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Current Opinion in Immunology

Role of neutrophils in allergic asthma

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The contribution of neutrophils to asthma pathogenesis has been mainly studied in the context of non-allergic neutrophilic asthma. However, neutrophils can also be rapidly recruited and are largely present in the airways of allergic eosinophilic asthmatic patients. Under these circumstances, they possess specific phenotypic features distinguishing them from resting blood neutrophils and are endowed with particular functions. The exact contribution of neutrophils to allergic asthma pathogenesis is still unclear, but growing experimental evidence supports the ability of neutrophils or neutrophil-derived products to influence the underlying allergic type 2 immune response and cardinal features of allergic asthma, thus shedding new light on neutrophil biology and functions in an allergic context.

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Current Opinion in Immunology 2018, **54**:28–34

This review comes from a themed issue on **Allergy and hypersensitivity**

Edited by **Onur Boyman**, **Alexander Eggel** and **Mario Noti**

https://doi.org/10.1016/j.coi.2018.05.006

Introduction

Neutrophils represent the most abundant immune cell type in the blood and are generated in the bone marrow under the control of key transcriptor factors such as C/EBPα, PU.1, Gfi-1 and C/EBPε [1]. They have long been known as short-lived (half-life: 6–12 hours [2]) innate immune cells specialized in pathogen killing through their high phagocytic potential and the secretion of cytotoxic granules once recruited in the tissues [1]. Today, a more complex picture of the neutrophil is emerging, with immunoregulatory properties and implications in various non-infectious disorders [3]. Of note, unlike previously appreciated, neutrophils are now thought to encompass distinct phenotypic and functional subsets in humans [4,5] and mice [6,7], some of them exhibiting an extended half-life in certain inflammatory conditions [3]. Furthermore, in 2004, Brinkmann and colleagues have discovered the ability of neutrophils to form neutrophil extracellular traps (NETs), whose roles in health and disease are currently under close scrutiny (Box 1), and which has arguably contributed to the renewed interest in neutrophils [8].

Asthma constitutes a heterogeneous group of respiratory inflammatory disorders characterized by a similar clinical pattern of cough, wheeze and reversible airway obstruction [9]. Asthma phenotypes can be categorized according to clinical symptoms, specific triggers, inflammatory or immune status, or treatment response [10,11]. If one refers to an inflammatory phenotype classification [12,13], allergic asthma belongs to the 'eosinophilic' phenotype (Table 1). Notably, while patients with more than 3% sputum eosinophils are considered 'eosinophilic', up to 60% sputum neutrophils can also be present [10,12,13]. Immunologically, allergic asthma is characterized by the development of an aberrant immune response with a predominant adaptive type 2 T helper cell (Th2) profile directed against inhaled allergens [9]. Such Th2 response, via the secretion of cytokines such as interleukin(IL)-4, IL-5, IL-13, orchestrates many cardinal features of allergic asthma, such as eosinophilic inflammation, mucus hypersecretion, airway hyperresponsiveness and increased serum levels of type E immunoglobulins (IgE) [14].

Neutrophil recruitment in allergic asthmatic lungs

While neutrophils are not steadily present in the airways of allergic asthmatic patients, they are one of the first innate immune cells recruited into the lungs during specific asthma-related events such as allergenic challenges [15–17], virus-induced asthma exacerbations [18••,19,20] or nocturnal crises [21]. In mice, airway exposure to clinically relevant allergens that promote features of allergic asthma is also associated with the airway recruitment of neutrophils [18••,22••,23•,24].

Like in other tissues, the recruitment of neutrophils into the respiratory tract comprises several steps that are

Box 1 Neutrophil extracellular traps.

Neutrophil extracellular traps (NETs) are web-like structures composed of nuclear or mitochondrial chromatin associated to modified (e.g. citrullinated) histone proteins and decorated with 20–50 different proteins, such as neutrophil elastase, myeloperoxidase (MPO), LL37, cathepsin G, proteinase 3 or high mobility group protein B1. NETs can be released in the extracellular space in response to various microbial (e.g. bacteria, viruses, parasites, lipopolysaccharide [LPS]) and non-microbial (e.g. phorbol 12-myristate 13-acetate (PMA), crystals) stimuli. The molecular mechanisms of NET formation are not yet fully understood and may differ according to the stimuli (reviewed in [48]). Reactive oxygen species (ROS) formation, activation of the MEK/ERK pathway downstream of membrane receptors (PSGL1, RAGE, TLR2/4, Dectin 2, FcγR, Siglec 14), activation of autophagy (through the inhibition of mTOR pathway or the activation of the PI3K pathway) and induction of necroptosis have all been implicated in NET formation. If NETs were originally discovered for their role in bacterial killing [8], they have been more recently associated with non-infectious disorders like thrombosis, vasculitis, systemic lupus erythematosus, diabetes, cancer, asthma or chronic obstructive pulmonary disease (COPD) [60].

