

Inflammation

Macrophages can contribute to asthmatic inflammation in several ways (Fig. 1). These include altered

(anti)inflammatory cytokine/chemokine production, induction of the inflammasome, and altered cellular processes such as defective phagocytosis. More M1 and M2 macrophages were found in lung tissue of patients with asthma but whether having M1 or M2 macrophages is related to different phenotypes of asthma has not been investigated yet [2,10]. Interestingly, inhibiting either M1 or M2 polarization switched airway inflammation to more eosinophilic or neutrophilic inflammation respectively in mice [6,7[■],28], suggesting that M1-polarized macrophages lead to selective recruitment of neutrophils whereas M2-polarized macrophages recruit eosinophils. We are not aware of any studies investigating which macrophage-related chemokines may be responsible for this switch, but investigating this would be of major interest for understanding the development of different asthma phenotypes.

The changes in macrophage polarization found in asthma and its different phenotypes are indicative of changes in cytokine production by these cells. Macrophages contribute to chronic airway inflammation in asthma through production of proinflammatory cytokines such as TNF α and IL-1 β . These cytokines are implicated in many types of asthma including neutrophilic, glucocorticoid-resistant [29,30], and allergen-induced atopic asthma [31].

Inflammasomes are a group of multiprotein intracellular complexes, which detect pathogenic microorganisms and sterile stressors and activate the production of pro-inflammatory cytokines like IL-1 β [32[■],33]. Activation of inflammasomes in macrophages starts with endogenous or microbial stimuli that activate nucleotide-binding oligomerization domain-like receptors (NLRPs), of which many different types exist. These subsequently assemble, bind, and activate caspase-1 and active caspase-1 proteolytically cleaves pro-IL-1 β to its active inflammatory form [34].

These inflammasomes and their product IL-1 β are particularly interesting in the context of asthma. The NLRP3 inflammasome for instance has been associated with the development of asthma [33] and single-nucleotide polymorphisms in the NLRP1 gene were shown to activate the inflammasome in reaction to asthma-related stressors in a cohort of Brazilian children [32[■]]. In addition, NLRPs that are mainly expressed in macrophages and neutrophils, are upregulated in neutrophilic asthma [32[■],34]. In fact, neutrophils were demonstrated to drive a proinflammatory phenotype in macrophages upon respiratory viral infection in mice by activating the NLRP3 inflammasome in alveolar macrophages [35]. Levels of NLRP3 have also been shown to correlate with asthma severity and steroid resistance [30,34,36[■]].

