

Difference of Inflammatory Cell Migration in Asthma: A New Hypothesis

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Article Info	ABSTRACT
<p>Article type: Review article</p>	<p>Background and Aim: Asthma is an inflammatory airway disease and T helper 2 cytokines (i.e., interleukin 4, interleukin 5 [IL-5], and interleukin 13) have an important role in asthma pathology. Blood vessels in lung parenchyma and airway wall serve as the sources for inflammatory cells. The IL-5 leads to eosinophilic inflammation. The adhesion molecules on the endothelium and immune cells allow for the translocation of eosinophils. The vessels of the lung may play the main role in the cell migration and pathophysiology of asthma.</p>
<p>Article History: Received: 17 November 2020 Revised: 24 February 2021 Accepted: 24 February 2021</p>	<p>Materials and Methods: Several keywords were searched in databases, and out of 495 manuscripts 178 studies were selected. At least, 19 manuscripts were used as support of the above-mentioned hypothesis.</p>
<p>Keywords: Airway Artery Eosinophil Inflammation Integrin Selectin</p>	<p>Results: We hypothesized that airway vessels highly have leaks for eosinophils, and eosinophil migration from the endothelium of these vessels is easier than the endothelium of other tissues. Severe vascular leak and easy eosinophil migration in lung vessels cause inflammation leading to severe asthma phenotype; however, similar inflammation does not occur in other organs. The treatment of asthma is difficult and the control of cell migration needs to manipulate cell adhesion molecules.</p> <p>Conclusion: The lung endothelial molecules may have the potential to develop new treatments for asthma.</p>

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Introduction

Asthma is a chronic airway disease and characterized by inflammatory airway, smooth muscle spasm, mucus hyper-secretion, breathlessness, and airway hyperresponsiveness. T helper 2 (Th2) cytokines, such as interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13), have an important role in asthma pathology (1, 2). Allergy is the main trigger of asthma pathophysiology and mediated by type 2 cytokines. In predisposed patients, dendritic cells take up arrived allergen and translocate it to the lymph nodes.

Allergen is presented to the allergen-specific T and B cells. Released cytokines from Th2 stimulate B cells to antibody class switching and immunoglobulin E (IgE) production that bound to Fc epsilon receptor on mast cells and basophils. When allergen re-enters, it leads to the crosslink of the bounded IgE and degranulation of the cells

(mediators, such as histamine, serotonin, and eicosanoids) and orchestrates allergic symptoms (1-3). The IL-4 forces B cell isotype switching to produce IgE that initiates allergy reaction. The IL-5 activates eosinophils to migration, leading to eosinophilic inflammation. The IL-13 increases goblet cell hyperplasia and mucus hyper-secretion, and all of these changes result in asthma exacerbation (2, 3).

Modern anti-asthma therapies are focused on the immune cells, allergic mechanism, and inflammatory response triggers; nevertheless, few treatments were discussed regarding the airway and lung parenchyma vessels. Blood vessels in the lung parenchyma and airway wall are the sources for inflammatory cells. The adhesion molecules on the endothelium and surface of the immune cells allow for the translocation of immune cells, such as eosinophils. In fact, eosinophilic inflammation with

a vascular leak can present as the main problem in severe asthma phenotype. Moreover, non-cardiogenic pulmonary edema in patients with asthma highlights the role of vascular leak in the pathogenesis of asthma (1, 4).

Dual blood supply permeates the respiratory system; the pulmonary and bronchial circulation both of which have different physiologically and pharmacologically roles. Pulmonary arteries are the bulk of blood flowing through the lungs and their branches run parallel to airways. The bronchial circulation plays a pivotal role in supporting the airway which arises as an outgrowth from the aorta, providing oxygenated blood (5-7). The bronchial circulation is also the primary portal for the immune system to initiate a rapid response to inhaled antigens (and allergens). There are notable changes in the vascularization of asthmatic airways, and increased angiogenesis, vascular permeability, and leakage are more than other organs and non-asthmatic lung. The aforementioned changes are related to asthma severity (5, 8, 9).

Inflammation in injured tissues is initiated by cell-cell interaction of leukocyte and endothelial cells, and leukocytes after adhesion to the endothelium migrate from the endothelial of the vessels to the tissue. Cell adhesion molecules play a key role in pathological phenomena. Selectins (as adhesion molecules) are involved in the early steps of leukocyte extravasation. There are three related members of the selectin family that are expressed on endothelial cells (i.e., E-selectin and P-selectin) and leukocytes (i.e., L-selectin/cluster of differentiation [CD]62L) and the interaction of these molecules lead to the transendothelial migration of leukocytes.

