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Adhesion Molecules in Inflammatory Diseases

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Abstract

Cell adhesion molecules (CAM) have a key role in the inflammatory response. Selectins, integrins and immunoglobulin (Ig) gene superfamily adhesion receptors mediate the different steps of the migration of leucocytes from the bloodstream towards inflammatory foci. The activation of endothelial cells (EC) upregulates the expression of several CAM and triggers the interaction of these cells with leucocytes. Selectins are involved in the initial interactions (tethering/rolling) of leucocytes with activated endothelium, whereas integrins and Ig superfamily CAM mediate the firm adhesion of these cells and their subsequent extravasation. During rolling, leucocytes are activated through the intracellular signals generated by CAM and chemokine receptors. Blockade of the function or expression of CAM has emerged as a new therapeutic target in inflammatory diseases. Different drugs are able to interfere with cell adhesion phenomena. In addition, new antiadhesion therapeutic approaches (blocking monoclonal antibodies, soluble receptors, synthetic peptides, peptidomimetics, etc.) are currently in development.

1. Cell Adhesion Molecules Involved in Inflammation

Cell-to-cell interactions and the adhesion of cells to extracellular matrix components have a key role in important physiological phenomena as well as in the pathogenesis of diverse conditions such as tumour cell metastasis, graft rejection, ischaemia/reperfusion injury, immune-mediated hypersensitivity reactions and autoimmune diseases.[1-3] Many diseases are characterised by inflammation, a phenomenon that involves the accumulation of leucocytes in a given tissue leading to varying degrees of cell damage, extracellular matrix disruption and

organ dysfunction. The migration of leucocytes towards inflammatory foci and the interactions of inflammatory cells at these sites are mediated by cell adhesion molecules (CAM).[1,4] Although inflammation is primarily a defence mechanism, this phenomenon frequently becomes an undesirable condition that requires therapy. In this article we review the role of CAM in inflammation and the current status of antiadhesion therapy.

Adhesion molecules involved in inflammation belong mainly to the families of selectins, integrins and the immunoglobulin (Ig) gene superfamily (table I).[1-4] The selectin family comprises 3 members that are expressed by leucocytes (L-selectin or CD62L), platelets (P-selectin or CD62P) and endothelial cells (EC) [P- and E-selectin or CD62E].[5] Under conditions that induce cell activation, the basal expression of P- and E-selectin is increased, whereas that of L-selectin is downregulated.[4] Selectins interact with carbohydrate structures, mainly the sialylated and fucosylated forms of the Le^x (CD15) and Le^a tetrasaccharides, bound to protein cores.[6] The main counter-receptors for selectins that have been characterised so far are: glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) [mainly expressed by high endothelial venules (HEV)], the glycosylated and sulphated form of CD34 (expressed by EC), mucosal addressin cell adhesion molecule-1 (MadCAM-1) [expressed by HEV from Peyer patches and mesenteric lymph nodes], P-selectin glycoprotein ligand-1 (PSGL-1) [detected on granulocytes and activated T lymphocytes], and E-selectin ligand-1 (ESL-1) [expressed by leucocytes].[6,7] Selectins are able to mediate transient interactions between EC and leucocytes and participate in the rolling of the latter cells on the endothelium of postcapillary venules. Despite their short intracellular regions, selectins are able, after interaction with their counter-receptors, to generate costimulatory signals that contribute to leucocyte activation.[8,9] All selectins have an important role in the early events of the inflammatory response.

The CAM that belong to the Ig gene superfamily possess one or more domains homologous to those found in immunoglobulins.[1] Members of this superfamily are expressed by EC [e.g. MadCAM-1 and vascular cell adhesion molecule-1 (VCAM-1 or CD106)], or by both EC and leucocytes [e.g. intercellular adhesion molecules-1 and -2 (ICAM-1 and -2, or CD54 and CD102, respectively) and the platelet-endothelial cell adhesion molecule-1 (PECAM-1 or CD31)].[4] ICAM-1 and VCAM-1 are detected on activated EC, whereas ICAM-2 is expressed by both resting and activated EC.[4] Ig superfamily CAM may interact among themselves

Table I. Major cell adhesion molecules involved in inflammation.