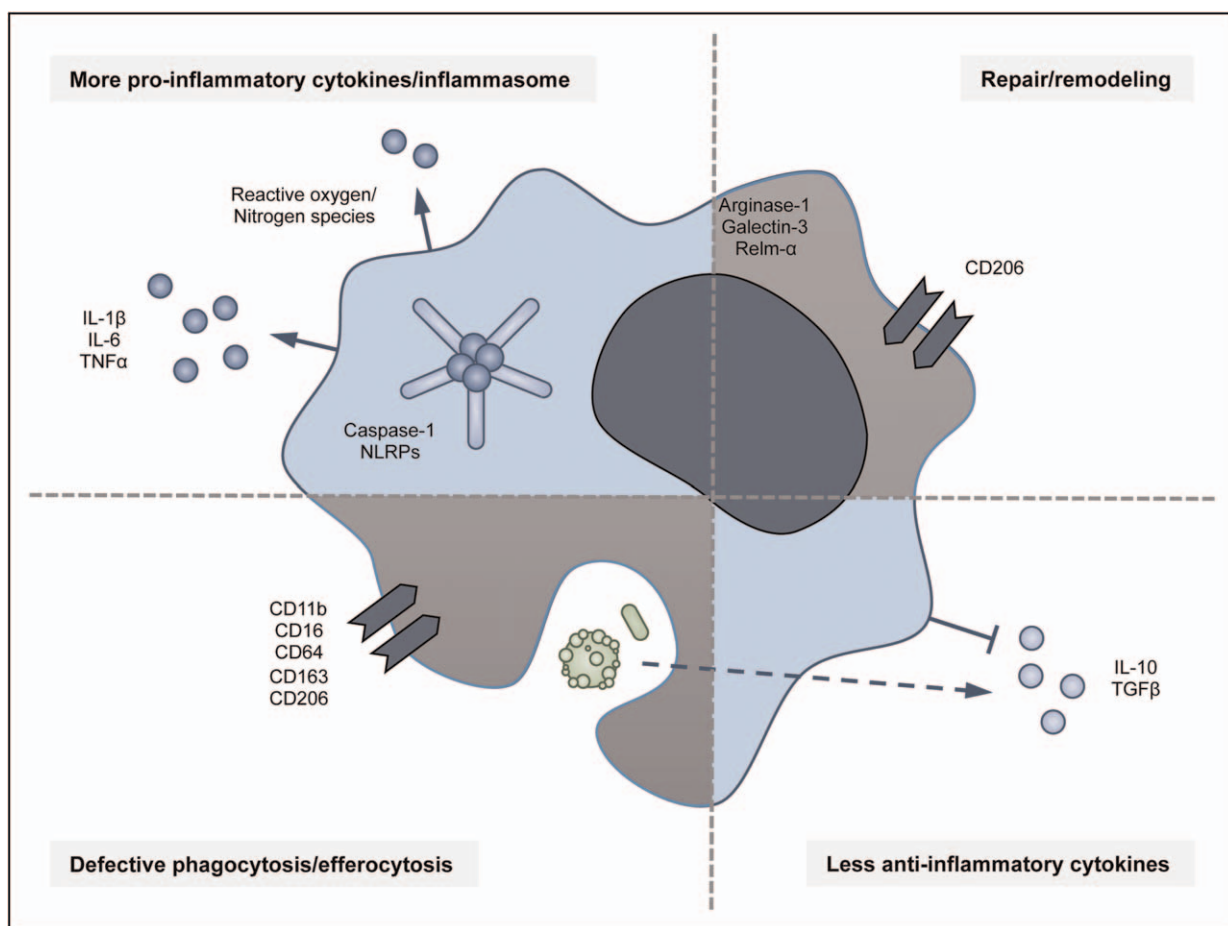


FIGURE 1. Summary of the contribution of macrophage functions to inflammation in asthma. Macrophages can contribute to asthma by inducing proinflammatory [29,30,31,34,57] and inhibiting anti-inflammatory cytokines [2,6,42], the inflammasome activation [32*,33,34], changes in repair and remodeling [58–60], and defective phagocytosis and efferocytosis [14,15,16,22,23].

Possible mechanisms for the higher levels of NLRP3 activation in asthma are among others apolipoprotein E, Charcot-Leyden crystals, and uric acid, all well known activators of the inflammasome [37,38]. Gordon *et al.* [39*] showed that apolipoprotein E secretion by human macrophages from bronchoalveolar lavage fluid is higher after house dust mite exposure and may therefore be responsible for inflammasome activation. Charcot-Leyden crystals, that form spontaneously from galectin-10 proteins upon eosinophil lysis, were found to induce release of IL-1 β in human monocyte-derived macrophages in an NLRP3-dependent manner and may therefore perpetuate and exacerbate eosinophilic airway inflammation [40*]. Uric acid is abundantly produced by human airway epithelial cells when challenged with house dust mite [41] and can subsequently activate the inflammasome in macrophages. Taken together, a role for inflammasome activation in macrophages in asthmatic airway inflammation is indicated and may be an interesting target for therapy.

With respect to anti-inflammatory behavior, fewer macrophages expressing the anti-inflammatory cytokine IL-10 were found in lungs of patients with asthma compared to controls [2]. The loss of IL-10⁺ macrophages may contribute to the pathogenesis of asthma, as IL-10⁺ macrophages were shown to prevent neutrophilic asthma in mice [42]. Indeed, we recently showed that boosting the number of IL-10⁺ macrophages, by pretreating them with PGE2 before adoptive transfer, resulted in less airway inflammation in mice. In summary, stimulating IL-10 production or resolving behavior is currently unexplored avenue for novel asthma treatments [6].

Tissue remodeling

Airway remodeling is an important feature of asthma, characterized by structural airway abnormalities as a result of collagen deposition, elastic fiber remodeling, and goblet cell hyperplasia and contributing to mucus hypersecretion and airway hyperreactivity

[43]. In mice, macrophages have been shown to play a role in repair and remodeling by detecting and eliminating damaged tissue and thereby inducing repair by regulating extracellular matrix production and by production of growth factors, matrix metalloproteinases, and their inhibitors.

However, there is little direct evidence of macrophages contributing to remodeling in patients with asthma. Several studies, including our own, investigated repair-associated macrophages (CD206⁺ macrophages) in airway wall biopsies or bronchoalveolar lavage fluid of asthma patients and controls [2,3,8,44]. We and others found that having more CD206⁺ macrophages was associated with more severe disease [2,3,44]. Although CD206⁺ macrophages are associated with remodeling, CD206 can affect collagen internalization and turnover *in vitro* [45,46], we did not find correlations between these macrophages and basement membrane thickness, goblet cell numbers, or collagen deposition in lungs of patients with asthma [2]. However, inhibition of M2 polarization in mice resulted in less collagen deposition around airways and more severe airway hyperresponsiveness, indicating collagen deposition may actually be a protective mechanism against airway hyperresponsiveness [7[■]]. In conclusion, CD206⁺ M2 macrophages are associated with asthma but solid evidence of their exact role in remodeling in humans is lacking.

