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MINIREVIEW

Adhesion Molecules in Host Defense

AMOS ETZIONI*

Department of Pediatrics and Clinical Immunology, Rambam Medical Center, and the Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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INTRODUCTION

Knowledge of host defense mechanisms has greatly expanded during the last 15 years. In the early 1980s, the subsets of cells involved in the immune response were defined by using monoclonal antibodies. Subsequently, the soluble factors (mainly interleukins) produced by these cells were investigated. During the last 5 years, it was demonstrated that close contact between the cells plays a major role in eliciting host inflammatory responses. This contact is mediated through adhesion molecules which are expressed on the surface of the different cells. Their importance in many biological processes has been recently demonstrated (2, 26, 35). This minireview will focus on the adhesion molecules which are involved in neutrophil-endothelial cell interactions, which ultimately lead to migration of neutrophils to the site of inflammation.

Neutrophils are the front-line defense against most microbial pathogens (11). They provide a rapid, relatively nonspecific defense mechanism, after which a more long-lasting, antigen-specific response is established by B and T lymphocytes. The process of neutrophil localization is dynamic and involves multiple steps. The orchestration of these steps must be precisely regulated to ensure a rapid response to isolate and destroy the invading pathogen yet cause minimal damage to healthy tissues. Neutrophil interactions with vascular endothelial cells are of central importance in guiding the acute inflammatory response and are mediated by three adhesion molecule families: the integrins, the immunoglobulin (Ig) superfamily, and the selectins (20) (Table 1). They take part in the various steps of neutrophil adherence to and migration through the endothelial cell layer.

β_2 INTEGRINS

The leukocyte β_2 integrin family comprises three α/β heterodimer membrane glycoproteins with a common β subunit, designated CD18. The α subunits of each of the three members—lymphocyte function-associated antigen-1 (LFA-1), macrophage antigen-1 (MAC-1), and p150,95—are designated CD11a, CD11b, and CD11c, respectively. Both the α and β subunits have a relatively small cytoplasmic domain which contains regions capable of binding to cytoskeletal elements (15). The extracellular domain is much larger, and the amino-terminal portion of the β subunit, which contains the ligand-binding region, is folded into a loop which is stabilized by disulfide bonds (15). The α and β subunits are initially assembled in the cytoplasm, and only then is the complete β_2 integrin expressed extracellularly. Both subunits are required for expression, and if CD18 is absent, CD11 expression on the surface of the cells is not detected, although intracytoplasmic expression of the CD11 molecule is normal (36).

CD18 integrin expression is restricted to leukocytes. LFA-1 is expressed by lymphocytes, monocytes, and neutrophils. MAC-1 and p150,95 expression is restricted primarily to myeloid cells, although they are also expressed by some lymphocytes and natural killer cells. They have a broad role in many leukocyte adhesion-related functions in addition to migration through the endothelial cells, such as phagocytosis and killing of bacteria (20).

The expression and function of the various integrin molecules are precisely regulated. Activation of leukocytes by a variety of mediators (e.g., C5a, platelet activating factor, and interleukin-8) results in a transient increase in adhesion by CD11- and CD18-dependent mechanisms. This increased adhesive ability occurs through qualitative changes, transformation of LFA-1 into the active state, and quantitative changes in the expression of MAC-1 and p150,95 (6).

Integrins mediate adhesion through their ligands, the intracellular adhesion molecules (ICAMs) 1 and 2. ICAM-1 and -2 are expressed primarily on endothelial cells. This adhesion is regulated by the cytoplasmic domain of the β subunit of the β_2 integrins (10).

The most dramatic demonstration of the importance of the integrins in neutrophil localization to inflamed sites was the discovery of a group of patients who are genetically deficient in CD18 integrin expression because of defects in β subunit assembly (1). The hallmark of this disease, termed leukocyte adhesion deficiency I (LAD I), is the presence of recurrent, life-threatening bacterial infections and the lack of neutrophils in the infected lesion despite high levels of circulating neutrophils (14) (Table 2).