Adhesion receptor	Family	Main ligands/counter-receptors	Expression in leucocytes and endothelium
L-selectin (LAM-1, CD62L)	Selectins	GlyCAM-1, CD34, MadCAM-1	Granulocytes, lymphocyte subsets, monocytes
E-selectin (ELAM-1, CD62E)	Selectins	ESL-1	Activated endothelial cells
P-selectin (PADGEM, CD62P)	Selectins	PSGL-1	Activated platelets and endothelial cells
VLA-4 ($\alpha4\beta1$, CD49d/CD29)	β1 integrins	VCAM-1, fibronectin, α4 integrin chain	Lymphocytes, monocytes, eosinophils
LFA-1 ($\alpha L\beta2$, CD11a/CD18)	β2 integrins	ICAM-1, -2, -3	All leucocytes
Mac-1 ($\alpha M\beta2$, CD11b/CD18)	β2 integrins	ICAM-1, iC3b	Myeloid cells, lymphocyte subsets
gpIIb/IIIa ($\alpha IIb\beta3$, CD41/CD61)	β3 integrins	Fibrinogen, von Willebrand factor, vitronectin	Platelets
$\alpha4\beta7$ integrin (CD49d/ ----)	β7 integrins	MadCAM-1, fibronectin, VCAM-1	Lymphocyte subsets
ICAM-1 (CD54)	Ig superfamily	LFA-1	Leucocytes, activated endothelial cells
ICAM-2 (CD102)	Ig superfamily	LFA-1	Leucocytes, endothelial cells
VCAM-1 (CD106)	Ig superfamily	VLA-4	Activated endothelial cells

ESL-1 = E-selectin ligand-1; **GlyCAM-1** = glycosylated-dependent cell adhesion molecule-1; **ICAM-1, -2** = intercellular adhesion molecule-1, -2; **Ig** = immunoglobulin; **LFA-1** = leucocyte function–associated antigen-1; **MadCAM-1** = mucosal addressin cell adhesion molecule-1; **PSGL-1** = P-selectin glycoprotein ligand-1; **VCAM-1** = vascular cell adhesion molecule-1; **VLA-4** = very late activation antigen-4.