initiated by the endothelial expression of adhesion molecules [25] and followed by extravasation and migration according to a chemokine gradient. In a mouse model of ragweed pollen extract challenge, Hosoki and colleagues demonstrated that lung neutrophil recruitment was substantially lower in mice lacking the LPS receptor Toll like receptor (TLR)-4 [22••]. Similarly, inhibition of CXCR2, the receptor for CXCL1, CXCL2 and CXCL5 in mice, inhibited allergen-induced innate recruitment of neutrophils [22••], and the production of CXCL1, CXCL2 and CXCL5 was shown to be dependent on TLR-4 and its co-receptor MD2 in response to cat dander and other relevant pollens [22••,23•]. Epithelial cells might be the source of such chemokines, as they have been shown, in humans, to secrete CXCL8 (i.e. IL-8, the human analogue of CXCL1, CXCL2 and CXCL5) following allergenic challenges [23•,26]. In addition, alveolar macrophages may also deliver CXCL1 and CXCL2 in response to allergen-induced and antibody-mediated activation of FCγIII receptors [27]. In humans, sputum levels of CXCL8 have been shown to be increased during acute allergic asthma exacerbations [19] and following allergenic challenge [15], which was associated with increased sputum neutrophils and blood neutrophil chemotaxis [15].

Oyoshi and colleagues demonstrated, in a model of skin allergy, that neutrophil-intrinsic leukotriene B4 (LTB4) synthesis and its receptor, BLT1, were involved in neutrophil recruitment [28]. Interestingly, LTB4 levels were increased in the BALF of asthmatic patients suffering from nocturnal asthma [29] and in exhaled breath condensate of asthmatic children [30] and adults [31]. In addition, the use of a LTB4 inhibitor in asthmatic patients triggered a substantial decrease in BALF neutrophils [32].

The Th2-associated cytokine IL-4 may control neutrophil recruitment during allergic asthma. Indeed, a recent study has demonstrated that IL-4 could dampen neutrophil expansion and migration through neutrophil-intrinsic IL-4 receptor signaling in mice [33••]. *Ex vivo* treatment of bone marrow neutrophils with IL-4 inhibited neutrophil migration in response to CXCL1 and CXCL2 by IL-4 receptor-dependent mechanisms [33••]. In a model of airpouch, CXCR2-dependent neutrophil recruitment was also inhibited when IL-4 biological half-life was prolonged [30]. The potential contribution of the IL-4/IL-4 receptor axis to the regulation of neutrophil numbers in the airways of allergic asthmatic patients or experimental animals will however require further investigations. Mast cells, whose allergen-dependent and IgE-dependent degranulation is thought to contribute to the acute

Table 1

Asthma inflammatory phenotypes

Phenotype	Inflammatory cells present in the airways	Immunological and inflammatory biomarkers	Severity	Triggers	Immune profile
Eosinophilic	Sputum eosinophils (>3%) Sputum neutrophils (<76%)	Specific IgE Th2-associated cytokines (IL-4, IL-5, IL-13) [61,62]	Mild to severe	Allergens (75%) Exercise Occupational (15%) Aspirin	Th2>>>Th17
Neutrophilic	Sputum Neutrophils (>76%)	IL-8 Neutrophil elastase IL-1β TNF-α micro RNA-629-3p, 223-3p and 142-3p [62]	Severe	Obesity Tobacco smoke Exposition to irritants	Th17>>>Th2
Paucigranulocytic	Levels of sputum eosinophils <3% and neutrophils <76%	?	Moderate	Not defined	?
Mixed granulocytic	High levels of sputum eosinophils (>3%) *and* neutrophils (>76%)	?	Severe	Not defined	Th2/Th17?

Source: Adapted from [9,12,13].