

Update on the role of alternatively activated macrophages in asthma

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Abstract: Lung macrophages link innate and adaptive immune responses during allergic airway inflammatory responses. Alveolar macrophages (AMs) and interstitial macrophages are two different phenotypes that differentially exert immunological function under physiological and pathological conditions. Exposure to pathogen induces polarization of AM cells into classically activated macrophages (M1 cells) and alternatively activated macrophages (M2 cells). M1 cells dominantly express proinflammatory cytokines such as TNF- α and IL-1 β and induce lung inflammation and tissue damage. M2 cells are further divided into M2a and M2c subsets. M2a cells dominantly produce allergic cytokines IL-4 and IL-13, but M2c cells dominantly produce anti-inflammatory cytokine IL-10. M2a and M2c cells are differently involved in initiation, inflammation resolution, and tissue remodeling in the different stages of asthma. Microenvironment dynamically influences polarization of AM cells. Cytokines, chemokines, and immune-regulatory cells interplay and affect the balance between the polarization of M1 and M2 cells, subsequently influencing disease progression. Thus, modulation of AM phenotypes through molecular intervention has therapeutic potential in the treatment of asthma and other allergic inflammatory diseases. This review updated recent advances in polarization and functional specialization of these macrophage subtypes with emphasis on modulation of polarization of M2 cells in asthma of human subjects and animal models.

Keywords: asthma, macrophage polarization, alternatively activated macrophages, M2 cells, cytokines

Introduction

Lung macrophages are a heterogenic population of mononuclear phagocytes that are divided into alveolar macrophages (AMs) and interstitial macrophages (IMs).^{1,2} AMs reside in the lung inner surfaces and have both proinflammatory and anti-inflammatory properties, whereas IMs reside in the interstitial area, maintain immune homeostasis in the respiratory tract, and exert immune tolerance to harmless antigens.^{1,3} According to different cell surface markers and cytokine expression levels, AMs are further divided into two major subtypes M1 and M2 cells (Figure 1).⁴ M1 cells are classically activated phenotype cells, expressing high levels of proinflammatory cytokines such as inducible nitric oxide synthase (iNOS), IL-1 β , and TNF- α and responsible for inflammation and protection against invading pathogens⁵, whereas M2 cells are alternatively activated phenotype cells and can be further divided into alternative activated cells (M2a), type II alternatively activated cells (M2b), or acquired deactivated cells (M2c) and

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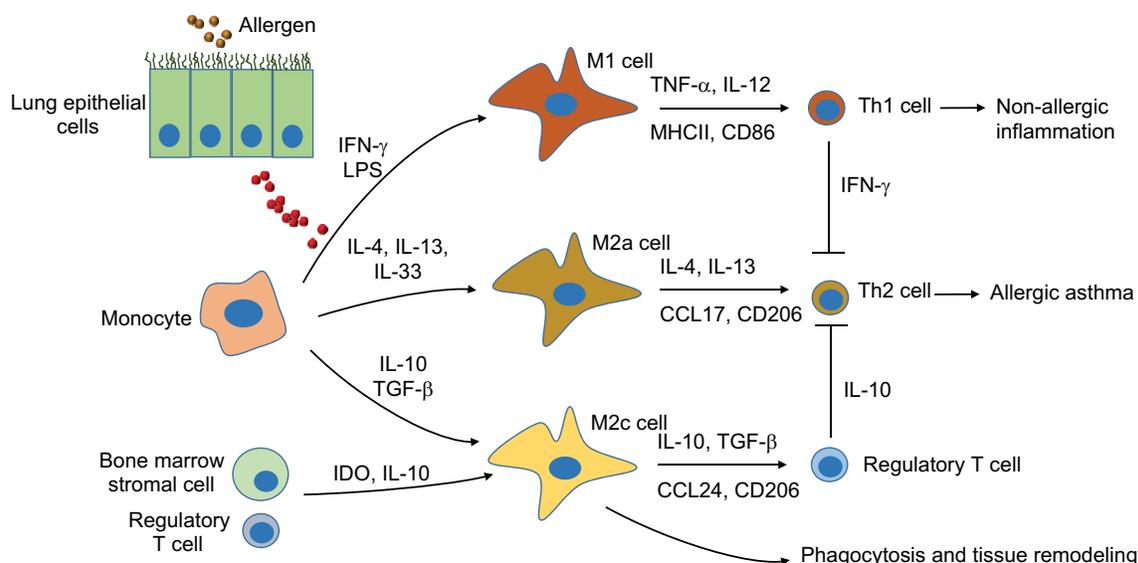


