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Cell Adhesion Molecules in Rheumatoid Arthritis

Implications for Therapy

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Summary

Rheumatoid arthritis is a systemic inflammatory disease of the joints and major internal organs that has an unknown aetiology. Cell adhesion molecules (CAMs) are expressed on the surface of cells, enabling homotypic and heterotypic cell-cell interactions that are fundamental in the process of the inflammatory reaction.

Three major families of CAMs are now recognised, with numerous subtypes. Many of these molecules play an important role in the mechanism of disease in rheumatoid arthritis. E-Selectin and intercellular adhesion molecule (ICAM)–1 are upregulated on the synovial endothelium, while vascular cell adhesion molecule (VCAM)–1 plays an important role in the synovial lining layer cells and within the synovial stroma.

The expression of CAMs may be blocked by monoclonal antibodies and modified by nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs. This has very important implications in the therapy of rheumatoid arthritis.

Rheumatoid arthritis (RA) is a complex disease of immune-mediated pathogenesis. It results not only in joint disease, but may involve the vasculature and other major organs, and is associated with a significantly increase in morbidity and mortality.[1]

The cause of RA is unknown; however, many of the pathological changes that occur have been defined, thus improving our knowledge of the mechanisms of immune activation and ultimately organ damage. We now have therapies that can be directed

Table I. Families of cellular adhesion molecules

Selectins
Immunoglobulin superfamily
Integrins

against specific molecular and cellular targets, which will lead to the development of new regimens of single agent and combination therapy. This should improve the rate of remission in RA and improve our ability to prevent joint damage and, ultimately, deformity and disability.

There was a growing realisation in the 1980s that the vascular endothelium was not a passive organ allowing cells to 'float through'. On the contrary, it was found to play a crucial active role in the efflux of leucocytes from the circulation into inflamed tissues. This has led to massive expansion of research in this area.

A number of molecules expressed on the surface of endothelial cells have been recognised as cell adhesion molecules (CAMs), which are involved in the process of leucocyte arrest and subsequent migration.[2-5] There are 3 families of CAMs (tables I and II). The elucidation of the mechanisms of interactions between endothelial membrane adhesion molecules and their leucocyte-expressed receptors has led to many advances in our understanding of these interactions. While a great many adhesion molecules are now known, it is beyond the scope of this article to mention them all. Instead we intend to concentrate on those most likely to be important in the pathogenesis and, therefore, the treatment of RA.

1. Pathological Role of Cell Adhesion Molecules (CAMs)

1.1 In the Inflammatory Process

CAM expression has been described in the synovial membrane in RA and other inflammatory arthropathies.[6-9] Recently, it has been recognised that CAMs are shed from the vascular endothelium and exist in a soluble form in the circulation.[10] These molecules form the initial step in the inflammatory pathway and thus may be considered a gateway to inflammation. This highlights their importance as a possible focus for therapy especially in RA.

Several CAMs seem to be important in leucocyte-endothelial binding in RA including intercellular adhesion molecule (ICAM)–1, a member of the immunoglobulin superfamily. The selectins, primarily E-selectin [previously endothelium-leucocyte adhesion molecule (ELAM)–1] and P-selectin, are glycoproteins on the surface of the cell membrane, and are important in the phase of rolling prior to arrest (in which the leucocyte rolls along the surface of the endothelium before sticking).[11] The integrins and sialomucins, for the most part expressed on the surface of leucocytes, act as receptors for these CAMs. Indeed, it has been suggested that the expression of CAMs may be tissue-specific and that this specificity may be conferred by expression of different combinations of molecules.[12]

1.2 In Rheumatoid Arthritis

Before considering the implications for therapy in RA, it is appropriate to examine the evidence for the roles of these molecules in RA in a little more detail.

Expression of ICAM-1 on the endothelium is constitutive;[13] however, this is markedly upregulated in the synovial membrane in RA and also in psoriatic arthritis.[6-9] Upregulation of the expression of ICAM-1 and induction of many of the other adhesion molecules is controlled by cytokines, predominantly interleukin-1 (IL-1), interferon-γ and tumour necrosis factor-α (TNFα).[14,15]

Levels of IL-1 and TNFα are markedly raised in the synovial membrane in RA. Furthermore, there is a significant correlation between levels of circulating ICAM-1 and TNFα in the serum of patients with RA.[16] The binding of leucocytes involving ICAM-1 via the integrin receptors CD11a/CD18 and CD11b/CD18 has been elucidated using monoclonal antibodies to block both ICAM-1 and the integrins.[17-19] The importance of ICAM-1 and CD11/CD18 interaction is further highlighted by leucocyte adhesion deficiency (LAD) type 1,[20] an autosomal recessive disorder in which there is partial or total absence of expression of β2 leucocyte

Table II. Major cell adhesion molecules (CAMs) showing cell expression and specificities