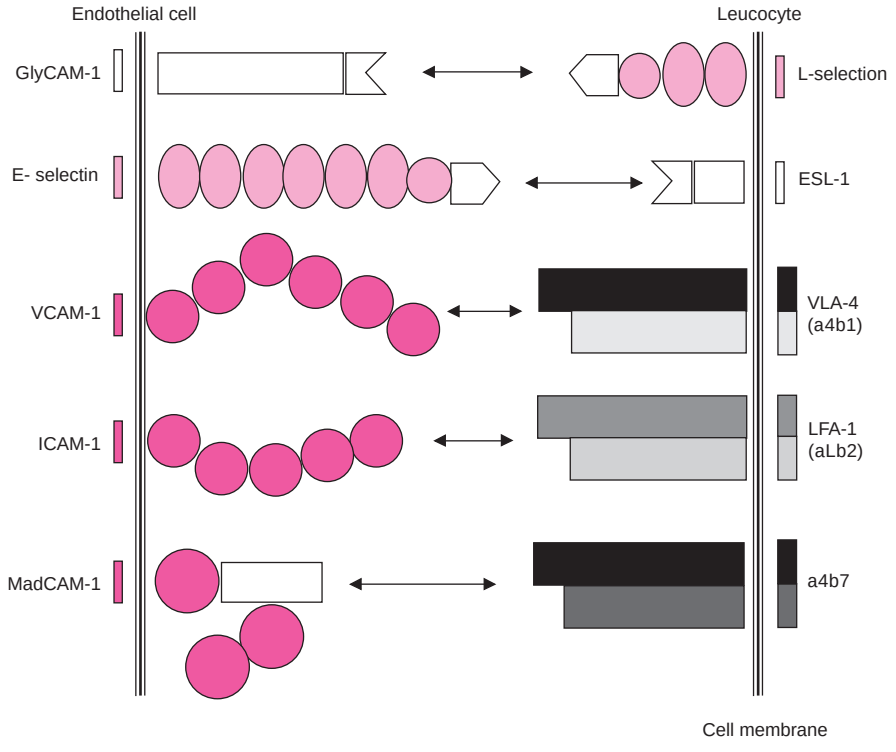

Fig. 1. Cell-to-cell interactions are mediated by cell surface transmembrane glycoproteins called adhesion receptors or adhesion molecules. Shown here are the interactions of several adhesion receptors that are expressed by endothelial cells and leucocytes and that have a key role in the extravasation of inflammatory cells. **ESL-1** = E-selectin ligand-1; **GlyCAM-1** = glycosylation-dependent cell adhesion molecule-1; **ICAM-1** = intercellular adhesion molecule-1; **LFA-1** = leucocyte function–associated antigen-1; **MadCAM-1** = mucosal addressin cell adhesion molecule-1; **VCAM-1** = vascular cell adhesion molecule-1; **VLA-4** = very late activation antigen-4.

in a heterotypic or homotypic fashion, or with CAM from the selectin and integrin families (fig. 1).

Integrins are heterodimeric transmembrane proteins that consist of non–covalently linked α and β chains.[10] Integrins that are involved in leucocyte-EC interactions and the inflammatory phenomenon belong mainly to the β1 and β2 subfamilies. The α4β1 heterodimer [very late activation antigen-4 (VLA-4) or CD49d/CD29] is expressed by lymphocytes, monocytes and eosinophils and interacts with VCAM-1, fibronectin (FN) and, homotypically, with other VLA-4 molecules.[11,12] The α4β1 integrin has an important role in leucocyte-EC interactions, whereas other β1 integrins are primarily involved in the adhesion of leucocytes to extracellular matrix components (laminin, collagen, vitronectin and FN).[10] The β2 integrin subfamily comprises the αLβ2 [leucocyte function–associated antigen-1(LFA-1) or CD11a/CD18], αMβ2 (Macrophage antigen-1; Mac-1) or CD11b/CD18), αXβ2 (GP150/95 or CD11c/CD18) and αDβ2 heterodimers.[10] LFA-1 is expressed by all leucocytes and interacts with ICAM-1, -2 and -3. The Mac-1 integrin, which interacts with ICAM-1, is stored in the intracellular granules of polymorphonuclear leucocytes and is translocated to the cell surface after cell activation. αXβ2 binds to fibrinogen and the complement fragment iC3b, whereas αDβ2 mainly interacts with ICAM-3. The β3 integrins (GPIIb/IIIa and αvβ3) are expressed mainly by

platelets and are involved in important phenomena (platelet aggregation, EC-platelet adhesion) that also occur in inflammatory conditions.[13,14] Finally, the β7 integrins (α4β7 and αEβ7) are mainly involved in the homing of lymphocytes to gut-associated lymphoid tissues.[10,11]

Integrins exhibit important functional features such as their ability to reversibly increase the avidity for their counter-receptors.[15] Under physiological conditions, the enhancement of integrin avidity (integrin activation) seems to be a consequence of intracellular signals that are generated through other cell surface receptors (inside-out signalling).[15] On the other hand, integrins are linked, through the cytoskeleton, to molecules involved in the generation of intracellular signals such as focal adhesion kinase or the PI-3-kinase.[16,17] Thus, the interaction of integrins with their ligands induces costimulatory signals that contribute to cell activation/differentiation (outside-in signalling).

