Biology and Medicine
ISSN: 0974-8369

Wang et al., Biol Med (Aligarh) 2018, 10:2
DOI: 10.4172/0974-8369.1000432

Review Article Open Access

Brief Introduction of Important Innate Cells in Roles of Asthma

Tao Wang[1#], Zhihong Feng[2#], Bing Wei[2], Lin Zhang[2], Ning Xia[2] and Xiuhong Nie[2*]

[1]*Department of Emergency Medicine, Beijing Chaoyang Hospital Affiliated to Capital Medical University, Beijing, China*

[2]*Department of Respiratory Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China*

[*]**Corresponding author:** Xiuhong Nie, Department of Respiratory Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China, Tel: +86 10 8391 1000; E-mail: niexiuhong@xwhosp.org

Received date: February 05, 2018; **Accepted date:** February 28, 2018; **Published date:** March 07, 2018

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#-These authors contributed equally to the work.

Abstract

Asthma is a chronic inflammatory disease with multifactorial disorder of the airways, and was associated with T helper type 2 (TH2) cells. It is considered the results of complicated interactions between innate cells and structural cells, including dendritic cells (DCs), epithelial cells, mast cells (MCs), basophils, eosinophils and group 2 innate lymphoid cells (ILC2s), which finally sustains Th2 immunity in the pathogenesis of asthma. In this narrative review the details of roles of important innate cells against asthma are discussed to facilitate the future study of asthma.

Keywords: Asthma; Innate cells; Chronic inflammatory disease

Introduction

Asthma is a disease with various degrees of airflow obstruction and airway hyperresponsiveness (AHR) in the conducting airways [1-4]. The development of the inflammation in asthmatic lungs is considered caused by the release of various inflammatory mediators secreted by the interaction of innate immune cells and structural cells. The function of innate cells in asthma, including mast cells, basophils, eosinophils, DCs, ILC2, has been studied using genetic methods, antibody-based depletion strategies, as well as the functional cells reconstitution experiments to make it clear of the roles and the interactions between innate cells. In this review, roles of different important innate cells in the pathogenesis of asthma and the interactions of the innate cells are discussed to lead the clear understanding of asthma.

Mast cells

MCs are derived from hematopoietic stem cells in the bone marrow, which are important effector cells in the immune system [5]. Most mast cells reside in tissues and survive from months to years. Mast cells can be distinguished by their high content of electron-dense secretory granules. Tissue MCs express the high affinity IgE receptor FceRI. Mast cells are best known for their role in IgE-associated allergic disorders. Cells' surface-FcεRI-bound IgE complex, initiates a complicated secretory response [6]. When binding with IgE, MCs can be triggered to release diverse mediators in allergic reaction, including histamine, serotonin, proteases, leukotrienes and cytokines, etc; some mediators are stored in cytoplasmic granules like histamine, serotonin, and proteases; while some lipid-derived mediators such as prostaglandins and leukotrienes will be newly formed and released in few minutes after allergen exposure; cytokines, chemokines, and growth factors will need several hours to be secreted after MC activation. The specific types of mediators secreted by mast cells can vary according to the strength of the activation signal [7]. The release of mediators is considered in inducing vasodilatation, and edema formation in airway. Another important receptors expressed in surface of mast cells are Toll-like receptors (TLRs). It has been reported that TLR ligands can induce cytokine and chemokine production in mast cells [8-10]. Mast cells also have [11] and IL-33 [12-14] receptors, which means that TSLP and IL33 can activate MCs directly. Mast cells can secret IL-4 and IL-13, which promote Ig class switching and IgE production [15,16]. Their production of IL-10 can limit skin inflammation during contact dermatitis or following UV exposure [17]. Worth noted, Mast cells can also express CD40L. This evidence highlights the possibility that mast cells can drive further IgE production in responses to allergic disorders, or in responses to parasites [18,19].