Since neutrophil-mediated tissue damage is prominent in ischemia-reperfusion type injuries as well as several other pathological conditions, anti-CD18 monoclonal antibodies were administered in various animal models, with marked improvement of the injured site (18, 24, 39). These studies confirm the importance of the integrin family in neutrophil adhesion.

Ig SUPERFAMILY—ICAMs

The ICAM family was originally functionally defined as LFA-1 ligands. This family includes three molecules, ICAM-1, -2, and -3. ICAM-1 has five Ig-like domains, with a short hinge region separating the third and fourth Ig-like domains (37). It is a ligand for both LFA-1 and MAC-1. The binding sites for LFA-1 and MAC-1 are distinct. LFA-1 binds to domains 1 and

* Mailing address: Department of Pediatrics, Rambam Medical Center, Haifa 31096, Israel. Phone: 972-4-522193. Fax: 972-4-515710.

TABLE 1. Adhesion molecules in leukocyte-endothelial cell interaction[a]

Molecule	Localization	Regulation	Ligand	Function
Integrins				
LFA-1 (CD11a/CD18)	Leukocyte	IL-1, TNF-α, IL-8, C5a, selectin binding	ICAM-1, ICAM-2	Cell-cell interaction, neutrophil adherence, migration
MAC-1 (CD11b/CD18)	Neutrophil, monocyte, natural killer cell	IL-1, TNF-α	ICAM-1	Cell-cell interaction, neutrophil adherence, migration
p150,95 (CD11c/CD18)	Neutrophil, monocyte, natural killer cell	?	?	Neutrophil adhesion
Ig superfamily				
ICAM-1	Endothelial cell, lymphocyte	IL-1, TNF-α	LFA-1, MAC-1	Neutrophil firm adhesion, transmigration
ICAM-2	Endothelial cell	Constitutively expressed	LFA-1	Neutrophil firm adhesion, transmigration
ICAM-3	Lymphocyte, neutrophil	Constitutively expressed	LFA-1	Cell-cell interaction
Selectins				
E-selectin	Endothelial cell	TNF-α, IL-1	SLeX, LeX	Neutrophil rolling
P-selectin	Lymphocyte, neutrophil	Histamine, thrombin	SLeX, LeX	Neutrophil rolling
L-selectin	Endothelial cell, platelet	Constitutively expressed	Carbohydrate?	Lymphocyte homing, neutrophil rolling

[a] IL-1, interleukin-1; TNF-α, tumor necrosis factor alpha.

2, while MAC-1 binds to domain 3 (10). ICAM-3 is defined functionally only, and its primary structure and its receptor site for LFA-1 are still unclear. ICAM-3 plays an important role in the generation of the immune response (8).

The distribution and regulation of the ICAM molecules are quite distinct. ICAM-1 is expressed only at low levels on some vascular endothelial cells and on lymphocytes. Several hours after activation with various cytokines, such as interleukin-1, tumor necrosis factor, and gamma interferon, ICAM-1 is expressed in abundance on vascular endothelium as well as on lymphocytes. This increased expression lasts for up to 48 h (31). Soluble ICAM-1 can also be detected in the circulation, even in healthy individuals, and its physiological significance is still unknown (32). ICAM-2 expression, in contrast to that of ICAM-1, is constitutive, is restricted to endothelial cells and mononuclear leukocytes, and is not regulated by the various cytokines. ICAM-3 is restricted to monocytes, lymphocytes, and granulocytes (25). As a counterreceptor to the integrin family, the ICAM molecules play an important role in guiding leukocyte adhesion to and migration through the endothelial cells. Pretreatment of endothelial cells with ICAM-1 antibodies reduced the adhesion of neutrophils by 50%, whereas the reduction in migration across the cytokine-stimulated endothelial cells was 85% (33). The same results were obtained when anti-CD18 antibodies were used. Recently, several animal studies have shown the beneficial effects of anti-ICAM-1 antibodies in various pathological situations such as kidney disorders (7, 18).