There are additional intercellular adhesion molecules that also participate in the inflammatory phenomenon. Cadherins are calcium-dependent adhesion proteins that mainly interact homotypically with themselves.[18] Members of this superfamily are expressed by and are responsible for the integrity of endothelia and epithelia. Cadherins found at intercellular endothelial junctions (e.g. vascular endothelial cadherin; VE-cadherin and desmosomal cadherin) seem to have a key role in the extravasation of inflammatory cells (see section 2).[19] Lastly, other molecules mainly involved in signal transduction such as the chemokine/chemokine receptor fractalkine/CX_3CR1 may also function as cell adhesion receptors.[20]

2. The Inflammatory Phenomenon

The inflammatory phenomenon is a consequence of the release of soluble mediators that induce activation of EC. This activation results in the expression or enhancement of expression of several adhesion molecules such as P- and E-selectins, ICAM-1 and VCAM-1,[4] which promote the extravasation of leucocytes. In addition, EC activation induces the release of proinflammatory cytokines (mainly chemokines, see below by these cells as well as a diminution in their anticoagulant properties (mainly as consequence of an increased expression of the procoagulant, tissue factor).[21,22] Thus, EC activation favours the adhesion of leucocytes to endothelium as well as platelet activation and microthrombi formation.

The main cytokines involved in inflammation are tumour necrosis factor-α (TNFα), interleukin-1 (IL-1) and chemokines. Other soluble mediators such as C5a, platelet activating factor (PAF), prostaglandins, etc., also have an important role in the inflammatory phenomenon. The main stimuli for TNFα synthesis and release are bacterial lipopolysaccharides.[23] TNFα induces the activation of EC, which express several inducible CAM such as ICAM-1 and VCAM-1, and neutrophils;[24] in the latter cells it induces the translocation of Mac-1 to the cell surface as well as the loss of L-selectin expression through a proteolytic mechanism.[4,5] Through these effects, as well as others, this pleitropic cytokine exerts a pivotal role in diverse inflammatory conditions, including septic shock.[23] Most cells, including platelets and EC, are able to release chemokines in response to proinflammatory stimuli such as TNFα, IL-1, bacterial lipopolysaccharides or ischaemia.[21,25] Chemokines exert their effects as soluble or cell surface–bound molecules and induce activation/attraction of leucocytes as well as cell shape changes and integrin activation.[26,27] In addition, chemokines such as MCP-1 are able to induce the expression of tissue factor by both monocytes and blood vessel smooth muscle cells.[28,29] Different chemokines induce the activation and attraction of distinct leucocyte subsets.[21,25] For this reason, it has been proposed that the selective release of certain chemokines determines the composition of the inflammatory cell infiltrate.

The extravasation of leucocytes towards inflamed tissues is a phenomenon that involves several sequential steps (fig. 2).[1,3,4] The EC from postcapillary venules at the vicinity of an inflammatory focus are activated by the soluble mediators of inflammation, mainly TNFα and IL-1, released by the resident and infiltrating cells. The *de*

