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Leukocyte adhesion - a fundamental process in leukocyte physiology

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Abstract

Leukocyte adhesion is of pivotal functional importance. The adhesion involves several different adhesion molecules, the most important of which are the leukocyte ß$_2$-integrins (CD11/CD18), the intercellular adhesion molecules, and the selectins. We and others have extensively studied the specificity and binding sites in the integrins and the intercellular adhesion molecules for their receptors and ligands. The integrins have to become activated to exert their functions but the possible mechanisms of activation remain poorly understood. Importantly, a few novel intercellular adhesion molecules have been recently described, which seem to function only in specific tissues. Furthermore, it is becoming increasingly apparent that changes in integrins and intercellular adhesion molecules are associated with a number of acute and chronic diseases.

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Introduction

Most leukocyte functions depend on adhesion. These include cytotoxicity by T lymphocytes and natural killer (NK) cells, immunoglobulin synthesis by B lymphocytes, phagocytosis and chemotaxis by granulocytes and macrophages and homing to lymphoid organs (1-7). It is furthermore essential that adhesion-dependent functions are strictly regulated, otherwise chaos would develop *in vivo*.

A number of adhesion molecules are needed and they must often cooperate to function properly. The most important for leukocytes are the carbohydrate-binding selectins, the CD11/CD18 or ß$_2$-integrins, and the intercellular adhesion molecules (ICAMs) (1,6,7). These molecular families include several members and a certain redundancy is evidently important. Thus, an individual leukocyte always contains more than one adhesion molecule belonging to a certain family.

Absence or defective ß$_2$-integrins are known to result in the hereditary disease, leukocyte adhesion deficiency type 1 (LAD1). Patients affected by this disease suffer from life-threatening infections due to defective granulocytes and macrophages and the inability to produce immunoglobulins (8,9). Impaired synthesis of selectin ligands due to malfunction of specific glycosyl transferases results in leukocyte adhesion deficiency type 2. Although this is a milder disease, infections are also common.

More important, however, is the fact that in several common diseases affecting man-

kind, adhesion is partially defective. Therefore, much effort is currently focused on the elucidation of how the adhesion molecules function at the molecular level. A detailed understanding may certainly facilitate the development of drugs, which would target adhesion.

In this short review we discuss the structures of adhesion molecules, how they may be regulated and the potential applications of adhesion-related drugs.

Selectins are needed for the initial interaction between leukocytes and endothelial cells

Currently three members of the selectin family are known (10). These are E-selectin, P-selectin and L-selectin (Figure 1A). E-selectin is often induced on endothelial cells, P-selectin is found in platelets and endothelial cells and L-selectin is leukocyte-specific. They are carbohydrate-binding lectins which recognize sialyl Le^x, sialyl Le^a and similar sugars (Figure 1B). L-selectin also binds to sulfated structures including sulfatide glycolipids (11). Their function is regulated in two major ways: 1) induced expression of the selectins themselves or 2) induced expression (synthesis) of their ligands.