TABLE 2. Comparison of leukocyte adhesion deficiencies

Parameter	LAD I patients	LAD II patients
Clinical manifestations		
Recurrent severe infection	+++	+
Neutrophilia	+++	+++
Gingivitis	++	++
Skin infection	++	++
Delayed separation of umbilical cord	Yes	No
Developmental abnormalities	No	Yes
Laboratory findings		
CD18 expression	Greatly decreased	Normal
SLeX expression	Normal	Greatly decreased
Neutrophil motility	Greatly decreased	Greatly decreased
Neutrophil adherence	Greatly decreased	Greatly decreased
Neutrophil rolling	Normal	Greatly decreased
Phagocytic activity	Decreased	Normal
T- and B-cell function	Decreased	Normal

SELECTINS

This new family of adhesion molecules was discovered in 1989, when the cDNA sequences of three cell surface glycoproteins found on endothelium (E-selectin), platelets (P-selectin), and lymphocytes (L-selectin) were reported (3). These molecules were previously called ELAM-1, PADGEM or GMP-140, and MEL-14, respectively. All three members of the selectin family have common structural features, most prominently an N-terminal lectin-like domain, which is central to the carbohydrate-binding properties of all three selectins. The lectin domain is followed by a domain homologous to the epidermal growth factor and a discrete number of molecules similar to those found in certain complement-binding proteins (28). The term selectin was proposed to highlight the amino-terminal lectin domain and to indicate the selective function and expression of these molecules.

All three selectins are involved in the recruitment of neutrophils to sites of tissue injury, but there are fundamental differences in their distribution, activation, and mode of expression.

E-selectin is expressed on endothelial cells only, and its expression is induced when the cells are activated by interleukin-1 or tumor necrosis factor alpha. These substances activate the transcription of E-selectin, resulting in peak cell surface expression at 4 to 6 h, decreasing to basal levels by 24 h (4). Although E-selectin expression is typically transient, it is chronically expressed in certain inflammatory conditions and is also detected in the serum (27).

P-selectin is expressed on platelets as well as on endothelial cells. Its expression does not require de novo synthesis because it is stored in secretory granules (Weibel-Palade bodies). Thus, within minutes of activation of either cell type by thrombin or

histamine, P-selectin is rapidly redistributed to the surface of the cells. Its expression is very short-lived, up to 15 min (13).

In contrast to the E- and P-selectins, L-selectin is constitutively expressed on some lymphocytes and neutrophils. After a transient increase in the level of this selectin after activation of leukocytes, it is shed rapidly (19). Thus, the activity of the selectins is controlled in large part by regulation of their appearance and disappearance from the cell surface. While L-selectin has a role in guiding lymphocytes to peripheral lymph nodes, all three selectins have a major role in neutrophil adherence to endothelial cells, which is mediated through binding to their ligand on the neutrophil. The ligand is a carbohydrate group which is typically found as a terminal structure of one or more glycoproteins and/or glycolipids. The lectin and the epidermal growth factor domains in the selectins play a crucial role in mediating binding to the carbohydrate. Several studies using different approaches have revealed that the ligand is a member of a class of sialylated and fucosylated structures related to the sialylated Lewis X blood group antigen (SLeX) (21). Monoclonal antibodies against SLeX block the binding of neutrophils to activated endothelial cells. Furthermore, cell lines which do not express this ligand show no binding, but after induction of SLeX by transfection, binding is observed (29). The most direct proof for the role of SLeX in neutrophil binding was obtained in studies of LAD II patients (Table 2). These patients presented clinically with a moderate form of LAD I (CD18 deficiency) but were found to lack SLeX on their neutrophils (12). Their neutrophils do not bind to activated endothelial cells or purified E- or P-selectin. The inability to express SLeX is due to a general defect in fucose metabolism in these children. In vivo comparison of LAD I and LAD II neutrophils revealed that LAD I cells had the ability to roll on endothelial cells but did not adhere to or migrate through them, whereas the opposite occurred with LAD II cells (40). This study demonstrates the specific in vivo role of the various adhesion molecules in the several steps which were proposed for neutrophil recruitment from the bloodstream to the site of inflammation.