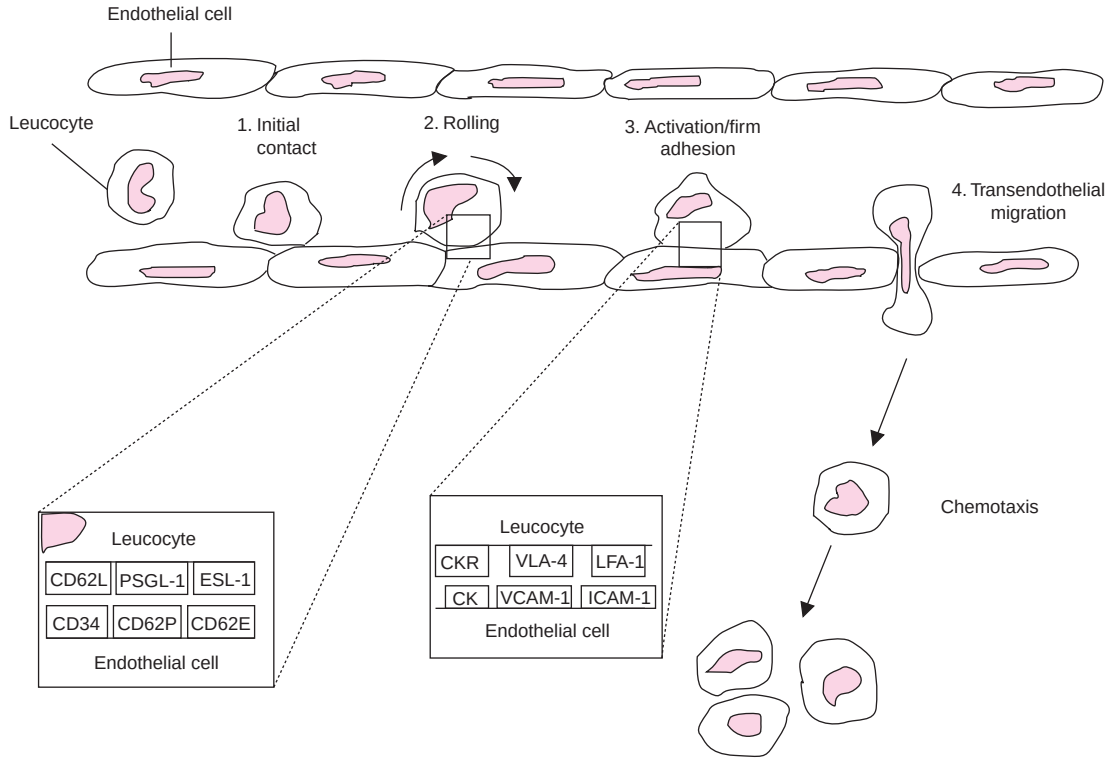

Fig. 2. Leucocyte-endothelial cell interactions during extravasation of leucocytes towards inflammatory foci. The initial contact and rolling of leucocytes on activated endothelium is mainly mediated by selectins. The activation of leucocytes takes place during rolling and is due to intracellular signals generated by selectins and chemokine receptors. The firm adhesion of leucocytes to endothelial cells and their subsequent extravasation is mainly mediated by integrins and adhesion receptors from the immunoglobulin (Ig) gene superfamily. **CK** = chemokines; **CKR** = chemokine receptors; **ICAM-1** = intercellular adhesion molecule-1; **ESL-1** = E-selectin ligand-1; **PGSL-1** = P-selectin glycoprotein ligand-1; **VCAM-1** = vascular cell adhesion molecule-1; **VLA-4** = very late activation antigen-4; **LFA-1** = leucocyte function-associated antigen-1.

novo expression of P- and E-selectin (which takes a few minutes and several hours, respectively) by EC, enables them to tether bloodstream leucocytes through the interaction of these CAM with their counter-receptors expressed on the leucocyte cell surface.[1,3,4] After this initial leucocyte-EC contact (first step or tethering; fig. 2), leucocytes roll over the endothelium (second step or rolling; fig. 2) due to both the shear force of the bloodstream and the transient and dynamic interactions mediated by selectins and their ligands.[1,4-6] It has been found that VLA-4 is also able to sustain the rolling of lymphoid cells both *in vivo* and *in vitro*.[30,31] During rolling, leucocytes are activated by both the intracellular signals generated through selectins (or VLA-4) and the interactions of chemokine receptors with chemokines bound to the EC surface (third step or activation/firm adhesion; fig. 2).[8,9,16,25] The activation of leucocytes induces a rapid loss of expression of L-selectin[5] as well as the activation of integrins.[15] The increased avidity of the leucocyte integrins has as a consequence the firm adhesion of leucocytes to EC (third step). Then leucocytes transmigrate between EC (diapedesis), or through them[32] following the chemotactic gradient generated by the inflammatory foci (fourth step or extravasation; fig. 2).

The molecular interactions that are involved in the extravasation of leucocytes are those that mediate the firm adhesion (LFA-1/ICAM-1, -2; Mac-

1/ICAM-1; and VLA-4/VCAM-1), but adhesion receptors located at the EC junctions such as CD31, VE-cadherin and desmosomal cadherin also have an important role in leucocyte extravasation.[19,33] Finally, the migration of leucocytes from the blood vessel wall towards the inflammatory foci involves the movement of these cells through the tissue with transient and dynamic interactions among the leucocyte adhesion receptors and components of the extracellular matrix such as collagen, fibronectin, laminin, etc.; the CAM involved in this process are mainly β1 integrins.