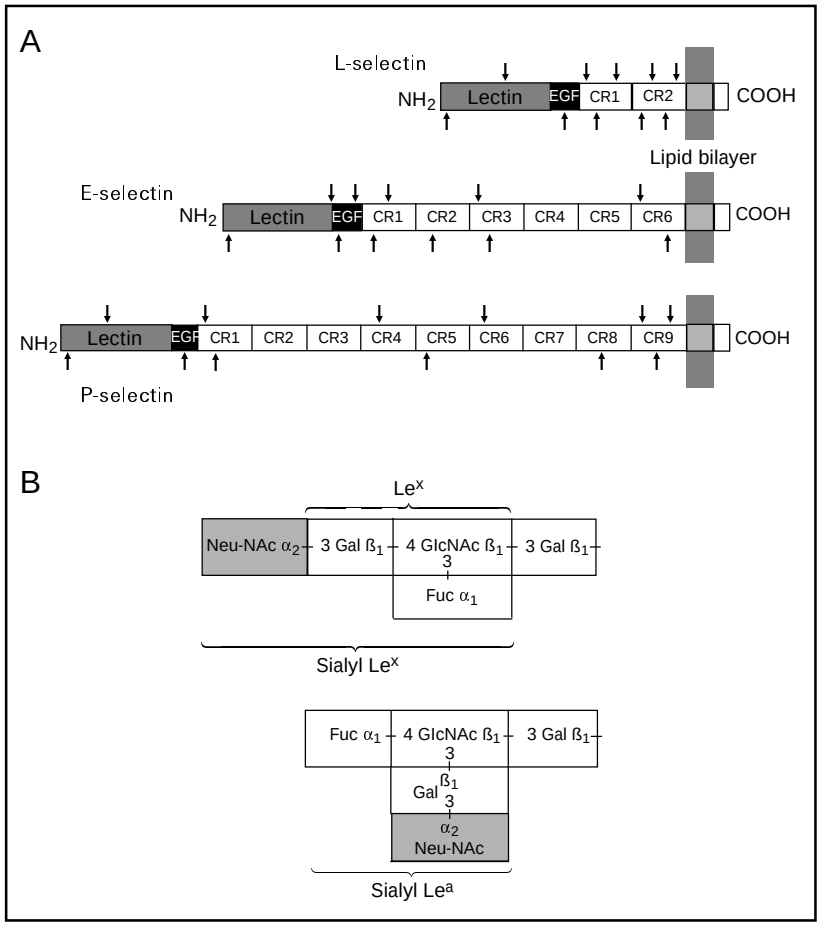

Figure 1 - Selectins and selectin ligands. *A*, Schematic structures of selectins. The lectin domains are at the NH_2-termini, followed by epidermal growth factor domains (EGF) and complement consensus repeats. *B*, Structures of the sialyl Le^x and sialyl Le^a ligands.

Endothelial cells contain low amounts of selectins in their resting state. When activated by cytokines P-selectin is rapidly translocated from intracellular Weibel-Palade bodies to the cell surface. This occurs in minutes and no protein synthesis is needed. The expression of E-selectin peaks later, approximately at 4-6 h and depends on new protein synthesis. L-selectin is present on different types of leukocytes and is easily shed from the cell surface upon activation, evidently due to cell surface proteolysis.

An increased expression of selectin ligands (sialyl Le^x, etc.) occurs in activated tissues, for example during transplantation rejection (12). In this way leukocyte adhesion may be increased.

The selectins induce "rolling" of leukocytes along the vessel walls. This means that due to relatively weak interactions, the leukocytes (mainly neutrophils) do not become firmly attached, but slowly move along the activated endothelial cell surfaces. This is, however, an important event during which integrins become activated resulting in firm adhesion.

The leukocyte CD11/CD18 integrins

A schematic structure of a leukocyte CD11/CD18 ($ß_2$) integrin is shown in Figure 2. Four $ß_2$-integrins are currently known. They are composed of a common $ß_2$-chain (CD18) forming heterodimers with four dif-

ferent α-chains (CD11). CD11a/CD18 (LFA-1, $\alpha_L\beta_2$) is primarily expressed on lymphocytes, CD11b/CD18 (Mac-1, $\alpha_M\beta_2$) on granulocytes and monocytes, whereas CD11c/CD18 and CD11d/CD18 are mainly expressed on monocytes/macrophages.

The integrins are glycoproteins containing a complex mixture of N-glycosidic oligosaccharides (13). There is no evidence for O-glycosylation. A large proportion (38%) of the oligosaccharides are high mannose-type oligosaccharides, which bind for example *E. coli* bacteria (14). Interestingly, the complex oligosaccharides contain large amounts of the sialyl Le^x epitope, and the integrins bind in fact E-selectin *in vitro* (15).

The α-chains contain an I (intervening) or A-domain, and this region is known to bind the ICAM-ligands. The I-domains from CD11b and CD11a have been crystallized and their structures determined (16,17). They form a metal ion-dependent adhesive site (MIDAS). An Mg^{2+}-ion is bound to the I-domain with one coordination site left free, and this may be utilized in ligand binding. It has been proposed that the I-domain sits on top of a "ß-propeller" structure formed by seven "feet" (18). This structural prediction is based on the homology with structurally known G-proteins.