The role of MCs in allergic inflammation has been extensively studied in mice models. In most of the mouse based models, mast cells are observed to promote the asthma. Increased numbers of MCs in airway smooth muscles were observed in these adult asthma models. However, it remains unclear in neonatal models. In human, patients with more severe asthma show a significant higher numbers of chymase+mast cells in the proximal airway epithelium [20-22]. MC-deficient mice (WBB6F1-KitW/Wv or C57Bl/6-KitW-sh/W-sh or CPA3cre) and MC-reconstituted mice are applicable to study the contribution of MCs to the pathogenesis of asthma [23-26]. Findings from human studies and work in mast-cell knock-in mice indicate that mast cells can promote local inflammation and directly or indirectly enhance goblet cell metaplasia and airway tissue remodeling [27-30]. In the remodeling process, mast cells can contribute to the migration, accumulation, and activation of T cells, DCs, and other cells of innate immunity [31,32].

MCs have been shown to induce immunosuppressive effects through their production of IL-10 and to limit skin inflammation during contact dermatitis or following UV exposure [23]. MC-derived IL-10 has also been shown to reduce B cell responses and antibody production [24]. Moreover, MCs also express sialic acid-binding immunoglobulin type lectins (Siglec)-8; a lectin shown to induce apoptosis in eosinophils [25,26]. In MCs, Siglec-8 engagement fails to induce apoptosis but inhibits inflammatory responses [26]. It is unclear whether this function of MCs to limit inflammation is due to some specificity of the models or truly represents an important function of

these cells. It is clear that many factors derived from MCs themselves or from other sources in the lungs of asthmatics can affect their number and their distribution. However, which factors are the most crucial in altering MC functions *in vivo* remains unknown. Also, whether MCs can be specifically targeted or reduced in diseased tissues in a safe way remains to be carefully addressed.

Basophils

Basophils which were discovered by Paul Ehrlich in 1879, are traditionally considered phenotypically and functionally related to mast cells, though in some situations, basophils and mast cells behave differently in role of asthma [33-35]. Basophils express the high affinity receptor FceRI and also produce mediators including histamine, Th2-associated cytokines, and lipid mediators. In comparison of mast cells, the lifespan of mature basophils is short and estimated to be 1 or 2 days [36].

Basophil development can be driven by IL-3 and TSLP [37,38]. Animal models have provided indications of contributions for basophils in role of development or propagation of allergic airway inflammation. An important role of basophils reported is that it is observed involved in Th2 cell polarization in mice, and directly promote optimal TH2 cytokine responses. Basophil depletion experiments and basophil-deficient mouse strain provide powerful evidence that the development of Th2 responses requires cooperation between DCs and basophils [39-42]. It has been shown that the depletion of basophils using antibodies against FceRI resulted in poor Th2 responses [41].

Basophils have also been shown to be activated in an IgD-dependent manner and alsoin IgE- and IgG- mediated activation processes. Basophils can secret multiple cytokines and chemokines after activation. For instance, IL-3 based activated basophils can release cytokines (IL-4, IL-6) and chemokines (CCL3, CCL4, CCL12, Cxcl2) in an IgE-independent manner in mice [37,43-47]. Following IgE-mediated activation, IL-3 can enhance the production of IL-4 and IL-13 from human basophils.IL-33 can also directly activate basophils and enhance their effector functions. IL-33 promotes IL-4 and IL-13 production from basophil populations in a MyD88-dependent manner [48-50].

Eosinophils

Eosinophils are considered important effector cells in asthma. Mediators released by eosinophils are relevant to the disease process; and removal of eosinophils is associated with an improvement in the disease [51]. Eosinophils are defined as granulocytes, which develop in the bone marrow from pluripotent progenitors in response to stimulations-induced cytokines [52,53]. These cytokines can be interleukin-5 (IL-5), IL-3 and granulocyte–macrophage colony-stimulating factor (GM-CSF). Interleukin 3 (IL-3), IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) promote eosinophil differentiation [53-57]. IL-5 is important for terminal differentiation of the eosinophil precursor. Eosinophil migration from the vascular space into the tissues is initiated by the interactions between surface receptors with ligands on vascular endothelial cells [58,59].

Eosinophils' granules can store cytokines, cationic proteins and enzymes, and release cytokines to regulate downstream signaling after receive stimulations. Eosinophils can express multiple receptors, including IL-5 receptor, CC-chemokine receptor 3 (CCR3), receptor sialic acid-binding immunoglobulin-like lectin 8 (SIGLEC-8) in human and SIGLEC-F in mouse [60-66]. Eosinophils can secrete a number of lipid mediators and proteins, including major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO). MBP is toxic for human respiratory epithelial cells and pneumocytes [67-70].