NEW THERAPEUTIC STRATEGIES TARGETING MACROPHAGES IN ASTHMA

Both novel and conventional asthma treatments affecting macrophage function have been extensively summarized by Fricker *et al.* [13] and include corticosteroids, macrolides, statins, phosphodiesterase inhibitors, leukotriene antagonists, and β -agonists. Here we have focused on the most recent findings in order to keep the reader up to date on the latest insights. However, most of the work has been done with *in vitro* or animal models, leaving their translation to the clinic for future research.

Targeting phagocytosis and efferocytosis

Phagocytosis and efferocytosis by alveolar macrophages is essential for lung homeostasis. Felton *et al.* [47[■]] recently showed that alveolar macrophage efferocytosis contributed to the resolution of allergic airway inflammation in mice, thereby making apoptotic cell clearance a potential therapeutic strategy. Since this was found to be dependent on Mer tyrosine kinase, augmentation of Mer activity may provide a specific mechanism to target efferocytosis. Likewise, angiotensin-(1-7) was able to promote

macrophage efferocytosis of apoptotic cells in an experimental mouse model of asthma [48]. This was associated with reduced eosinophil counts, an increase in apoptotic eosinophils, decreased nuclear factor- κ B phosphorylation, and decreased airway remodeling and collagen deposition and therefore resulted in resolution of inflammation and restoration of homeostasis. Stimulation of efferocytosis could also be achieved by treatment with galectin-3 [21,24[■]]. In humans, efferocytosis by monocyte-derived macrophages was found to be higher in patients with asthma upon treatment of the cells with galectin-3. Interestingly however, when stratifying for asthma phenotypes, this effect was only seen in noneosinophilic asthmatics and not in eosinophilic asthmatics. In addition, galectin-3 treatment did not result in increased efferocytosis in healthy controls.

Similarly, inhalation of hydrogen gas improved alveolar macrophage phagocytosis of *Escherichia coli* in ovalbumin-induced asthmatic mice and alleviated airway hyperresponsiveness and inflammation, possibly because of its antioxidant effects and via activation of nuclear factor erythroid 2-related factor two (Nrf2) [49].

Modulating inflammation

Reduction of inflammation is an important goal in the treatment of asthma. For example, corticosteroids have anti-inflammatory effects on macrophages by suppressing pro-inflammatory cytokines like IL-1 β and enhancing IL-10 production [2,13]. Recently, a few more studies have described new therapeutic strategies to dampen inflammatory effects of macrophages in asthma. These include protostemonine and emodin, which were found to attenuate dust mite-induced, ragweed-induced, and aspergillus-induced asthmatic inflammation in a murine model and inhibit alternatively activated macrophage polarization [50,51]. Furthermore, the muscarinic M3 receptor antagonist tiotropium was shown to alleviate allergic airway inflammation through inhibition of resistin-like molecule- α and arginase-1 expressing (M2) macrophages in mice, further showing the importance of M2-polarized macrophages in asthma pathology [52]. Likewise, treatment of RAW 264.7 macrophages with the anti-inflammatory drug brevenal resulted in less expression of CD86 (M1-associated) and CD206 (M2-associated), suggesting a less active state, which resulted in less secretion of proinflammatory cytokines [53]. Other work in lung macrophages from mice indicated that pharmacological inhibition of sirtuin-2 not only resulted in less recruitment of inflammatory cells, but also led to less

expression of chitinase-like protein three (YM1) and resistin-like molecule alpha, both markers associated with M2 polarization [54].

Another promising strategy for asthma treatment is targeting the NLRP3 inflammasome. Inhibition of the NLRP3 inflammasome by the cytokine release inhibitory drug CRID3 prevented airway hyperresponsiveness and inflammation in a mouse model of severe asthma, which was accompanied by lower expression of IL-1 β , Th2 cytokines, and chemokines associated with eosinophils, neutrophils, and macrophages [36^{***}]. Other compounds found to inhibit NLRP3 include estrogen and some traditional herbs. Estrogen was found to suppress allergen-induced airway inflammation in mice by inhibiting NLRP3 transcription and activation [55] and traditional herbal recipes used for asthma treatment in Rwanda have recently been found to have inhibitory effects on the interactions between NLRP3 and caspase-1 [56].

CONCLUSION

This summary of recent literature shows that the altered function of macrophages found in asthma may contribute to disease pathology. Current therapies, primarily directed against inflammation, may also target macrophages and modulate macrophage function. New therapeutic strategies aiming at rescuing certain macrophage functions (e.g. efferocytosis) indeed coincide with reduced airway inflammation, although most of these studies still require translation to the clinic. Future studies are needed to pinpoint the actual consequences of macrophage (dys)function and macrophage-directed treatment in human asthma.

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Conflicts of interest

There are no conflicts of interest.

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