Divalent cations are needed for integrin activity. Thus, EDTA inhibits their function. Mg^{2+} is probably essential, but can be replaced by Mn^{2+}, which shows a stronger activation ability (19). The role of Ca^{2+} is more controversial. In some systems it is inhibitory, but it may also be important in integrin clustering in the plane of the membrane and in this way increasing the avidity of integrin interactions.

One of the most important but also still poorly understood questions is how integrins are activated. This topic has recently been extensively discussed (6). Most probably there exist two major routes of activation, one from the outside of the membrane and one from the inside. Several monoclonal antibodies are known, which react with the β_2-integrins and activate them. We have found a peptide, derived from the ligand ICAM-2, which binds to CD11a/CD18 and CD11b/CD18 and strongly activates these integrins (20,21). How this happens is not exactly known, but most probably it involves a conformational change in the integrins. Monoclonal antibodies to several other cell surface glycoproteins such as CD3, CD43, CD44 and CD45 may also activate the integrins. In these cases, the activation most probably involves intracellular signals, with final activation by inside-out activation.

Phorbol esters have long been known to be potent activators of leukocyte integrins (22). Their cellular receptor is protein kinase C, a Ca^{2+}-dependent serine/threonine protein kinase. Several groups have therefore studied the possible phosphorylation of integrins. By labeling with ^{32}P-phosphate it became obvious that the α-chains are constitutively phosphorylated, whereas the ß-chain is phosphorylated only upon activation (23-26). The major phosphorylated amino acid was found to be serine-756 (Figure 3). However, when this amino acid was mutated, no effect on adhesion was observed (27). If, however, the threonine residues at positions 758-760 were mutated, all adhesion was abrogated. Although no clear phosphorylation of these residues had been observed, we then found that in the presence of the phosphatase inhibitor, okadaic acid, in fact a strong threo-

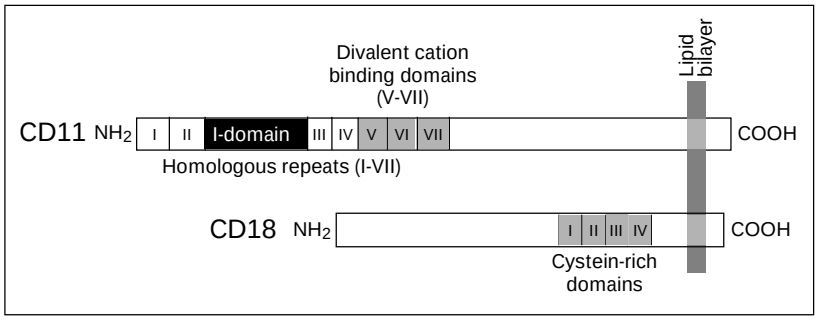

Figure 2 - Schematic structure of a leukocyte CD11/CD18 integrin. The α-chains (CD11) contain 7 homologous repeats and the important binding domain (I). The ß-chain (CD18) contains a cysteine-rich region, which may be important for the stabilization of the polypeptide.

nine phosphorylation was seen (28). Evidently, in activated cells there is a continuous rapid threonine phosphorylation/dephosphorylation cycle, which is not easily observed because of strong phosphatase activity. Importantly, threonine phosphorylation was also seen after stimulation of the T cell receptor using anti-CD3 antibodies (28).

Our recent experiments now show that phosphorylation increases the binding of integrins to the cytoskeleton (Valmu L, Fagerholm S, Suila H and Gahmberg CG, unpublished results). An attractive hypothesis is that the lateral mobility of membrane proteins is increased by phosphorylation (29), resulting in clustering of the integrins and increased avidity for their ligands.

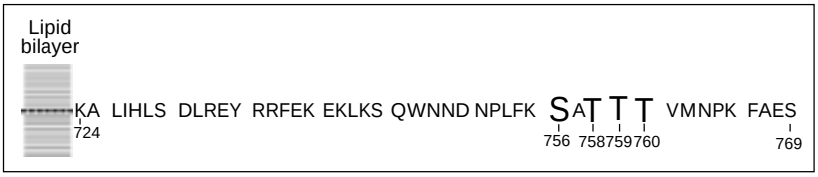

Figure 3 - The cytoplasmic region of CD18. The major phosphorylation site is serine-756, but the three consecutive threonines are functionally important and partially phosphorylated.