Eosinophils are used to define features of allergic asthma in humans and animal models, and are considered an early source of Th2 cytokines in asthma. Allergen-induced IL-5 produced by Th2 cells or ILC2s can induce eosinophils to mature [71-73]. Mature eosinophils are released into the peripheral blood and enter lung tissues in response to chemokines produced by airway epithelial cells with the stimulation of IL-13 [74-76].

Eosinophils are important for airway remodeling in mouse model. Exposure of Ddbl-GATA mice on a Balb/c background to an asthma protocol showed that the absence of eosinophilscannot protect mice from AHR development [61]. Evidence also shows that C-kit mutant mice (WBB6F1/J-KitW/KitW-v/J) and CPA3-cre knockout mice (C57BL/6-Tg(Cpa3-cre)4Glli/J) are easily acquire asthma [77,78].

Eosinophils are serving as effector cells and actively involved in the adaptive immune response by modulating CD4+ T cells and asthma features. Eosinophils can promote Th2 polarization via IL-4 [79,80], and induce activation/migration of DCs via eosinophil-derived neurotoxin (EDN) [81,82]. Several studies have showed that Eosinophils induce the activation/proliferation of antigen-specific memory T cells in mouse models of asthma and in patients of asthma through the presentation of antigens by MHCII, which eventually cause the production of Th2 cytokine [83-85].

Dendritic cells and epithelial cells

Dendritic cells (DCs) play critical roles in initiating and directing immune responses, and are serving the main predominant MHCII antigen-presenting cells in asthma. DCs involve in directing TH1 responses and determining the nature of T-lymphocyte differentiation in response to allergen exposure [86,87]. DCs can secret a panel of cytokines that can direct T-lymphocyte differentiation, including IL-12, IL-10, IL-6, and TGF-b, but not IL-4. In lung, DCs have different subsets, including two dominant subsets: cDCs, and moDcs. In situation of inflammation, three distinct subsets of lung conventional DCs (cDCs) can be recognized based on the expression of specific cell surface markers: CD103+ cDCs; CD11b+cDCs; and plasmacytoid (p) DCs. Monocyte-derived DCs (moDCs) are also observed in lungs under inflammation [88-92].

DCs can determine the type of TH response to allergens, and drive the differentiation of TH cells into TH2 cells, which are important in allergic airway inflammation [89,93,94]. Th2 responses in asthma require antigen presentation by DCs. First, DCs can capture inhaled allergens and transport them in a chemokine CC receptor (CCR)7-dependent way to the T cell. Second, during ongoing inflammation, DCs contribute to inflammatory cell recruitment and gronchial hyperresponsiveness (BHR) development. The subsets of lung DCs presenting inhaled allergen to T cells are considered CD11b+cDCs and moDCs. CD11b+cDCs are recruited forTh2 sensitization, and moDCs are responsible for recruitment of inflammatory cells (Th2 cells and eosinophils) to the lungs by producing chemokines. Airway epithelium also involves in the process of allergens sensitization through secreting mediators that activate immune cells against environmental triggers. IL-1 is a typical mediator released by epithelia cells in lung [95].

In murine models of asthma, IL-1 contributes to induce asthma features. IL-1R triggers lung epithelial cells to promote the innate immune response to natural. The pathway of Nlrp3–IL-1b is shown in role of Th2 responses via the skin. IL-1a induces production of granulocyte–macrophagecolony-stimulating factor (GM-CSF) and IL-33, which is required for development ofTh2 immunity *in vivo*, and controls the Th2 cascade [96-98]. ST2, the receptor for IL-33, can be expressed in several innate cell types including DCs, macrophages, basophils, MCs, and eosinophils. Thus epithelial cells are important in cross talk between different innate cells. IL-33 is also shown to support the survival these innate cells. Another important role of IL-33 is that it can contribute to the expansion and activation of ILC2s. In patients suffering from allergic asthma and children with severe treatment-resistant asthma, tissue IL33was highly expressed [99-101].

