CMLS, Cell. Mol. Life Sci. 54 (1998) 549–555
1420-682X/98/060549-07 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

Leukocyte integrins and inflammation

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Abstract. Leukocyte adhesion is of pivotal functional importance. Without adequate adhesion, T lymphocytes and natural killer cells are not cytotoxic, B cells cannot develop into antibody secreting plasma cells, leukocytes do not home into inflamed tissues and myeloid cells are not able to phagocytize or exhibit chemotactic responses. During evolution several leukocyte adhesion molecules have developed belonging to a few molecular families. Among these, the leukocyte-specific integrins (β_2 integrins, CD11/CD18 molecules) are among the most important. Much progress has taken place during the past few years, and at present we have a considerable knowledge of their structure and function. Inflammation is critically dependent on integrin activity, and its regulation forms the topic of this short review.

Key words. Integrin; leukocyte; ICAM; phosphorylation; inflammation.

Introduction

During inflammation leukocytes accumulate in affected tissues, resulting in characteristic inflammatory symptoms including pain, elevated temperature, and reddish and swollen tissues. In order to reach their destination, leukocytes have to accomplish several tasks: sense the presence of infecting microbes, or diseased areas, attach to endothelial cells lining the capillaries in the affected regions, penetrate between the endothelial cells out into the surrounding tissues and destroy the invading microbes.

In order to accomplish this, several molecular mechanisms have evolved comprising several members of different molecular cell adhesion families. Among these, the leukocyte integrins, notably the leukocyte-specific β_2 integrins (CD11/CD18)[1] [1–8], play a pivotal role. The β_2 integrins bind to intercellular adhesion molecules (ICAM) and to several soluble proteins, many of which are involved in inflammation.

It is important that, the leukocyte integrins are not constitutively active, but need activation to become adhesive. In spite of much effort, the mechanisms of activation are still poorly understood. At present, four β_2 integrins have been described, CD11a/CD18 (LFA-1, $\alpha_L\beta_2$), CD11b/CD18 (Mac-1, $\beta_M\beta_2$), CD11c/CD18 (p150/95, $\alpha_X\beta_2$) and CD11d/CD18 ($\alpha_D\beta_2$). Their pivotal importance is perhaps best evident from the fact that individuals lacking functional CD11/CD18, due to mutations in β_2 (CD18), develop the LAD I (leukocyte adhesion deficiency syndrome type I) syndrome. This syndrome is characterized by repeated infections [9]. Affected patients exhibit a number of leukocyte defects, which can be explained by malfunction of the β_2 integrins. In this review we do not deal with the β_1 integrins expressed on leukocytes (VLA-antigens) or the $\alpha_4\beta_7$ integrin, although they also are important under certain conditions.

CD11a/CD18 is primarily expressed on lymphoid cells, but to some extent on all leukocytes (table 1). CD11b/CD18 is enriched on cells of the myeloid lineage, whereas CD11c/CD18 and CD11d/CD18 are most strongly expressed on monocytes and macrophages. Individual cells often express several different types of integrins. They may partially overlap in function, and this is probably the reason why no human disease has been described with defects in individual α chains.

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Table 1. CD11/CD18 integrins.

	CD11a/CD18	CD11b/CD18	CD11c/CD18	CD11d/CD18
Cellular distribution	all leukocytes	mainly on myeloid cells, monocytes, macrophages	monocytes, macrophages	monocytes, macrophages
Ligands	ICAM-1, ICAM-2, ICAM-3, ICAM-4, ICAM-5	ICAM-1, ICAM-2, ICAM-3	ICAM-1 (probably) fibrinogen, iC3b	ICAM-3
Structure of I-domain determined	yes [10]	yes [11]	no	no
Number of N-glycosylation sites	12/6 (CD11a/CD18)	19/6	8/6	11/6