Figure 1 Schematic diagram of subtypes of lung macrophages during allergic immune responses after exposure to allergen. **Notes:** Exposure to allergens activates lung epithelial cells and other innate immune cells. The activated cells release a variety of cytokines and distinctly affect AM polarization and migration. Classically activated macrophages (M1 cells) can be activated by IFN- γ and LPS, inducing nonallergic immune responses through releasing TNF- α and IL-1 β . Alternatively, activated macrophages (M2 cells) are divided into M2a and M2c cells. M2a cells can be activated by IL-4, IL-13, and IL-33, inducing allergic immune responses through releasing IL-4 and IL-13. M2c cells can be activated by IL-10 and TGF- β , inducing lung inflammation resolution and tissue repair through releasing IL-10. Bone marrow-derived stromal cells and regulatory T cells also drive M2c cell polarization through IDO and IL-10. M2c cells have low activation markers and are more potent in phagocytosis of invading pathogens than other macrophage phenotypes. **Abbreviations:** AM, alveolar macrophage; LPS, lipopolysaccharide; IDO, indoleamine 2,3-dioxygenase.

Table 1 Characteristics and molecular release from activated macrophages

Subtypes	Inducers	Cell markers	Cytokines	Chemokines	Function
M1	IFN- γ , LPS, bacteria GM-CSF, oxidative fatty acid/LDL, HMGB1	CCR7, CD25, CD86, CD127, MHCII, ROS, iNOS, arginase-2	TNF- α , IL-1 β , NO, IP-10, IL-6/8/12/15/17/23	RANTES, CCL-8/15/19/20, CXCL-9/10/11/13	Proinflammatory function Pathogen clearance, tissue damage
M2a	IL-4, IL-13, M-CSF, NLRP3	CD206, CD209, Fizzl, Ym1/2, RELM- α , arginase-1	IL-4/10/13/33/35, MMP-9, MMP-14, IGF-1	CCL-8/13/14, CCL-17/18/23/26	Allergic inflammation
M2b	LPS, IL-1 β , immune complex/IL-1Ra	CD206, CD209, Fizzl, Ym1/2, RELM- α , arginase-1	IL-10, TGF- β , CCL-1/20, CXCL-1/2/3	CCL-1/20, CXCL 1/2/3	Tissue remodeling, fibrosis
M2c	TGF- β , IL-10, PGE2, Tregs, BM-MSC, ADSCs, IDO	CD163, CD206, Fizzl, Ym1/2, arginase-1, PPAR-delta, SRA-1 TLR1/8	IL-10, TGF- β , IGF-1, PGE-2	CCL-8/17/18/22/24	Anti-inflammatory function Phagocytosis, tissue remodeling, fibrosis

Notes: M1 cells are classically activated macrophages; alternatively activated macrophages (M2 cells) can be divided into subtypes of M2a, M2b, and M2c. **Abbreviations:** LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony-stimulating factor; LDL, low-density lipoprotein; HMGB1, high-mobility group box 1; iNOS, inducible nitric oxide synthase; Tregs, regulatory T cells; ADSCs, adipose tissue-derived stromal cells; IDO, indoleamine 2,3-dioxygenase; PPAR, peroxisome proliferator-activated receptor; SRA-1, scavenger receptor A-1; PGE2, prostaglandin E2.

