THE ROLE OF EOSINOPHILS IN ASTHMA

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Summary. Asthma is a common respiratory disease. The prevalence of asthma has been increasing over the past twenty years in most countries, and it affects up to 10% of the population of developed countries. Airway inflammation is a major factor in the pathogenesis of asthma. The presence of peripheral blood eosinophilia and activated eosinophils in the chronic inflammatory infiltrate of the airways is a characteristic of both allergic and non-allergic asthma. This review article describes the mechanisms of eosinophilic inflammation in asthma: eosinophilia, role of eosinophil growth factors (IL-3, IL-5 and GM-CSF), phases in the recruitment of eosinophils from bone marrow to airway mucosa, activation and eosinophil effector functions in the pathogenesis of asthma.

Key words: Eosinophils, asthma, inflammation, cytokines, chemokines

Introduction

Asthma is a common respiratory disease. The morbidity and mortality of asthma are increasing, making it a global health concern. Symptoms of chest tightness, coughing, wheezing and dyspnea, as well as characteristic physiologic abnormalities of variable airflow obstruction and airway hyperresponsiveness to bronchoconstrictor stimuli characterize asthma (1). The primary underlying abnormality in the disease is a chronic inflammation of the airway mucosa that gives rise to reversible obstruction and hyperresponsiveness. The predominant inflammatory cell in asthmatic inflammation as determined by fiberoptic bronchial biopsy, bronchoalveolar lavage, and induced sputum, is the eosinophil, accompanied by T-lymphocytes, mast cells and basophils (2). Eosinophilic inflammation of the airways, with an increase in activated and degranulated eosinophils is the key feature of both allergic and non-allergic asthma (3,4). Significant correlation exists between the activation of eosinophils and the severity of asthma as reflected in bronchial hyperresponsiveness and asthma symptom (Aas) score (5). Increase in number of activated EG2+ eosinophils in the airways is present even in patients with mild asthma.

Eosinophilopoiesis

Eosinophils are produced in the bone marrow from CD 34+ pluripotent progenitor cells, which are common to both eosinophils and basophils under the influence of growth factors, including interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-5. IL-3 and GM-CSF are active on early precur-
Eosinophil morphology

The mature eosinophil is usually round or ovoid, having a diameter of 12-17 μm, and a bilobed nucleus. There are three types of granule in the eosinophil: specific, small and primary (30). Judged by electron microscopy, specific granules have a distinct structure, being composed of a electrodense, crystalloid core and an electrolucent matrix. These granules are characterised by their marked affinity for the reddish-orange collored acid dye eosin. Primary granules are round and develop early in eosinophil maturation. Small granules contain acid phosphatase and arylsulphatase (31). Another constituent of eosinophils is the Charcot-Leyden protein, (bipyramidal crystals) often found in sputa of asthmatic patients. This protein possesses lysophospholipase activity (32). In healthy, non-allergic persons, circulating eosinophils comprise 1-2 % of white blood cells. eosinophilia is classified as mild (351-1500 cells per cubic millimeter), moderate (> 1500 to 5000 cells per cubic millimeter) or severe (> 5000 cells per cubic millimeter) (19)

Pathogenetic role of eosinophils in asthma

The recruitment of eosinophils into bronchial mucosa in which allergic inflammation occurs is a critical contributor to the late asthmatic reaction of congestion and mucus hypersecretion (33) (fig.1). When these cells arrive they degranulate and perpetuate underlying airway inflammation. Eosinophils are a rich source of cytotoxic proteins, lipid mediators, oxygen free radicals and cytokines (34). In asthmatic patients, after transendothelial migration, eosinophils transmigrate and adhere to bronchial epithelium where they degranulate and release substances (eosinophil cationic protein ECP, major basic protein MBP, eosinophil peroxidase EPO and superoxide) which are toxic for epithelial cells (35). Damage and desquamation of cells, cellliosis, and epithelial secretion (36) manifest the toxicity to airway epithelium. MBP is a selective, allosteric antagonist for M2 muscarinic receptors (autoreceptors) (37). The loss of M2 muscarinic receptor function results in increased airway tone due to increased release of acetylcholine and potentiation of vagally mediated reflex bronchoconstriction and bronchial hyperresponsiveness (38). MBP also stimulates histamine release from basophils and mast cells.