Acute inflammatory phenomena are usually accompanied by a variable degree of small blood vessel damage with thrombosis and necrosis, phenomena in which CAM are involved. The EC damage that occurs in inflammatory conditions is a consequence of the combined effect of cytokines (mainly TNFα), the cytotoxic effect of activated leucocytes and the increased sensitivity of activated EC to apoptosis.[22] Leucocytes induce cell lysis through different mechanisms that involve cell-to-cell interactions, which are mainly mediated by the LFA-1/ICAM-1, -2 and LFA-2/LFA-3 adhesion pathways.[34] In addition, endothelial cell activation/damage induces platelet adhesion to the endothelium (via P-selectin and activated GPIIb/IIIa integrin)[3,13] and its aggregation on the vessel wall.[3,35] In such circumstances, platelets contribute to the inflammatory phenomenon through the release of soluble mediators (including chemokines)[21,25] and are responsible for the formation of thrombi with occlusion of blood vessels. Platelets are also able to further trigger endothelial cell activation via the CD40/CD40L signalling pathway.[36]

3. Antiadhesion Therapy

As stated above, the cell-to-cell interactions that take place in the inflammatory phenomenon are mediated by CAM. Therefore, the blockade of expression and/or function of CAM may be a potential target for inhibiting the inflammatory response. Drugs with immunosuppressive properties such as cyclophosphamide, methotrexate, glucocorticoids, cyclosporin, tacrolimus and sirolimus are able to inhibit intercellular adhesion phenomena by 2 indirect mechanisms: blockade of leucocyte activation and interference with expression and activation of CAM by other cells (e.g. EC) as a consequence of the inhibition of cytokine synthesis.[37] Interestingly, several immunosuppressive drugs show additional anti-inflammatory effects that do not seem to be related to their main immunosuppressive mechanisms of action. For example, methotrexate, glucocorticoids and low-dose cyclosporin therapy interfere with the expression and/or function of different CAM.[38-42] Other immunosuppressive drugs such as leflonumide may also have an inhibitory effect on CAM function.[43]

Blockade of the activity of proinflammatory cytokines is another (indirect) approach to antiadhesive therapy in inflammatory conditions. The neutralisation of chemokines and TNFα with monoclonal antibodies (mAb), or the pharmacological inhibition of the synthesis of the latter cytokine, have a noticeable anti-inflammatory effect.[44,45]

The crystal structure of integrins is in the process of being fully elucidated and the aminoacids involved in their interactions have been recognised.[46-48] Several integrins interact with RGD (Arg-Gly-Asp) motifs, whereas VLA-4 interacts with the fibronectin fragment CS-1 and the LDV (Leu-Asp-Val) motif. This information is providing a rational basis for the development of reagents that specifically block the function of integrins. Anti-CAM mAb and peptides that contain integrin-binding motifs (e.g. RGD or LDV sequences), or soluble counter-receptors of CAM, are able to effectively interfere with the function of these molecules.[49-52] A significant advance in this field has been the generation or isolation of synthetic and natural substances that bind to integrins and block their function.[53-56] On the other hand, soluble carbohydrates that specifically react with selectins (e.g. sulfatide, fucoidins or sialyl Le^x are also able to block the function of these CAM.[57,58]

Several drugs affect the expression and/or function of CAM. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin, aceclo-

fenac or diclofenac downregulate the expression of L-selectin and adhesion of granulocytes to EC under conditions that resemble the rolling phase of the adhesion cascade.[59,60] When healthy volunteers receive the recommended therapeutic doses of indomethacin or diclofenac, they show a significantly diminished expression of L-selectin in their peripheral blood granulocytes[59]. Meloxicam and piroxicam do not inhibit the rolling of granulocytes on EC but they prevent the translocation of Mac-1 integrin to the cell surface and the downregulation of L-selectin expression induced by TNFα or the bacterial chemoattractant fMLP.[61] In addition, piroxicam inhibits the activation of β1 and β2 integrins induced by chemokines.[61] Therefore, some NSAIDs inhibit the first/second steps (tethering/rolling) of the leucocyte-EC interaction, whereas others interfere with the third step (activation/firm adhesion) of the adhesion cascade.[62]