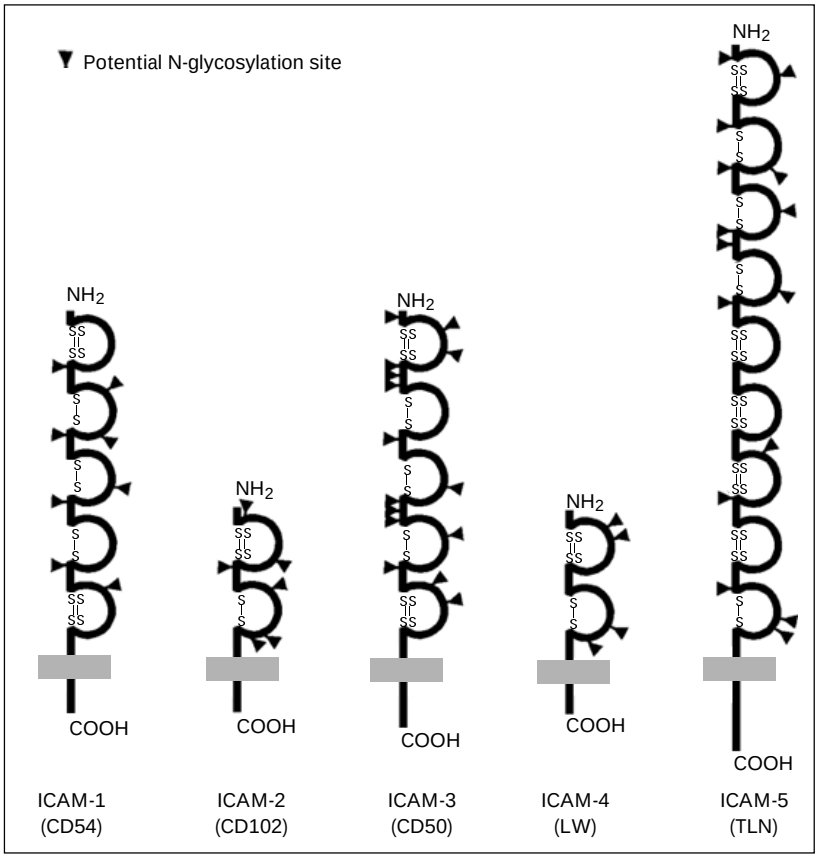

Figure 4 - The ICAMs schematically shown. The CD-names and previous names (LW = Landsteiner-Wiener and TLN = telencephalin) are indicated.

The intercellular adhesion molecules

The cellular ligands for the leukocyte integrins are the ICAMs. They are members of the immunoglobulin superfamily, which contain characteristic Ig-domains composed of two ß-sheets connected by conserved cysteines. Presently, five ICAMs have been described, ICAM-1-ICAM-5 (1,6,7,30-32). ICAM-1 and ICAM-3 contain five Ig-domains, whereas ICAM-2 and ICAM-4 contain only two. ICAM-5 (telencephalin) is unusually complex with its nine Ig-domains (Figure 4).

ICAM-1 (CD54) was the first to be described. It is present on leukocytes and endothelial cells, but it is also expressed in several other tissues. Characteristic is its easy induction by cytokines such as tumor necrosis factor-α, interferons, etc. It is probably the major ligand for integrins in most organs.

ICAM-2 (CD102) is also present on leukocytes and endothelial cells. It shows a more stable expression and is not easily induced (33). It can, however, be induced as seen in lymphomas (34). A major function of ICAM-2 may actually be its stimulatory action on leukocytes. Evidence for this has come from studies on a peptide from the first domain of ICAM-2. This peptide inhibits the binding between endothelial cells and integrins (20), but also shows a strong stimulatory activity on various leukocytes including NK cells. The cytotoxicity and migration of NK cells strongly increased after treatment with the peptide (21,35). A similar activity has also been observed with a soluble construct of the external portion of ICAM-2 (Kotovuori A, unpublished results).