THE ADHESION CASCADE

The recruitment of leukocytes from the blood is one of the most dramatic cellular responses to tissue damage and inflammation and is central to the physiological trafficking of the leukocytes. Recent studies revealed that the migration of neutrophils from the bloodstream to the tissue takes place in several steps (5). First, adhesion is loose and causes the cells to roll on the endothelial cell. This is a transient and reversible step but is a prerequisite for the next step, activation of neutrophils; only then do firm adhesion and migration occur. Each of these steps involves different adhesion molecules, and thus the process can be controlled at any one of the three steps.

Step 1: rolling, selectin dependent. Neutrophils in the circulation must resist tremendous shear forces in order to stop along the vascular endothelium. Indeed, under normal conditions, neutrophils move rapidly and do not adhere to the endothelium. The phenomenon of neutrophil rolling has been known for more than a century, but its physiology was delineated only very recently. Several elegant studies (23, 41) have shown that although anti-CD18 antibodies will not block rolling, anti-L-, P-, or E-selectin antibodies will completely block the rolling process. During tissue injury or an inflammatory process, several cytokines activate the endothelial cells to express P- and E-selectins. P-selectin is expressed in a few minutes, whereas E-selectin is expressed later, for up to 24 h. They bind to SLeX, which is expressed on the neutrophil. The presentation of the SLeX to the E- and P-selectins is mediated through L-selectin, which is expressed constitutively on the leukocytes. The preferential localization of L-selectin on microvillous processes in the leukocyte, structures previously demonstrated to mediate the initial contact between leukocyte and endothelial membrane, is consistent with the proposed role of this molecule in the rolling process (30). The rolling process is transient because L-selectin is shed quickly from the leukocytes. Furthermore, at the site of inflammation, free SLeX produced by hepatocytes and bound to glycans appears and competes for binding to the selectins (9).

Step 2: activation, integrins. The transition from selectin-mediated adhesion to CD18-mediated adhesion occurs rapidly and involves the activation of CD18. Various mediators, mainly interleukin-1 and -8 and tumor necrosis factor alpha, can upregulate CD18 expression. During rolling, the slowly moving neutrophils are exposed to these mediators, which are present at the site of inflammation and of activated endothelial cells. The molecular interaction of E-selectin with the leukocyte cell surface ligand stimulates integrin function (22). This increased adhesive capacity occurs through both qualitative (conformational) and quantitative (upregulation of surface expression) changes in the integrin molecules.

Step 3: firm adhesion plus migration, integrins with ICAM. The CD18 integrins undergo a confirmational change after activation which results in increased affinity for their ligands, ICAM-1 and -2, on the endothelial cells. This event ensures that binding is firm enough to withstand the continuous shear forces in the blood vessels. At the same time, the expression of ICAM-1 increases markedly, strengthening the adhesion (31). Furthermore, the activated neutrophils show increased adhesiveness for each other because of the expression of the various adhesion molecules, resulting in neutrophil aggregation, which presumably helps to slow blood flow and allow further neutrophil accumulation. In vitro (33) as well as in vivo (41) studies showed that monoclonal antibodies against both integrin and ICAM block the adhesion of leukocytes to endothelial cells. Neutrophils from patients with LAD I, who lack the CD18 molecule, do not adhere to endothelial cells (14). The final event, the transendothelial migration of the neutrophils to the site of inflammation, is also dependent on CD18-ICAM interaction. Monoclonal antibodies against these molecules prevent neutrophil migration (33).

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