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ADHESION MOLECULES AND ALLERGIC RHINITIS

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Allergic rhinitis like the other allergen-induced disease is characterised by a mucosal inflammatory reaction in which the recruitment and activation of eosinophilis, basophils, neutrophils, lymphocytes and mast cells are observed within hours after allergen exposure (1). A number of cytokines and adhesion molecules play an integral role in this inflammatory immune response (2). In this review, the basic mechanism of inflammation and three important adhesion molecules families, such as selectins, integrins and immunoglobulins superfamily which are involved this inflammation will be discussed.

Inflammation

Inflammation is a uniform response to a variety of stimuli such as bacterial and viral infection, chemical or physical trauma, radiation, irritation by pathological metabolites, enzymes or tumour products or ischaemia followed by reperfusion. Inflammation is characterised by vasodilatation, increased blood flow, microvascular permeability and the recruitment of circulating leucocytes to the inflammatory site. Recent studies in understanding of inflammation have emphasised the importance of adhesion molecules between leucocytes and extracellular component of tissue (3).

The adhesion cascade for leukocyte endothelial adhesion consists of some sequetial steps:

1. The granulocyte does not interact with the endothelium in the absence of inflammation. Integrins, LFA-1 (Leukocyte function associated antigen-1) and Mac-1, are on granulocytes with their nonadhesive conformation. L-selectin and sialyl-Lewis x ligand for P-and E-selectin are also present on the granulocytes. Endothelial cells express intercellular adhesion molecule-2 (ICAM-2) and some ICAM-1 without any selectin or selectin ligand.

2. Initial inflammatory activation of endothelial cells resulting in a pro-inflammatory condition express P-selectin and a ligand for L-selectin within 1 to 5 minutes by the effect of some inflammatory mediators such as trombin or histamine. It initiates rolling step of granulocytes along the endothelium. At that time leukocyte integrins and immunoglobulin supergene family molecules stay in the resting state without any chances on their expression.

3. When a chemoattractant affects the granulocytes, the integrins change into their adhesive conformation and attach to endothelial ICAM-1 and ICAM-2. L selectin is shed from the leukocyte surface and the expression of Mac-1 and ICAM-1 are increased. The local activation of leukocyte causes into firm adhesion to endothelium. On cytokine stimulation, some changes observed on endothelial cells look like high endothelial venule in lymp-hoid organs and E selectin is expressed.

4. Leukocyte diapedesis between endothelial cells into extravascular tissue and following migration of leukocytes into subendothelial tissue are the last steps of adhesion cascade. This sequence quite similar for mononuclear cells but Mac-1 and ICAM-1 are replaced by VLA-4 (Very late antigen) and VCAM-1 (Vascular cell adhesion molecule) respectively (4-6).

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Selectins

The selectin family contains three members; L-selectin, E-selectin, P-selectin, with a common structure containing an N terminal lectin domain. L-selectin (Endothelial leukocyte adhesion molecule: ELAM-1, CD62L) is expressed on normal circulating leukocytes. Although it is recognised as a lymph node homing receptor, it has also been shown to participate in adhesion of leukocyte to endothelium and leukocyte rolling. L selectin deficiency cause of defect in the lmphocyte homing into secondary lymphoid tissue and in a reduction of neutrophil accumulation in acute inflammation site (7,8).

P-selectin (Platelet activation dependent granule to external membrane protein: PADGEM, CD62P) is stored in a granules of platelets and Weibel-palade bodies of endothelial cells and expressed on activated platelets and endothelium cells within 5 minutes after stimulation with thrombin, histamine or platelet activating factor (PAF). P-selectin is an important molecule of the first stage of adhesion cascade (4).

E selectin (CD62E) is not expressed under resting conditions but synthesised after cytokine stimulation such as Interleukin-1 (IL-1) and Tumour necrosis factor-a (TNF-a). On cultured human umbilical vein endothelial cells, E selectin expression reach a maximum at 4 hours and back to baseline level at 24 hours. The contribution of E selectin in vivo leukocyte adhesion, seemed to be unclear as far; however, a recent study which was done by Frenette et al (7) showed that the absence of P-and E-selectins severely affect leukocytes homeostasis in mice and make these animals susceptible to opportunistic bacterial infections. In human, the deficiency in the synt-hesis of fucosylated carbohydrates, ligand for the selectins, described as a leukocyte adhesion deficiency Tip 2 (LAD-2). This syndrome associated with recurrent bacterial infection, neutrophilia and development defects (9).