M2d cells (Table 1).^{6,7} However, identification and dynamic changes of these M2 subtypes are not well documented in the asthmatic mouse model and human subjects so far.⁸⁻¹⁰ These cell subtypes express specific cell surface markers and several anti-inflammatory mediators and chemokines, such as IL-10, IL-13, and CCL-17.¹¹⁻¹³ They are critically involved in the initiation and resolution of lung inflammation during allergic immune responses. Their polarization and function are greatly influenced by the microenvironment, such as several cytokines and chemokines. This review updates the recent advances of polarization of lung macrophages and their specialized function in asthmatic animal models and patients with asthma.

Macrophages in asthma

Asthma is a heterogeneous lung allergic disorder and is divided into atopic and nonatopic phenotypes, which share common features of lung hypersensitivity. Atopic asthma is mediated by IgE and is usually caused by allergens, air pollution, and genetic factors; however, nonatopic asthma is not mediated by IgE and is usually caused by virus infection, drugs, chemical irritants, cigarette smoking, stress, etc. The activated Th2 cells and type 2 innate lymphoid cells together with basophils drive infiltration of eosinophils in asthmatic lungs, but in some cases, neutrophils and Th17 cells are largely present and are controlled by the Th17 cell subset.¹⁴ As a first line of the cell component, mononuclear macrophages

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are activated and proliferated during the early phase of disease and play a pivotal role in the clearance of pathogens, initiation of lung inflammation, and inflammation resolution during later phases. The study of Ji et al³ in bleomycin-induced lung injury mouse model showed that circulating Ly6C(hi) monocytes peaked on day 3 and their magnitude was positively associated with pulmonary inflammatory response, whereas M2-like AMs (F4/80+CD11c+CD206+) peaked on day 14 and were positively correlated with the magnitude of lung fibrosis. Although lung-resident macrophages are well investigated, the cell origin is still elusive. A recent study suggested that resident AMs are derived from Csf1r(+) erythro-myeloid progenitors and yolk sac but myeloid-derived macrophages cells originate and renew from bone marrow hematopoietic stem cells.¹⁵ Their development and renewal into a distinct macrophage phenotype require granulocyte-macrophage colony-stimulating factor¹⁶ and expression of discrete tissue-selective transcription factors such as MafB and c-Maf.^{17–21}

Recent reports showed that lung macrophages in different compartments have proinflammatory and anti-inflammatory functions. Lung-resident macrophages are reported to have immune regulatory function because depletion of AMs by clodronate liposomes can cause Th2-type allergic immune responses in the mice sensitized by house dust mite (HDM)²² and adoptive transfer of AMs from naïve animal can completely abolish Th2 cell polarization and lung dendritic cell-mediated allergen capture and migration to the lymph,²³ but the data are contradictory to the report by Lee et al²⁴ showing that depletion of AMs in a mouse allergic asthma model attenuated Th2-type allergic lung inflammation and airway remodeling, accompanied by the enhanced Th1 immune responses. In addition, the number of circulating-derived monocytes increased in the inflamed lung and participated in lung allergic immune responses. Zaslona et al²⁵ recently observed that depletion of circulating monocytes can attenuate allergic inflammation. Therefore, macrophages in different compartments exert distinct biological functions in the allergic responses. Further investigation should be performed to define the underlying molecular and immunological mechanisms.

Classically activated macrophages (M1 cells) in asthma

M1 cells play an important role in host defense against pathogen invasion via phagocytosis and release many proinflammatory cytokines and chemokines. This cell phenotype is characterized by expression of high levels of MHCII and CD86.^{5,26,27} It was reported that M1 cells were greatly increased in nonallergic lung inflammation after exposure to

farm dust extract, in association with increased Th1 and Th17 cell population.²⁸ The increased polarization of M1 cells has properties of antiallergic responses because patients with less severe asthma have more M1 cell population than those with severe asthma.²⁹ Multiple factors affect polarization of M1 cells, from either naïve M0 or polarized M2 cells. In vitro studies showed that the polarized cells can be switched back to M0 state in a cytokine-deficient medium for 12 days or switched to another cell phenotype after culture in an alternative polarizing medium.³⁰