The cellular ligands for the leukocyte integrins are members of the immunoglobulin superfamily. In most cases they show a relatively restricted cellular distribution [8]. ICAM-1 (CD54) is present on leukocytes, endothelial cells and many other tissues, albeit normally at low expression levels. Characteristic of this molecule is its upregulation in activated cells and inflamed tissues. It is perhaps the most important integrin binding ligand [8]. Redundancy between various ICAMs is probably important. This is also evident from ICAM-1 gene knockout mice, which develop few if any symptoms [12, 13]. ICAM-2 (CD102) is expressed on leukocytes and endothelial cells [14–17]. Like ICAM-4, it contains only two immunoglobulin domains. It is relatively stably expressed, and is not induced by commonly used cytokines [17]. Its expression is, however, increased in lymphomas [18]. The reason for this is not known, but it may be due to the presence of specific unknown inducers or perhaps to suitable combinations of already characterized cytokines. ICAM-3 (CD50) shows similar behaviour [19]. It is present at relatively high concentrations on leukocytes, and it may have an important function in signal transduction [20–22]. Like ICAM-1 it contains five immunoglobulin domains. ICAM-4, first characterized as the blood group Landsteiner-Wiener (LW) antigen is exclusively expressed on red cells and their precursors [23]. It binds to CD11a/CD18 and CD11b/CD18 integrins [24]. Its physiological function is not known. Originally it was confused with the Rhesus (Rh) antigen, but this protein is very different in structure [25]. Actually, it may form a molecular complex with the Rh antigens, because rare individuals lacking Rh antigens (Rh_{null}) also lack ICAM-4. ICAM-5 (telencephalin) is exclusively confined to the brain, to the grey matter of the telencephalon [26]. It is a more complex molecule than the other ICAMS which have been described, containing nine immunoglobulin domains. It binds to CD11a/CD18 [27, 28]. It is not known whether it has a physiological function. One possibility is that it binds to leukocyte integrins on microglial cells, which are brain-specific macrophage-like cells.

During early phases of inflammation the selectins play an important role in adhesion. They are carbohydrate-binding lectins, which bind to sialyl Le^x and sialyl Le^a and related carbohydrate epitopes. Three selectins have been described: L-selectin, E-selectin and P-selectin [29]. L-selectin is confined to leukocytes, E-selectin to endothelial cells, and P-selectin is expressed on platelets and endothelial cells. L-selectin is constitutively expressed, but it is easily shed from the leukocyte surface upon activation. P-selectin is stored in endothelial intracellular Weibel-Palade granules, and it is translocated to the cell surface during early phases of inflammation. No protein synthesis is needed. E-selectin is induced by proinflammatory cytokines, and its synthesis is increased later during inflammation. Its expression peaks in 4 to 6 h.

An important fact is that the selectins can induce the 'rolling' of leukocytes along the vessel wall. This rolling is due to weak interactions between the selectins and their carbohydrate ligands. The β_1 integrin VLA-4 (very late antigen-4) may also induce rolling [30]. During the rolling phase, leukocyte integrins become activated, and subsequently bind to endothelial ICAM molecules. After this transient adhesion, integrin-mediated adhesion is weakened, and the cells are realised and migrate out between the endothelial cells into the tissues, after which they accumulate into infected or altered areas resulting in inflammation.

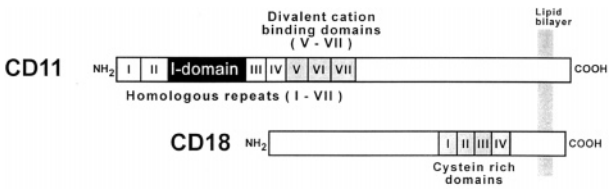

Figure 1. Schematic structure of a CD11/CD18 leukocyte integrin. The CD11 α chain contains the ligand-binding I-domain and divalent cation-binding domains. The CD18 β_2 chain is noncovalently associated with the α chain to form a functional complex.

Structure of leukocyte integrins

The leukocyte integrins are composed of specific α chains (CD11) and a common β_2 chain (CD18) (fig. 1). The α chains are coded for by genes clustered on chromosome 16, whereas the gene for CD18 is on chromosome 21 [31, 32]. The polypeptides are glycopolypeptides containing N- glycosidic carbohydrates, and the carbohydrate structures have been determined [33]. An important characteristic is that they contain an abundance (38%) of high mannose-type oligosaccharides and several different complex-type oligosaccharides. It is interesting that the complex-type oligosaccharides have sialyl Le^x-containing terminal structures, which are able to bind E-selectin [34]. There is no evidence for O-glycosylation.