ICAM-3 (CD50) was actually found

rather early, but only when it was cloned and sequenced did it become obvious that it could be an ICAM. It is strongly expressed on leukocytes, and again it may be that it is not most important as an adhesion molecule, but more as a signaling component. Interestingly, it binds well to CD11d/CD18 (36).

ICAM-4 has been known for a long time as the Landsteiner-Wiener (LW) blood group antigen. Initially LW was thought to be the same as the Rh-antigen but subsequent genetic and serological studies showed that this was not the case. It is red-cell specific. When it was cloned and sequenced it turned out that it had a clear homology with the then known ICAMs (37). Subsequently, it was shown to be able to bind to leukocyte integrins and an ICAM-4 antibody blocked the adhesion (30). Its physiological function(s) is still not known.

ICAM-5 is brain-specific. It was first characterized and named telencephalin, reflecting its distribution in brain. Also here, sequence analysis showed its homology to the ICAMs and later work showed that it is an ICAM (31,32). Thus, it is able to bind leukocytes through the $ß_2$-integrins, but whether it solely acts as a leukocyte-binding protein in brain is not known. In some of the ICAMs the integrin-binding domain and the adhesion sites have been mapped. CD11a/CD18 binds to all studied ICAMs and the first Ig-domain seems most important in integrin binding (6,7,38,39). CD11b/CD18, however, binds to the third Ig-domain in ICAMs and is thus different in this respect (40). It also binds to ICAM-2 and the ICAM-2-derived adhesion peptide, but the binding may be weaker than the binding to ICAM-1 (41).

Most ICAM genes are clustered on chromosome 19 p13-2, with the exception of the ICAM-2 gene, which is located on chromosome 17 q23-25 (6). This indicates that they have arisen from gene duplication.

The recent discoveries of ICAM-4 and ICAM-5 show that organ-specific ICAMs exist. It is anticipated that in the future more such ICAMs will be found.

Adhesion molecules evidently possess some general "stickiness", which makes them suitable to act as receptors for various microbes. ICAM-1 was found to act as a major rhinovirus receptor (38,42) and as receptor for *Plasmodium falciparum*-infected red cells (43). Interestingly, the binding site of rhinoviruses, which is in the first domain of ICAM-1, is different from that used by CD11a/CD18, although it is also located in the first Ig-domain. This fact is important when drugs are developed, which specifically could inhibit microbe attachment but not leukocyte adhesion. Otherwise, side effects would be a major problem.

Developments in the future

Obviously, when the interaction between integrins and ICAMs is known in molecular detail, it should facilitate the development of highly specific drugs, which can either interfere with or possibly enhance adhesion. Although peptides corresponding to adhesion or regulatory sites may prove useful for scientific studies, their clinical use will always be limited because they cannot be taken orally. Therefore, nonpeptide peptidomimetics will be more important. A major problem will then be how to avoid side effects, which may easily occur, because several physiologically important leukocyte functions may be wiped out. But the occurrence of several leukocyte integrins and many ICAMs makes it possible to specifically interfere with a limited number of receptor-ligand interactions. This would be especially important when treating chronic or relatively mild diseases. Acute life-threatening conditions could be treated with broader-acting drugs. Such severe diseases could for example be cardiac infarction, transplantation rejections and acute dangerous infections. For example, during cardiac infarction a major problem is the postischemic accumulation of neutro-

phils in the damaged cardiac tissue, which may result in further destruction of the tissue. Preliminary results using monoclonal antibodies to leukocyte integrins and ICAMs look promising (6,44).

In some instances it could be important to develop drugs which would enhance integrin/ICAM adhesion. The results with the ICAM-2 peptide P1 already show that such an approach could be useful (21,35). During infections it could be advantageous to increase integrin activity in order to increase the accumulation of leukocytes in infected tissues. An especially important field of application could be to enhance the activity of cytotoxic T lymphocytes and NK cells in patients with malignant diseases. Reagents are now becoming available which increase integrin activity, and certainly some of them could be developed to become clinically useful. But also here the necessary basic knowledge of the mechanisms of activation of leukocyte adhesion is very limited, which makes drug development difficult.

We think that during the years to come we will witness a rapid development in the clinical application of adhesion research, and it will be especially rewarding to be part of that effort.

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