The polarized M1 cells can efficiently activate Th1 cells by secreting IP-10, IFN- γ , IL-8, IL-23p40/p19, TNF- α , IL-1 β , and RANTES, but not IL-12 (p40/p35) after pathogen infection, including (myco)bacteria.^{30,31} Lipopolysaccharide, IFN- γ , and granulocyte-macrophage colony-stimulating factor are potent inducers for the polarization of M1 cells.³² Mice that lack IFN- γ have low M1 cells but have a large amount of M2 cells, with the decreased ratio of iNOS to arginase.³³ Other mediators such as oxidized low-density lipoprotein, fatty acid, caveolin-1 (Cav-1), and high-mobility group box 1 (HMGB1) protein were also involved in M1 cell-biased polarization.^{34–37} van Tits et al³⁴ reported that the oxidized low-density lipoprotein-loaded macrophages can enhance macrophage chemotactic protein expression via a downregulating Krüppel-like factor 2, a nuclear transcription factor.³⁴ Cav-1, a membrane scaffolding protein, can promote the polarization of M1 cells. Shivshankar et al³⁶ reported that Cav-1 null macrophages had a more pronounced M2 profile activation in response to IL-4 stimulation. HMGB1 protein is released from IMs and can significantly induce the expression of M1 marker iNOS, while decreasing M2 marker IL-10 in kidney injury and fibrosis animal model. However, it remains unknown whether there are similar effects in the asthma mouse model.

Alternatively activated macrophages (M2 cells) in asthma

M2 cells are potent macrophage subtypes and have multiple functions in different diseases and disease phases. The variable function is related to the distinct cytokine expression profile and activation status of the cells. It is reported that M1 cells are predominantly presented 1–3 days after the nitrogen mustard-induced lung injury, whereas M2 macrophages were significantly increased at 28 days.³⁸ However, the dynamic changes of M2 cells in asthma is still not well identified in animal models and patients with asthma. In asthmatic animals, this cell phenotype is characterized by low expression of MHCII, CD86, and iNOS2 but high levels of arginase-1,

family proteins chitinase-like Ym1/2 and Fizz1/RELM- α (found in inflammatory zone 1), and cell surface receptors such as macrophage mannose receptor, also called CD206. CD206 has an important function in the phagocytosis of M2 cells via increasing efferocytosis of invading pathogens and apoptotic cells.^{5,9,39–42} It is reported that CD206 facilitates the scavenging and degradation of ricin. CD206-deficient mice were more susceptible to toxin-induced death than wild-type mice due to compromised efferocytosis activity of M2 cells.⁴³ Therefore, high levels of CD206 would be beneficial to phagocytosis and pathogen clearance of M2 cells; which may explain the underlying mechanisms of higher potency of M2 cells in the binding and more uptake of pathogens than the M1 cells.³¹ Among M2a and M2c subtypes, M2c cells have lower NF- κ B activation and lower expression of antigen-presenting and costimulatory molecules (HLA-DR, CD86, and CD40)³¹ but greater expression of IL-10 than M2a cells in the renal injury animal model.⁴⁴ Our previous results also revealed that lipoprotein-associated phospholipase A2 deficiency increased macrophage phagocytosis and IL-10 expression in M2c cells in *Aspergillus fumigatus*-sensitized mice.^{45,46} Similar results are also observed in the asthmatic mouse model with surfactant protein A deficiency, in which a high level of IL-13 was expressed in M2a cells.⁴⁷ Thus, M2c cell subtype is considered a major subtype in the initiation of inflammation resolution. The upregulated CD163 (a member of hemoglobin scavenger receptor of cysteine-rich family) and CD206 on M2 cells might participate in the process. However, it was reported that lipopolysaccharide, IFN- γ , and TNF- α from M1 cells and other activated cells can suppress CD163 expression, whereas IL-6 and anti-inflammatory IL-10 can increase CD163 expression in monocytes and macrophages, indicating that the role of cytokine microenvironment affects polarization of M2 cells possibly through regulation of key cell scavenger receptors.⁴⁸ Therefore, M2c cells can be a useful cell target in the treatment of lung inflammatory diseases such as asthma.