All selectins can bind to sialylated sugars such as sialyl-Lewis x, however novel ligands have been identified and accepted for selectins. These are glycoproteins and named as mucin-like molecules containing endothelial mucin (Glycosylation dependent cell adhesion molecule-1: GlyCAM, Mucosal addressin cell adhesion molecule: MAdCAM-1, CD34) and leukocyte mucin (PSGL-1) (6,10).

Integrins

The integrins are heterodimeric transmembrane molecules consisting of non-covalently bound a large a2 and a smaller b subunit with an extracellular ligand binding site and an intracellular part linked to the cytoskleton. A total 21 different integrin combination have been found up to now. This group is divided into subgroups accor-ding to the b subunit. The b2 integrins; LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18) and p 150, 95 (CD11c/CD18) are constitutively expressed on all circulating leukocytes but especially on peripheral blood lymp-hocytes (4).

The b1 integrins consist of 6 molecules: VLA (1-6) expressed on eosinophils, monocytes and certain subsets of lymphocytes and connective tissue cells. The b2 sub-family integrins are involved in the firm adhesion to endothelial cells of rolling leukocytes, in the transmigration of leukocytes through endothelium and in the migration and activation of leukocytes within the tissue (3,11). The syndrome of b2 integrin deficiency type 1 (LAD-1) underlined their clinical importance in the inflammatory conditions. This disease is manifested by recurrent bacterial and fungal infections without pus formation, and granulocyte recruitment in response to local bacterial infection and deficiency in wound healing (12).

Immunoglobulin Supergene Family

These family is the largest family with the five endothelial adhesion molecules called ICAM-1 (CD54), ICAM-2 (CD102), ICAM-3 (CD50), VCAM-1 (CD106) and MAdCAM-1, Platelet endothelial cell adhesion molecule-1 (PECAM-1) (CD31). The first three molecules of Ig supergene family are counter receptor for the β2 integrin LFA-1. ICAM-1 is constitutively expressed at low levels on the vascular endothelium in a number of tissue sites such as the skin, kidney, liver, thymus, tonsil, lymph nodes, airway and intestine but in the same time it can be expressed on mast cells, macrophages, reticular cells, dendritic cells and occasionally on peripheral blood leukocytes.

Tablo 1. Endothelial-leukocyte adhesion molecules

Family	Receptor	Ligand	Distribution
Integrins	LFA-1	ICAM-1/2/3	All leukocytes
	Mac-1	ICAM-1	Monocytes, granulocytes, NK lymphocytes
	p.150.95	C3bl, others	Monocytes, granulocytes, macrophages
Immunoglobulin gene superfamily	ICAM-1	LFA-1	Endothelium-constitutive, active
		Mac-1	Epithelium-tonsils, thymus, renal tub, respiratory tract, fibroblast, dendritic cells, leukocytes, mast cells
	ICAM-2	LFA-1	Endothelium, leukocytes
	ICAM-3	LFA-1	Leukocytes
	VCAM-1	VLA-4	Endothelium-activated, bone marrow stromal cells, kuppfer cells, renal epithelial cells
	MAdCAM-1	a4b7 integrin	Mucosal venules, Peyer's patch HEV, mesenteric lympnode
	PECAM	PECAM	Endothelium, leukocytes
Selectins	L-selectin	GlyCAM-1 MAdCAM-1	Leukocytes
	E-selectin	sialyl Lewis x	Endothelium-activated
	P-selectin	sialyl Lewis x	Endothelium-activated, Platelets-activated

Following the stimulation with lipopolysaccaride (LPS), TNF-a and IL-1, IFN-b, the increasing of ICAM-1 expression by endothelial cells start at 2-4 h, peak at 24 h and maintain at least 48 hours. In contrast to ICAM-1, ICAM-2 is also expressed in high levels on resting endothelial cells without showing any response to cytokine stimulation. ICAM-3 has been recently identified as a member of Ig superfamily. It has a similar structure to that of ICAM-1 and a high degree of expression on resting leukocytes. It seems to be related with leukocyte-leukocyte interactions as a ligand for LFA-1.