Lipid bodies (intracellular lipid rich domains) are induced to be developed in the activated eosinophils, and are the sites for enhanced synthesis of both lipoxygenase and cyclooxygenase-derived eicosanoids (39). Eosinophils are capable of producing significant quantities of cysteinyl leukotrienes (especially LTC-4). Cysteinyl leukotrienes contract airway smooth muscle (100-1000 fold more potent bronchoconstrictors than histamine), increase vascular permeability, stimulate mucus secretion, decrease mucociliary clearance, stimulate
Eosinophil and neutrophil recruitment into the airways (40), stimulate smooth airway muscle proliferation and cause neuronal dysfunction (41).

Eosinophils have the potential to synthetize and release a number of cytokines and chemokines. Cytokines produced by eosinophils include the autocrine-eosinophil active growth factors (IL-3, IL-5, GM-CSF), immunoregulatory cytokines (IL-2, IL-4, IL-1, TGF-β, IFN-γ), proinflammatory cytokines (IL-1, IL-6, TNF-α, IL-16) and chemokines (IL-8, MIP-1α, RANTES) (42). Transforming growth factor-β (TGF-β) is an immunoregulatory factor with a direct effect on growth of some cell types (stimulation on fibroblast growth and inhibition of epithelial cell growth) and upregulation of the synthesis of ECM proteins, inflammatory mediators and cytokines, making it an important factor in the remodelling process (43).

Activation of the eosinophils

After eosinophils arrive at inflammatory site in the airways, they become activated with hypodense phenotype (44). Activated eosinophil expresses a number of receptors for cytokines, chemokines, immunoglobulins and complement. During the inflammatory response, locally produced complement-derived anaphylatoxins C3a and C5a bind to specific cellular receptors and activate respiratory burst in eosinophils. C5a acts as a chemoattractant for neutrophils and eosinophils and represents a major metabolic activator for eosinophils inducing the release of granule proteins and free oxygen radicals that cause damage to the airway tissue (45). Secretory IgA-IL-8 complex is a potent eosinophil chemoattractant and stimulus for degranulation. Its potency is mediated by the secretory component (46). The three cytokines that simulate eosinophilopoiesis (IL-3, IL-5, GM-CSF) can activate their effector functions too. These cytokines bind to the receptor that has a common β-chain and different α-chains (47). IL-3, IL-5, GM-CSF prime eosinophil response to chemoattractants, increases their degranulation, prolongs their survival, and increases free oxygen radical production. IL-5 also activates eosinophils to express the EG2 epitope (activated EG2+ eosinophils) (48). The mechanism of prolonged eosinophil survival by these cytokines is by eliminating apoptosis.

Eosinophil apoptosis

The signaling pathways involved in antiapoptotic effect of the cytokines involve the Lyn, Jak2, Raf1, transduction of survival and death signals (49). Corticosteroids induce eosinophil apoptosis with programmed cell death (an eosinophil dies and doesn’t release harmful inflammatory mediators) (50). Treatment of asthmatics with inhaled corticosteroids leads to the depletion of mucosal eosinophils, which is associated with clinical improvement (51). Inhaled corticosteroids have many effects on eosinophilopoiesis including: abrogation of cytokine production by airway tissues, reduction in peripheral blood eosinophil-basophil progenitors after corticosteroid inhalation during asthmatic exacerbation and decreasing or phenotypic changes in human bone marrow progenitor after corticosteroid inhalation (52).

Theophylline induces apoptosis by functioning as phosphodiesterase (PDE) inhibitor on the activated eosinophil to increase intracellular cyclic adenosine monophosphate (cAMP), and indirectly through the inhibition of cytokine (IL-5,GM-CSF) production (53).
References


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ULOGA EOZINOFLA U ASTMI

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Kratak sadržaj: Astma je česta respiratorna bolest. Tokom poslednjih dvadeset godina u većini zemalja prevalencija astme beleži porast, i zahvata do 10% stanovništva u razvijenim zemljama. Zapalenje disajnih puteva je glavni faktor u patogenezi astme. Prisustvo eozinoofilije periferne krvi i aktivisanih eozinoofilija u hroničnom zapaljenjskom infiltratu disajnih puteva, je karakteristično i za alergijski i nealergijski oblik astme. Ovaj pregledni članak opisuje mehanizme eozinofilne inflamacije u astmi: eozinofilopoietu, ulogu faktora rasta eozinofilija (IL-3, IL-5 and GM-CSF), faze u prelasku eozinofilija iz kostne srži do sluzokože disajnih puteva, aktivaciju i efektorske funkcije eozinofilija u patogenezi astme.

Ključne reči: Eozinofil, astma, zapalenje, citokini, hemokini