Selectins are binding transmembrane glycoproteins and mediate low-affinity leukocyte-endothelial cell interaction that leads to leukocyte rolling on the surface of endothelial cells. Integrins (as other types of adhesion molecules) mainly interact with extracellular matrix components. The integrins are transmembrane heterodimer glycoproteins, comprised of α (15 different types) and β (9 different types) chains. Eosinophils expresses $\alpha_L\beta_2$, $\alpha_M\beta_2$, $\alpha_D\beta_2$, $\alpha_X\beta_2$, $\alpha_4\beta_1$, $\alpha_6\beta_1$, and $\alpha_4\beta_7$ integrins. The β_1 and β_2 integrins mediate eosinophil recruitment to the respiratory system. Lymphocyte function-associated antigen 1 (LFA-1) (i.e., CD11a/CD18 or $\alpha_L\beta_2$) is expressed at leukocytes, implicated in reactions between leukocytes and endothelium. In addition, leukointegrin $\alpha_d\beta_2$ binds to intracellular adhesion molecule-3 (i.e., an intercellular adhesion molecule) that is located on the endothelium (10-12). Therefore, the vessels of the lung and

adhesion molecules of cells can play the main role in the pathophysiology of asthma.

Materials and Methods

According to the main keywords (i.e., inflammation, cell migration, asthma vessel, and adhesion molecules), searching was performed in main published manuscripts and databases (e.g., Google Scholar, PubMed, and Scopus). All of the 495 manuscripts were classified and 178 of them were selected based on the main concept. At least, 19 manuscripts were used as background and support of the hypothesis of the present study. After the final summarization and conclusion, the hypothesis was proposed according to the available data.

Results

After searching the related documents and published studies on immune cell migration, adhesion molecule, vessels, inflammation, and asthma, we hypothesized that the vessels of the airways highly have leaks for eosinophils and eosinophil migration in the airway blood vessels is easier than other tissue vessels. In asthma, the adhesion molecules on the endothelial cells may be different and especially allow for eosinophil translocation. This translocation is not allowed for eosinophils in other organs or non-asthmatic lungs. Probably, the asthmatic lung has changes in adhesion molecule in comparison to the healthy lung that leads to ease of eosinophil migration.

Vascular leak causes eosinophil inflammation which leads to severe asthma phenotype; however, similar inflammation does not occur in the non-asthmatic lung (for example, eosinophils almost have weak migration and no effect on food allergy but a strong effect and high level of migration in allergic asthma). We hypothesized that there are unknown changes in adhesion molecules on the endothelium cells of the lung arteries (especially in asthma attack) that perform easier eosinophils translocation and the endothelium of lung vessels are different from other tissues and in the allergoinflammation conditions allow eosinophils to diapedesis and migration.

Furthermore, the binding forces of selectins and integrins between eosinophils and endothelial cells in the lung may be higher than other endothelial cells and probably eosinophils change the distribution of adhesion molecules on the surface of endothelial cells. These changes of endothelial cells in asthma are different from edema condition and in edema more changes are physical (and non-cellular interaction); nonetheless, in asthma, more changes are functional (and cell-cell interaction) (Figure 1).