Vascular cell adhesion molecule-1 is not constitutively expressed on endothelium but like E-selectin and ICAM-1 it is upregulated by LPS, TNF, IL-1 and IL-4. VCAM-1 also expressed on a variety of cells including bone marrow stromal cells, kuppfer cells, renal epithelial cells. Endothelial VCAM-1 participates in the adlesion of lymphocytes, monocytes, NK cells, eosinophils and basophils with VLA-4 counter receptors on these leukocytes. After cytokine stimulation, VCAM expression upregulates within 2-4 h and this high level remains up to 72 h. Platelet endothelial cell adhesion molecule-1 is expressed by endothelial cells, neutrophils, monocytes, eosinophils and T cell subsets. Since its expression is maximal at cell-cell junction in endothelium, it appears to be involved in the migration of neutrophil and monocytes through the endothelium.

MAdCAM-1 is a also a member of the vascular mucin family. It participates in lymphocyte emigration as a ligand both for a4b7 and L selectin binding via its expression on high endothelial venules of mucosal vasculatures (4,5,8,111,13,14). Three groups of adhesion mo-lecules were shown in Table 1.

Adhesion Molecules in Allergic Rhinitis

Although the responsible mechanisms are not completely understood, there has been a considerable increase in the prevalence of allergic rhinitis over the past three decades (15). A variety of inflammatory cells, such as lymphocytes, eosinophils, mast cells and neutrophils are involved the inflammation in allergic rhinitis (2).

In the sensitised individuals on the re-exposure to antigen via surface IgE, mast cells degranulate within minutes releasing multiple inflammatory mediators such as histamine and leukotriene. These mediators are res-ponsible of some nasal symptoms including sneezing, itching, rhinorrhea and congestion and treated with antihistamines and leukotriene receptor antagonists (16). In some individuals 3 to 11 hours after the early reaction, an inflammatory cell influx into the airways in rhinitis inclu-ding eosinophils, neutrophils, basophils and mononucleear cells do occur. Eosinophils and basophils are the two crucial inflammatory cells in allergic inflammation. Mediators derived from these cells deeply affect the pathophysiological mechanism of the allergic inflammation. Since there are some strong evidences which suggest that these cells selectively localised in the allergic inflammation sites, the responsible mechanisms of those cells recruitment have been getting a growing interest. It is generally accepted that leukocyte recruitment into tissue sites during allergic inflammation, involves a variety of adhesion mmolecules including an initial selectin-mediated tethering and rolling, followed by firm adhesion and diapedesis (17). In nasal biopsy taking from peren-nial allergic rhinitis patients, the expression of ICAM-1 and VCAM-1 but not E-selectin were more intense than nonallergic control subjects (18).

In the study by Lee et al (19), 24 hours after localised allergen challenge, baseline expression of ICAM-1 was observed in all mucosal specimens of inferior turbinates of patients with allergic rhinitis and nonallergic control subjects. Vascular cell adhesion molecule-1 expressed basally and was significantly upregulated by allergen challenge and weakly correlated with submucosal eosinophils in addition to minimal expression of E selectin. They suggest that activated endothelium with inc-reased VCAM-1 expression on it, may play a role via its counter ligand VLA-1, is present on eosinophils, in the eosinophil accumulations to the nasal mucosa. The inc-reased expression of VCAM-1 in allergic rhinitis can be related with local cytokines profiles, such as IL-4 and TNF-a which are released from degranulated mast cells and TH_2 lymphocytes in local inflammation site (2,8).

Saito et al (20) performed an immunohistological study on nasal mucosa of allergic and non-allergic rhinitis patients to examine the T cell profile and its association with the expression of ICAM-1. There were no diffe-rence in the number of CD8 positive cells and the intensity of ICAM-1 expression between the groups. The number CD4 and CD45RO positive cells were increased and accompanied with intense ICAM-1 expression in the lamina propria of allergic rhinitis patients.