Different from M2c cells, M2a cells are characterized by expression of high levels of IL-13, a cytokine critically involved in allergic immune responses and mucus production.⁴⁹ In addition, CCL-17, CCL-18, CCL-22, and eotaxin-2 (CCL-24) are highly expressed from M2 cells and facilitate Th2 and eosinophil infiltration into the inflamed lungs.^{12,30,50} However, recent findings reveal that these mediators and M2 cell-specific transcription factors are responsible for lung tissue remodeling and fibrosis. IL-13 can increase expression of MUC5AC and TGF- β 2 while decreasing beta IV Tubulin in human bronchial epithelial cells.⁵¹ Forced expression of

recombinant *Fizz1* in rat lung fibroblast cell line can enhance production of collagen type I and α -smooth muscle actin.⁵² Therefore, lung fibrosis can be controlled by modulation of M2 cell phenotype during the early stages of airway remodeling.

Polarization of M2 cells Cytokines and other mediators

Owing to the distinct role of M1 and M2 cells in the pathogenesis of asthma, it has become important to maintain an optimal balance between the population of M1 and M2 cells. Modulation of polarization of M1 and M2 cells has therapeutic potential. It is documented that IL-13,³⁰ IL-33,⁸ and M-CSF³² are potent inducers of M2 cell-biased polarization. IL-13 was greatly increased in M2 cell-dominant allergic mice, in association with upregulation of Fizz1/RELM- α and YM1.^{5,53,54} In IL-13 transgenic mice, a greater amount of M2 cells was also observed after *Cryptococcus neoformans* infection.⁵⁵ In addition, IL-33 is involved in the polarization of M2 cells. Lung epithelial cells are a major source of IL-33 after the first allergen challenge, but after the third challenge, ~20% and ~10% respectively, of the IL-33-producing cells in the lungs were M2 macrophages and conventional dendritic cells.⁵⁶ The increased M2 cell-biased polarization by IL-33 was possibly mediated by upregulation of IL-4, IL-5, IL-13, CCL-17, CCL-18, and CCL-24 after binding to the IL-33 receptor ST2.^{57,58} Moreover, there are elevated levels of serum IL-35, IL-17A, basophil activation marker basogranulin, and eosinophilic airway inflammation biomarker periostin in allergic asthmatic patients, but it is unclear whether or not they have direct effects on the polarization of M2 cells.⁵⁹ Recently, Draijer et al reported that prostaglandin E2 (PGE2) can promote IL-10-expressing M2c cells in HDM-induced asthmatic mice. The effects were further confirmed by direct free PGE2 treatment or adoptive transfer of PGE2-treated macrophages, in which the treated mice had fewer infiltrating eosinophils in lungs.⁹ Therefore, it would be a promising strategy in asthma therapy to induce M2c-biased polarization through molecular intervention.

Transcription factors

Recent studies have indicated that transcription factors and intracellular proteins, such as tuberous sclerosis complex 1 (TSC1),⁶⁰ stress-responsive activating transcription factor 7 (ATF 7),⁶¹ STIP1 homology and U-Box containing protein 1 (STUB1),⁶² ten eleven translocation (Tet) methylcytosine dioxygenase (Tet2),⁶³ microRNA (MiR-511),⁶⁴ docosahexaenoic acid, peroxisome proliferator-activated receptor gamma