The polypeptides are type 1 membrane proteins with their NH_2-terminals outside the cell, and the COOH-terminals in the cytoplasm. Divalent cations are needed for activity, and the α chains contain several external potential metal-binding sequences (fig. 1). About three Ca^{++}-ions have been found to bind to α chains [35], but Mg^{++} is evidently the physiological ion most important for activity [36]. The α chains contain an intervening I-domain (or A-domain) composed of about 200 amino acids, similar to the A-domain found in von Willebrand factor. A similar domain may be present in the β_2 chain. The I-domains from CD11b and CD11a have been crystallized, and their three-dimensional structures determined [10, 11]. They are formed by six β strands surrounded at the surface by seven α helices. An Mg^{++} ion is coordinated to two aspartic acids, two serines, one threonine and one glutamic acid from a second I-domain. A possible coordination site is Glu-34 in ICAM-1 and the corresponding residues in the other ICAMs. It is interesting that ICAM-4 contains an arginine residue in this position, which shows that glutamic acid residues are not essential here, although mutational analyses have indicated that they are important [8]. It has been proposed that the I-domain sits on the top of a β-propeller structure [37]. In this structural model seven peptide loops form the 'feet' of the structure, which is based on homology to G proteins.

The cytoplasmic portions of the integrins are functionally important. The α chains contain a conserved basic sequence near the membrane-spanning region, GFFKR (fig. 2). When this sequence is deleted, the integrins become constitutively active [38]. This finding indicates that the GFFKR sequence normally fixes the integrins in an inactive state, which is released upon activation. The α chains are constitutively phosphorylated, and the α chain phosphorylation does not seem to change upon activation [39]. Deletion of the β_2 chain abrogated leukocyte adhesion after activation by phorbol esters [40], which shows that it has an important role in adhesion (see below) (fig. 2).

The β_3 chain of the platelet integrin IIb/IIIa has been especially well studied, and several functionally important regions have been identified, including potential phosphorylation sites [41].

Activation of leukocyte integrins

As mentioned above, the leukocyte integrins are not constitutively active, but have to be activated in order for leukocytes to be able to adhere to target cells or to bind soluble ligands. A considerable amount of work has been performed in order to elucidate how adhesion is activated, and it has become evident that at least two major pathways of activation may exist: activation from the outside in, and reciprocally from inside out. Recent work indicates that fundamentally different mechanisms operate here. A combination of both pathways may also be a possible activation mechanism. Here ligands, which bind to nonintegrin cell surface glycoproteins, may first transduce signals to the cytoplasm, followed by inside-out activation.

Direct activation from the outside by ligand-integrin interaction

Integrins need divalent cations for activity, notably Mg^{++}, and this ion is probably able to alter conformation of leukocyte integrins as seen by using the monoclonal antibody (mAB)24. This antibody only binds to activated integrins [36]. We cannot, however, exclude

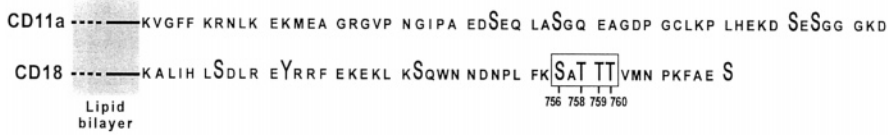

Figure 2. The cytoplasmic domains of CD11a/CD18. The cytoplasmic portion of CD11a and CD18 contain several potential phosphorylation sites (big letters). Probably the most important phosphorylation region in CD18 is boxed.

that the increased binding of this antibody could be due to integrin clustering or other gross changes. Mn^{++} was found to activate β_1 integrins [42], and this ion also strongly activates leukocyte β_2 integrins [43]. The mechanism is possibly due to structural changes in the I-domains [10].