Many other drugs and substances are known to influence the expression and/or function of CAM. Antirheumatic drugs such as sodium aurothiomalate, sulfasalazine, nimesulide and colchicine exhibit these effects.[63-65] Other substances such as tepoxalin (a cyclo-oxygenase/lipoxygenase inhibitor) and tenidap (an antirheumatic drug that has now been discontinued) also interfere with the activation of leucocytes and the EC-leucocyte interaction.[66,67] Substances that inhibit the activation of NFκB, such as sodium salicylate or antioxidant agents (e.g. *N*-acetylcysteine) interfere with both the expression of CAM and the synthesis of proinflammatory cytokines.[68,69] In this regard, peptidic compounds that block the proteasome also inhibit CAM expression, since this intracellular multicatalytic complex is necessary for the activation of NFκB.[70]

Other drugs that are not considered as anti-inflammatory agents, such as iloprost, lovastatin and probucol, also interfere with the expression and function of CAM.[71-73] Phosphodiesterase inhibitors and histamine receptor blocking agents are also able to interfere with certain adhesion pathways.[74,75] Leumedins are novel compounds with anti-inflammatory properties that inhibit the adherence of neutrophils mediated by Mac-1.[76,77] Pentoxifylline (oxpentifylline) inhibits different leucocyte adhesion pathways, including those mediated by β1 and β2 integrins.[78,79] In addition, this drug interferes with the activation and proliferation of T lymphocytes[78] and blocks the synthesis of TNFα.[45]

New approaches to the inhibition of CAM expression have emerged in recent years. Antisense oligonucleotides, which bind to complementary mRNA and inhibit their translation, are new tools for the specific inhibition of protein expression.[80] Studies in animals have shown that antisense oligonucleotides have a beneficial effect in experimental inflammatory diseases. In this regard, antisense ICAM-1 oligonucleotides are able to prevent and reverse the development of dextran sulfate–induced colitis in mice.[81] In the same way, similar oligonucleotides block allograft rejection in rats.[82] In addition, infectious and neoplastic diseases are also candidates for treatment by this therapeutic approach.[80] Although initial pharmacokinetic and safety studies suggested that antisense oligonucleotide administration may be associated with serious side effects, additional studies in both animals and humans have shown that these agents are usually well tolerated.[83,84]

Thus, antisense therapy for the blockade of expression of both cell adhesion molecules and proinflammatory cytokines may be a significant advance in the treatment of inflammatory conditions. However, several issues require clarification before antisense oligonucleotides can enter wide clinical use; these include potential toxicity, site-specific delivery, *in vivo* stability and clearance of metabolites.[80] The second generation of synthetic antisense oligonucleotides should facilitate this therapeutic approach.[84]

Another interesting approach to antiadhesive therapy is the use of synthetic double-stranded DNA molecules possessing specific consensus sequences that compete for the binding of transcription factors necessary for gene expression. Such an effect has been observed, *in vitro* and *in vivo*, in the case of NFκB.[85] Lastly, gene expres-

sion can also be selectively blocked with triplex-forming oligonucleotides.[86]

4. Antiadhesion Therapy and Disease

Antiadhesion therapy has been tested in different conditions, mainly in experimental models of inflammatory disease, with varying degrees of success.[49-51] Several antiadhesive therapies have been employed in experimental models of sepsis and patients with septic shock.[87-89] Unexpectedly, patients in whom TNFα or IL-1 was blocked tended to show a higher mortality than the placebo groups.[88-90] However, it is feasible that in a subset of patients with septic shock, mainly those with very high serum concentrations of proinflammatory cytokines, the blockade of TNFα may have a beneficial effect. Furthermore, a favourable effect has been noted in experimental sepsis with other antiadhesive therapies such as sulfatide, a soluble ligand of P- and E-selectins, and anti–β2 integrin mAb.[57,91,92]