(PPAR γ),⁴² and programmed cell death protein 4 (Pcd4)⁴⁰ can modulate polarization of M2 cells by influencing gene expression. NLRP3 (also known as Nacht, Lrp, and Pyd domain-containing protein 3, NALP3, or cryopyrin) is an intracellular protein and forms protein NALP3 inflammasome complexes with ASC and pro-caspase-1 that drive the activation of inflammatory caspases. Recent studies indicated that NLRP3 inflammasome has been implicated in the pathogenesis of several acquired inflammatory diseases including asthma. NLRP3 can promote IL-4 expression by Th2 cells via binding to IL-4 promoter in conjunction with the transcription factor IRF4.^{65,66} Although there is no report so far about the effects of NLRP3 on the polarization of M2 cells, we expect that NLRP3 may drive M2a cell-biased polarization through IL-4 upregulation. Downregulation of NLRP3 expression may attenuate allergic responses as well as suppress cell pyroptosis.⁶⁷ In addition, jumonji domain containing-3 (Jmjd3; also known as Kdm6b) is a histone 3 Lys27 (H3K27) demethylase. Satoh et al previously reported that Jmjd3 is essential for polarization of M2 macrophages in response to helminth infection and chitin. The effects depend on demethylase activity of Jmjd3 and downstream Irf4, a key transcription factor. Overexpression or activation of Jmjd3 is beneficial to host defense against helminth infection and the alleviation of asthma.⁶⁸ Therefore, Jmjd3-mediated H3K27 demethylation is crucial for regulating the development of M2 macrophages leading to anti-helminth host responses.

Immune-regulatory cells

In addition to Th2 cells, some immune-regulatory cells, such as CD4+CD25+ regulatory T (Treg) cells and stem cells, are able to drive M2 cell-biased polarization. For example, mice infused with syngeneic CD4+CD25+ Treg cells have more population of CD206+ peritoneal macrophages, with low levels of CD80 and MHCII.⁶⁹ Macrophages cocultured with Treg cells have increased CD206, CD163, and CCL-18 as well as an enhanced phagocytic capacity. CD4+CD25+CD127(low) Foxp3+ Tregs produced IL-10, IL-4, and IL-13, partially responsible for the upregulation of CD163, CCL-18, and phagocytosis, respectively.⁷⁰ Furthermore, it is well documented that bone marrow-derived mesenchymal stem cells (BM-MSCs) have immune-regulatory property. A recent study also indicated that BM-MSCs can induce M2 cell-biased polarization.⁷¹ Intravenous injection of BM-MSCs can normalize and stabilize lung function in the HDM-induced asthmatic mouse model. A further study indicated that the beneficial effects are associated with M2-biased polarization of resident macrophages after resident macrophages engulfed

the injected MSC in vivo.⁷² Similarly, Yin et al also recently reported that polarization of M2 cells can be enhanced by adipose tissue-derived stromal cells. The macrophages have downregulated IL-6, TNF- α , iNOS, and CD86 but increased Arg1, CD206, Fizz1, Ym1/2, and IL-10 after coculture with adipose tissue-derived stromal cells.⁷³ The effects might be mediated by the released immune-regulatory mediators, such as IL-10 and indoleamine 2,3-dioxygenase from stromal cells.^{74,75} Therefore, adoptive transfer MSCs have therapeutic potential in the treatment of inflammatory diseases, such as asthma, through increasing M2 cell-biased polarization.

Conclusion and therapeutic perspectives

Lung M1 and M2 cells are distinct cell subtypes and participate in the pathogenesis of asthma. M1 cells express high levels of proinflammatory cytokines, and M2 cells express high levels of Th2-type cytokines. Owing to their different cytokine expression profiles, M1 and M2 cells play different roles in the pathogenesis of asthma. A variety of regulatory cytokines, chemokines, mediators, and immune-regulatory cells affect polarization and chemotaxis of lung macrophages. These mediators interplay and influence disease duration and severity through the altered polarization of M1 and M2 cells. Therefore, modulation of phenotypes of lung macrophage has therapeutic potential in the treatment of asthma and other lung inflammatory diseases.

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Disclosure

The authors report no conflicts of interest in this work. None of the authors affiliated with this manuscript have any commercial associations that might pose a conflict of interest. The authors alone are responsible for the content and writing of the article.

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