Direct activation of integrins may take place through ligand binding, and this could be an important physiological mechanism of activation. We first observed that a 22-mer peptide from the first immunoglobulin domain of ICAM-2 strongly activated leukocyte aggregation, migration and cytotoxicity of natural killer cells [44] (fig. 3). This peptide binds both to CD11a/CD18 and CD11b/CD18 but apparently not to CD11c/CD18 [45]. Still, all three integrins become activated. How this takes place is not understood. The activation of CD11a/CD18 and CD11b/CD18 could be due to direct conformational changes induced by the ligand, but this cannot explain the activation of CD11c/CD18. With soluble ICAM-1 as ligand it was shown that the affinity of the integrins increased after peptide treatment (A. Kotovuori et al., unpublished observations). Soluble recombinant ICAM molecules were also able to activate the integrins, and it is interesting that ICAM-2 seems to be a more efficient activator than ICAM-1 or ICAM-3 [46].

Activation of integrins through ligand binding to nonintegrin surface molecules

mABs, which bind to various cell surface glycoproteins, have been shown to be able to activate leukocyte integrins. Such proteins include CD2, CD3 (T-cell receptor), CD19, CD40, CD43 (leukosialin) and CD44 [8]. The activation through CD3 has been particularly well studied. It involves tyrosine phosphorylation, but the pathway from CD3 to the integrins remains poorly understood. Phorbol esters most probably act through a similar mechanism but bypass some of the initial steps by activating protein kinase C directly.

Activation through protein kinase C must involve serine/threonine phosphorylation, and several groups have therefore studied integrin phosphorylation [39, 47–49]. The results show that the α chains are constitutively phosphorylated, whereas the β_2 chain is not. Only on leukocyte activation by phorbol esters did it become phosphorylated. The major phosphorylation site was shown to be Ser-756, and no or very weak threonine phosphorylation was observed [49] (fig. 2). However, when Ser-756 was mutated to cysteine, no effect on adhesion was observed. In contrast, mutation of threonines 758–760 strongly decreased adhesion. These findings were therefore difficult to correlate with phosphorylation [50].

Nevertheless, threonine phosphorylation actually occurs, but it is evidently transient and labile. In the presence of the Ser/Thr-phosphatase inhibitor okadaic acid, a strong threonine phosphorylation was indeed observed [50]. This was seen both by CD3 stimulation or by the use of phorbol esters. Evidently a phosphorylation/dephosphorylation cycle operates, which is not seen without phosphatase inhibition (fig. 4).

The threonine phosphorylation is most probably functionally important. We have recently synthesized several peptides from the cytoplasmic part of CD18 containing phosphate at various positions, and used the peptides to study interactions with cytoskeletal proteins (S. Fagerholm et al., unpublished observations). The results show that in T-cell lysates, threonine-phosphorylated peptides bind to the cytoskeletal protein talin. Because phorbol esters do not increase the affinity of integrins [45, 51] avidity changes must be essential for adhesion. An

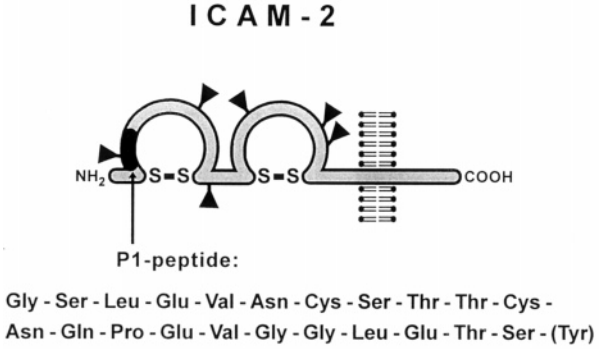

Figure 3. ICAM-2 and the location and sequence of peptide P1. The P1 peptide inhibits binding between endothelial cells and leukocyte integrins, but it is also able to strongly activate leukocyte-leukocyte adhesion and migration. It is derived from the first immunoglobulin domain of the ICAM-2 protein (marked in black).