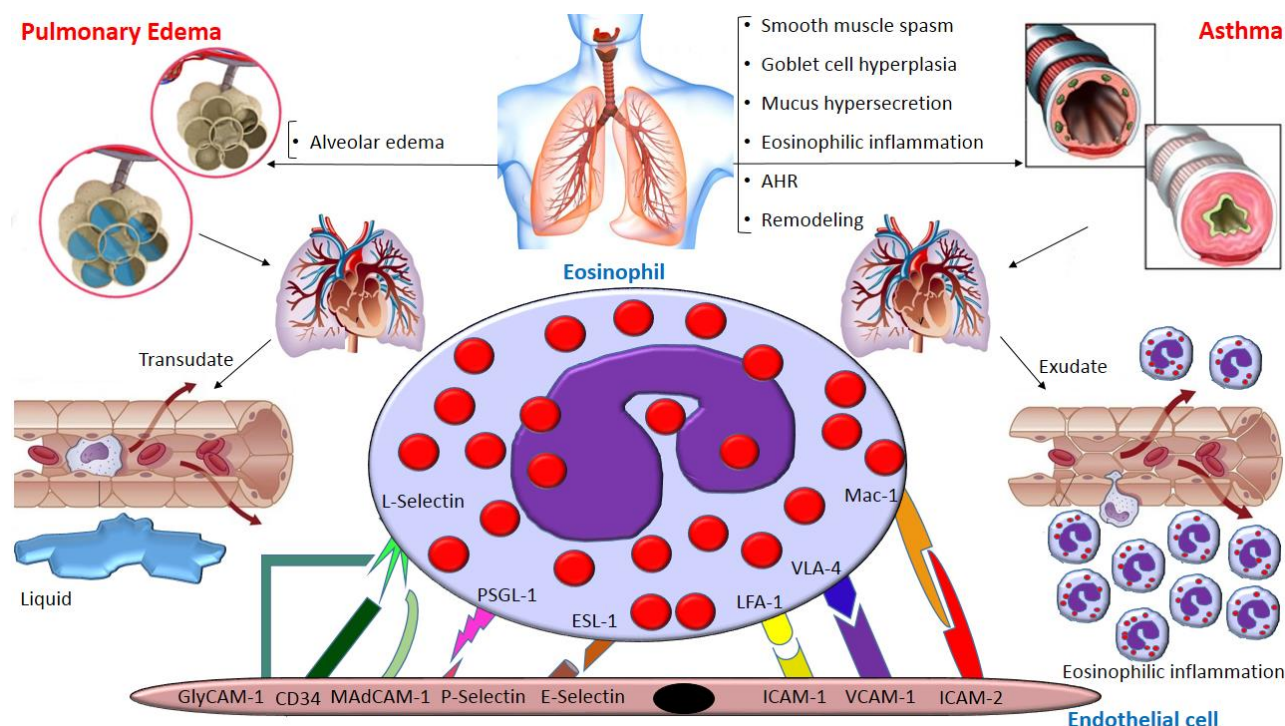


Figure 1. Allergic asthma and pulmonary edema. In edema, alveolars are filled with liquid (transudate) and not with cells; however, in asthma, alveolars are not involved and only airways can be affected by cells, mucus, and allergic-inflammatory mediators. Asthma is characterized by eosinophilic inflammation of the airway, perivascular smooth muscle spasm, goblet cell hyperplasia, mucus hyper-secretion, airway hyperresponsiveness (AHR), and at least remodeling. Interleukin 5 regulates eosinophils migration and the vessels of the airways highly have leaks for eosinophils migration. The adhesion molecules on the surface of the endothelial cells, selectins (i.e., E-selectin, P-selectin, cluster of differentiation [CD34], mucosal addressin cell adhesion molecule 1 [MAdCAM-1], glycosylation-dependent cell adhesion molecule 1 [GlyCAM-1]), and integrins (i.e., intracellular adhesion molecules [ICAM] 1 and 2 and vascular cell adhesion molecule 1 [VCAM-1]) have interaction with adhesion molecules on the surface of eosinophils, selectins (i.e., L-selectin, P-selectin glycoprotein ligand 1 [PSGL-1], and E-selectin ligand-1 [ESL-1]), and integrins (i.e., lymphocyte function-associated antigen 1 [LFA-1], very late antigen-4 [VLA-4], and macrophage-1 antigen [Mac-1]), which leads to eosinophil inflammation and severe asthma. Probably, there are unknown adhesion molecules or changes on the endothelium cells of the lung arteries.

Discussion

The results of studies showed that the rate of vascular leak in the airway capillaries can contribute to the development of asthma pathophysiology; however, this leak is for immune cells and immune cells (with adhesion molecules, chemotaxis factors, and cytokines collaboration) can transmigrate through endothelial cells and that process is known as transcellular transmigration. The epithelium of the airway produces vascular endothelial growth factor (VEGF) in response to allergen exposure and the number of blood vessels increases in the airway walls of asthmatic cases. The overexpression of VEGF in the airway epithelium increases angiogenesis, IL-13 secretion and mucous production, leukocyte infiltration, and smooth muscle hyperplasia (4, 13). Therefore, allergic inflammation can drive angiogenesis, and angiogenesis mediators can drive asthmatic inflammation with involving immune cells. This can initiate a vicious cycle.

In asthma, Th2 cytokines (i.e., IL-4, IL-5, and IL13) promote the expression of VEGF;

nevertheless, Th1 cytokines (especially interferon gamma) block this expression. In addition, IgE increases VEGF secretion by sensitized mast cells and basophils. On the other hand, eosinophils can directly promote angiogenesis through the secretion of proangiogenic mediators in inflamed airways (4, 14, 15). It is concluded that the strong interaction of endothelial cells with eosinophils promotes allergic immune response in asthma that leads to allergic airway inflammation and initiation of the remodeling paradigm of the airway.

Eosinophil adhesion molecules are upregulated in asthma and eosinophils in bronchial of asthmatic patients overexpress cell migration-related adhesion molecules, such as macrophage-1 antigen, LFA-1, and very late antigen-4. Blocking L-selectin and intracellular adhesion molecule-1 reduces the influx of inflammatory cells into the lung and decreases asthma severity. On the other hand, patients with asthma also demonstrate increased expression of VEGF in a similar way to chronic bronchitis patients.

Furthermore, vascular endothelial cadherin (VE-

cadherin; as an endothelial adhesion molecule) is an important factor in angiogenesis. Blocked VE-cadherin decreases angiogenesis, IgE production, and eosinophil infiltration in the airway of the asthmatic lung (16-19). The inflammation mechanism is different from edema and the clinical aspect of asthma is different from pulmonary edema. In cardiogenic or non-cardiogenic pulmonary edema, there is a leak of liquid; nonetheless, in asthma, cells, especially eosinophils, migrate from vessels and penetrate to the lung (peribronchial and bronchial).

The treatment of asthma is very difficult from edema and the control of cell migration needs to manipulate cell adhesion molecules. It is needed to pay more attention to lung endothelial adhesion molecules and interaction with eosinophil adhesion molecules for the development of new treatments for asthma.

Conclusion

The inflammation mechanism in asthma is different from pulmonary edema and the treatment of asthma is difficult from edema. For control of inflammation in asthma, manipulation of the cell adhesion molecules is needed. For development of new treatments for asthma, more attention to lung endothelial adhesion molecules is necessary.

Conflicts of interest

There is no Conflict of interest.

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