The blockade of TNFα has been employed as a therapeutic tool in other inflammatory diseases. The infusion of genetically engineered anti–TNFα mAb is an effective short term treatment for Crohn's disease.[93,94] TNFα–blocking therapy also induced a significant improvement in different clinical and laboratory parameters in patients with rheumatoid arthritis.[95,96] As expected, this kind of therapy decreased the cellularity and CAM expression of rheumatoid synovium, as well as the serum levels of ICAM-1 and VCAM-1.[97,98] Direct antiadhesion therapy has been also employed in rheumatoid arthritis (administration of an anti–ICAM-1 mAb) with encouraging results.[99,100] These data, together with the fact that anti-β2 and anti–VLA-4 mAb prevent and reduce the inflammatory phenomenon seen in experimental models of arthritis,[101-103] warrant further clinical trials of antiadhesion therapy in rheumatoid arthritis.

The late phase of acute asthma is due to an inflammatory phenomenon of the bronchial wall with a noticeable infiltration by eosinophils.[104] Blockade of CAM may ameliorate the influx of inflammatory cells to the bronchial wall and interfere with eosinophil degranulation.[105,106] Anti-β2 integrin, anti–ICAM-1 and anti–E-selectin mAb are able to reduce the airway hyper-responsiveness and inflammatory cell infiltrate in different experimental models of asthma.[51,107,108] A more specific antiadhesive therapy in asthma is achieved with anti–VLA-4/VCAM-1 reagents, since this adhesion pathway is important for the extravasation of eosinophils, but not neutrophils.[105,109,110] Although no clinical trials with VLA-4 blockers have been reported in humans to date, the suitability of these substances for aerosol delivery will facilitate their development.[111]

There are other conditions in which a selective antiadhesion therapy is feasible. As stated above, the α4β7 and αEβ7 integrins mediate the localisation of a subset of lymphocytes to intestinal mucosa and associated lymphoid tissue. The α4β7 interacts with the mucosal addressin MadCAM-1 (and VCAM-1), whereas αEβ7 interacts with E-cadherin. Interestingly, administration of anti-α4β7 antibodies induces a rapid resolution of chronic colitis in the cotton-top tamarin.[112] Furthermore, the blockade of either α4β7 or MadCAM-1 with specific mAb significantly reduces the colonic inflammatory infiltrate in scid mice reconstituted with $CD45RB^{high}$ CD4+ T lymphocytes.[113] These studies strongly support the idea that both α4β7 and MadCAM-1 may be organ-specific therapeutic targets for the treatment of inflammatory bowel disease.

Thrombotic/ischaemic conditions are usually accompanied by an inflammatory phenomenon that contributes to the reperfusion damage.[114] Therefore, antiadhesion therapy in these conditions is not aimed only at inhibiting platelet activation/aggregation but also at blocking leucocyte activation/recruitment.[4,51] In fact, several *in vivo* studies in animals have shown that selectin-blocking agents, mainly synthetic sialyl Le^x-containing compounds and sialyl Le^x analogues, are able to reduce the size of the infarct and to diminish neutrophil accumulation after experimental coronary artery occlusion-reperfusion.[115-118] A similar effect has been observed in other tissues.[119,120] Furthermore, the blockade of cell adhesion molecules other than

selectins also reduces the tissue damage associated with ischaemia-reperfusion.[121,122]

5. Concluding Remarks

Significant advances in our knowledge of the role of CAM in physiological and inflammatory conditions have been made in recent years. Although antiadhesion therapy seems to be a promising approach for the treatment of inflammatory disease, it is necessary to keep in mind that the blockade of CAM might have important adverse effects. The immunodeficiency observed in patients with genetic defects in the expression of β2 integrins or selectin ligands, or impairment in the activation of β2 integrins supports this point.[123-125] Nevertheless, with the exception of the cytokine blockade studies in sepsis,[88-90] clinical trials of antiadhesive therapy in humans have not reported serious adverse effects.[95,96,99,121] Different experimental models of antiadhesion therapy have confirmed this point.[51,126] The development of new and more specific agents that interfere with the function and/or expression of CAM will provide novel approaches not only for the therapy of inflammatory diseases but for the treatment of other common disorders such as thrombosis or tumour cell metastasis.

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