Bachert et al (21) compared the expression of adhesion molecules in allergic nasal mucosa to biopsies from normal subjects. They found increased expression of ELAM-1, ICAM-1 and LFA-1 in nasal biopsies of allergic subjects than those of the control subjects. Although ICAM-1 was detected on endothelial epithelial and on mononuclear cells, ELAM-1 was only detected on vascular endothelium and LFA-1 on granulocytes and mononuclear cells. Their findings showed some consistency with the findings of Monteford et al (22). In that study, ICAM-1 VCAM-1 expression on endothelium cells were increased in perennial rhinitis with a significant correlation with LFA-1 and ICAM-1 positive cells, although ICAM-1 was prominent on the endothelium of the normal nasal mucosa with less expression of ELAM-1 and minimal expression of VCAM-1.

Wardlaw et al (23) investigated the expression of endothelial adhesion molecules in nasal polyps by using immunohistochemistry. Although ICAM-1, E-selectin and P-selectin were well expressed on vascular endothelium of polyps, VCAM-1 expression was weak or absent. By in vitro eosinophil adhesion to nasal polyp endothelium study they could not block eosinophil adhesion with mo-noclonal antibodies against ICAM-1, VCAM-1, E-selectin, L-selectin, VLA-4 and LFA-1 except an antibodies against Mac-1 and P-selectin. In conclusion they suggested that P-selectin was constitutively expressed on airway epithelium and played a role as an integral molecule of the initial step of eosinophil adhesion to vascular endothelium.

In addition to adhesion molecules, a various kind of cytokines and mediators seem to play an important role in the allergic inflammation within nasal mucosa. These proteins are released from nucleated cells showing a wide range of function including upregulation of adhesion molecules on vascular endothelium and their counter receptors on circulating cells, priming the cells to respond to chemotactic stimuli and augmentation of cell activation and eosinophil survive in the nasal mucosal site (2).

In two studies by Bachert et al (24,25) using ELISA assays significantly elevated baseline levels of IL-1b, IL-6 and IL-8 were found in nasal lavage of patients with seasonal allergic rhinitis compared with control subjects. In the second study, following the nasal allergen challenge, IL-1b and TNF are secreated within 2 h, although IL-6 and IL-8 are secreted within 6-8 h. In their previous study, they demonstrated the increased expression of the adhesion receceptors ELAM-1, ICAM-1 and LFA-1 in biopsy of allergic mucosa (25). Using fresh biopsy of nasal mucosa, they also showed that allergen, IL-1b and TNF had caused the strong and rapid induction of E-selectin on endothelial cells.

Terada et al (26) were able to show that the recombinant human IL-5 induced ICAM-1 gene expression in endothelial cells of the nasal mucosa of patients with allergic rhinitis by using gene expression quatification method. Interleukin-5 did not induce ICAM-1 m-RNA in endothelial cells from nasal mucosa of nonallergic rhinitis. They indicate that IL-5 can upregulate the expression of adhesion molecules in addition to its role as an eosinophil chemotactic factor. Terada et al (27), in their previous study, had reported basally expressed ICAM-1 mRNA in the nasal mucosa with an increase six hours after challenge. In the same study, serum level of soluble ICAM-1 in allergic rhinitis patients was significantly hig-her than that of the normal controls.

Mast cells, eosinophils and TH_2 lymphocytes in nasal biopsies of rhinitis patients have been shown to contain some cytokines such as, IL-4, IL-5, IL-6, TNF-a, and GM-CSF. Following nasal allergen challenge, it was found that the mucosa eosinophilia had accompanied to activated T lymphocytes (2).

Platelet activating factor, platelet factor 4, RANTES are low molecular weight cytokines and also named to chemokine family. Kakazu et al (28) reported that RANTES, which is released from trombin stimulated platelets and has chemotactic activity for eosinophils, augmented isolated human eosinophil adhesion to plates coated with recombinant soluble ICAM-1 without enhancing the expression of β2 integrin adhesion molecules.

Adhesion molecules, pro-inflammatory cytokines and mediators are obviously involved in inflammatory cell recruitment; activation and consequent expression of di-sease situation and symptoms of allergic patients. The downregulation or inhibition of these adhesion molecules or pro-inflammatory cytokines seem to attractive targets in the new therapeutic approaches to the allergic diseases.

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