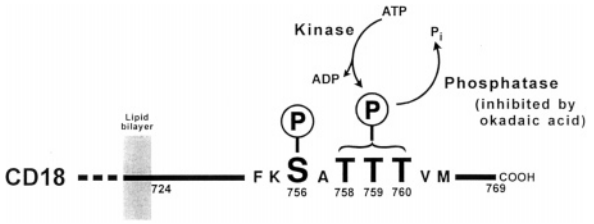

Figure 4. A proposed threonine phosphorylation cycle of CD18. Serine-756 is phosphorylated on CD3- or phorbol ester-induced activation, and the phosphorylation is relatively stable. The threonine phosphorylation is transient and is easily observed upon activation in the presence of the phosphatase inhibitor okadaic acid.

increase in avidity can be achieved by clustering the integrins in the plane of the membrane [8], and here talin could have an essential function.

Inhibition of inflammation could be beneficial in several diseases

Probably most human diseases involve inflammatory components. Often inflammation is necessary to successfully combat invading microorganisms, and in such cases it could be possible to increase the inflammatory response by using integrin-activating reagents such as the ICAM-2 peptide P1. Activation of natural killer cell cytotoxicity could also be advantageous in treating of malignant diseases [7].

However, in many cases of inflammation, both acute and chronic, inhibition of leukocyte accumulation and subsequent reactions would be advantageous for the patient. In principle, one could envision at least the use of the following types of reagents: (i) inhibitory mABs to adhesion molecules, (ii) competing ligands to adhesion molecules, and (iii) agents affecting adhesion acting at the inside of the cell. The latter group would include reagents involved in signal transduction.

mABs to leukocyte adhesion molecules and their ligands have been available for some time, and used either alone or in combination in several experimental disease models. Examples include kidney transplantation, the cardiac postperfusion syndrome, where leukocytes accumulate in the damaged tissue, rheumatic diseases, asthma and so on [7, 52–56]. The results are promising, but not definitive. In some instances only limited inhibition has been obtained. An obvious problem is that prolonged infusion of mABs would be expected to wipe out essential leukocyte functions, resulting in serious side-effects. The use of 'humanized' antibodies where large portions of the immunoglobulin molecules have been replaced by human immunoglobulin portions would circumvent the problem of development of antiantibodies.

Use of competing reagents to adhesion receptors and their ligands is of large potential interest. Such reagents could include soluble recombinant integrins or portions of them such as I-domains, or ICAMs and their derivatives, or various carbohydrates affecting selectin-mediated adhesion.

The use of reagents of relatively large molecular mass would have the advantage that they remain in the circulation for a relatively long time. Obvious disadvantages would be the fact that they have to be injected, and that they often are relatively difficult and expensive to prepare in pure form. Smaller derivatives such as peptides and oligosaccharides would probably be lost into the urine relatively rapidly. Potentially, active low molecular weight compounds could be polymerized or attached to larger carrier molecules. However, little has yet been done along these lines.

In the long run, peptide or carbohydrate mimetics seem most promising. The development of such compounds is still in its infancy, but the rapid development of structural analysis and computer-aided chemistry could result in important breakthroughs. Perhaps the development of selectin ligand mimetics has advanced most rapidly [57].

Low molecular weight reagents that would react intracellularly would be potentially very useful. As discussed above, integrin activation involves intracellular signaling and agents affecting the signaling systems would be expected to affect adhesion. At present, a large research effort is focused on the elucidation of integrin signalling and much useful information is accumulating. However, we are still just beginning to understand of these complex phenomena. Up to now no useful reagents of this type specifically affecting adhesion have become available.

Conclusion

Such a large research effort is now being focused on leukocyte integrins, their structure and activation that we may expect clinically useful applications during the coming few years. When we learn to regulate leukocyte integrin activity in a specific manner in different leukocytes, we should be able to apply the methods in clinical practice. This could profoundly affect the treatment of a variety of important diseases now affecting humankind.

Acknowledgements. The studies from the author's laboratory were supported by the Academy of Finland, the Sigrid Jusélius Foundation and the Finnish Cancer Society. We thank Yvonne Heinilä for secretarial assistance.

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