Similar as IL-33, IL-25 is another important cytokine released by epithelial and inflammatory cells in the airways of allergen-challenged mice and human asthmatics. IL-25 contributes to Th2 immunity and drive the expansion of ILC2s and granulocytic myeloid cells that produce IL-5 and IL-13 in mice and humans. IL-25 also contributes in orchestrating airway remodeling, and induces collagen by lung fibroblasts to promote angiogenesis [102].

ILC2 cells

Innate lymphoid cells (ILCs), which are important in Th2 immunity, can serve as sources of Th1, Th2, or Th17 cytokines. ILCs thus can be generally referring to nuocytes and natural helper cells showing morphologically similar ityas T cellsbut lack rearranged antigen receptors. According to the sources they served, they have been named ILC1, ILC2, and ILC3, respectively. ILC2s were initially discovered in the peritoneal cavity, which are RORa-dependent ILCs. ILC2 includes nuocytes, natural helper cells (NHCs) and innate helper 2 cells (Ih2s). However, whether these cells are different subsets or the same cell at different stages of development remains unknown [103,104].

ILC2 can express CD25 (IL-2Ra), CD90 (Thy1), CD117 (c-Kit), CD127 (IL-7Ra), CD278 (ICOS), ST2 (IL-33R) and IL-17BR, and are IL-25-responsiveand IL-33-responsive [105,106]. Human ILC2s also express the receptor for lipoxin A4; which can decrease IL-13 production. ILC2 can secrete large quantities of cytokines, including IL-5, IL-9and IL-13, which belongs to the type II immune response against allergic asthma. ILC2 arise from a common lymphoid progenitor in the bone marrow [107]. IL-7, IL-33, the transcription factors Id2 and RORa are essential for their development and function. The cells proliferate stimulated by IL-25 and IL-33, and other pathogens such as helminths, viruses and fungi, is considered the central step in type 2-mediatedimmunity. In response to IL-33, ILC2s produce high amounts of IL-5.The role of ILC2s can induce lung inflammation in response to aeroallergens or proteolytic antigens [108,109]. Reconstitution of ILC2s into Rag/mice showed that ILC2s, which are the major source of IL-5 and IL-13. In papain-induced models, ILC2s transiently produce IL-9 that is dependent on IL-2 produced by adaptive immune cells. The depletion of ILC2s causes lung repairmen and tissue recovery. ILC2 produces amphiregulin, which linked to tissue remodeling and repair in asthma [110,111].

Conclusion

In mouse model of asthma, mast cells have been shown to promote the transport of inhaled antigen by dendritic cells [112-115]. Although mast cells have mainly been considered as asthma-promoting cells due to their IgE-induced effects, recent data suggest that they might have the potential suppressive function in inflammation due to the complicated cross talk of the innate cells (unpublished data). In response to inhaled allergens, cytokines including IL-33, IL-25, IL-1, and GMCSF are released by epithelial cells. IL-33 and GM-CSF released by epithelium will regulate ILC2 expansion, and lung DC differentiation [13,14,116,117]. Mast cells will release histamine, IL-6, and tumor necrosis factor (TNF) a to enhance cDC migration. Under the stimulation, DCs drive the Th2 responses in the lungs, by activating naive T cells to differentiate into effector Th2 cells. Then basophils and eosinophils will start to work on Th2 polarization induced by IL-4 [118,119]. Monocytes will produce chemokines to trigger the immigration of eosinophils, basophils, mast cells and Th2 cells to the lung. The release IL-33 from epithelial cells in asthma model and increase of IL-25 and IL-25R expression in basophils and eosinophils, increased the proportion of ILC2. In the lung, ILC2 plays a direct role in type 2 immune pathologies. Administration of recombinant IL-25 or IL-33 induced the expansion of an ILC2 population. The production of IL-5 and IL-13 by ILC2 is necessary for eosinophilia and mucus secretion. However, details about the cross talk among innate cells are remaining unknown. ILC2s could, or not, enhance eosinophil differentiation and survival is unknown. And the roles of neutrophils and macrophages in asthma are still unclear. Interaction occurring between lung DCs and ILC2s remains to be fully addressed.

Acknowledgements

This review was supported by projects of the Basic-Clinical Research Cooperation Issues of Capital Medical University (NO.17JL90).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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