CAM	Cell expression	Ligand	Binding
Selectins			
E-selectin	EC	Sialyl Lewis-X	PMN MØ
L-selectin	WBC	Mucin +	HEV
P-selectin	Platelets EC	Sialyl Lewis-X	Platelets PMN MØ
Immunoglobulin superfamily			
ICAM-1 (ICAM-2/3)	Inflammatory cells	LFA-1 (CD11a/CD18)	WBC
VCAM-1 (CD106)	EC/MØ Fibroblasts	VLA-4	Lymphocytes
PECAM-1 (CD31)	Platelets/T cells EC/MØ	?Self	Platelets/T cells EC/MØ
HCAM (CD44)	WBC/epithelial cells Fibroblasts	Self + others	EC/matrix

Integrins	**Structural/cellular binding molecules**
α and β subunits	
VLA subtypes	Laminin, collagen, fibronectin, VCAM-1
LFA-1, Mac-1 and p150	ICAM-1, ICAM-2, ICAM-3 Fibrinogen, C3bi
vitronectin	Fibrinogen, fibronectin, von Willebrand factor, thrombospondin

Abbreviations: EC = endothelial cell; HCAM = hyaluronan cell adhesion molecule; HEV = high endothelial venule; ICAM = intercellular adhesion molecule; LFA = leucocyte function–associated antigen; MØ = monocyte; PECAM = platelet endothelial cell adhesion molecule; PMN = polymorphonuclear leucocyte; VCAM = vascular cell adhesion molecule; VLA = very late antigen; WBC = white blood cell.

integrins. This results in failure to recruit neutrophils to the site of inflammation and clinically results in recurrent infections such as pneumonia.

The selectins are important in the process of rolling of leucocytes along the endothelial cell surface and for the binding of leucocytes prior to transmigration.[11] P-Selectin is synthesised and stored in platelet cell and endothelial cell granules,[21] and acts as the adhesion receptor for neutrophils and monocytes, and for some T cell subsets also. E-Selectin expression is more restricted than that of ICAM-1 or P-selectin; there is minimal constitutive expression, although upregulation of expression occurs in inflammation, such as that in the RA synovial membrane and lesional skin in psoriasis.[22,23] E-selectin binds the molecule sialyl Lewis-X on the surface of leucocytes and is responsible for binding a variety of cells including monocytes and T cells.[24] Recent evidence suggests that levels of soluble P-selectin are raised in the serum of patients with RA and that this may normalise following treatment.[25] In contrast, levels of circulating E-selectin do not appear to be significantly different from that in healthy controls, either before or after treatment.

2. Clinical Aspects of CAMs in Rheumatic Diseases

Some clinicians may doubt the relevance of CAMs to the clinical setting and patient management, especially in RA. However, the importance of understanding the mechanisms of the pathogenesis on a molecular level relates to the development of specific therapeutic approaches to RA.

2.1 Correlation with Clinical Course

There is now some evidence, in at least 2 rheumatic diseases (including RA), of close clinical correlation with serum measures of soluble CAMs,[25,26] and there is at least one pilot study of therapy directed against ICAM-1 in the treatment of RA.[27] The severity of the skin involvement in

patients with systemic sclerosis appears to show a close correlation with the change in soluble levels of ICAM-1 following endothelial stimulation. Furthermore, levels of P-selectin and ICAM-1 change over a period of 12 weeks of disease-modifying antirheumatic drug (DMARD) therapy in RA patients, with either sulfasalazine or intramuscular gold.[25] This study further revealed a close association between disease activity, represented by C-reactive protein level, over the treatment period and changes in soluble ICAM-1 levels. A previous study reported a reduction in the tissue expression of E-selectin in RA synovial membrane following intramuscular gold therapy for 12 weeks.[28]

It may be that changes in synovial membrane expression and soluble CAM levels in response to DMARD therapy reflect a reduction in disease activity, although it remains to be seen whether a direct effect on cell adhesion *in vivo* is part of the mechanism of action of these drugs.

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) in the process of cell adhesion, predominantly neutrophil-endothelial adhesion, has been studied in some detail. Cronstein et al.[29] demonstrated a reduction in adhesion of polymorphonuclear leucocytes to endothelial cells *in vitro* following exposure to several NSAIDs; this effect was found to be independent of expression of the CD11b/CD18 ligand on the neutrophil. In an earlier study,[30] the novel NSAID tenidap was noted to reduce neutrophil-endothelial adhesion under both stimulated and unstimulated conditions.

The expression of specific CAMs (E-selectin, ICAM-1 and VCAM-1) has also been studied *in vitro* following the introduction of 2 further novel NSAIDs – PD-144795[31] and NPC-15669.[32] Both of these drugs inhibited upregulation of CAMs on endothelial cells.[31,32] In a further study,[33] gene expression of ICAM-1 and VCAM-1 was inhibited by PD-144795. Finally, shedding of CAMs from the surface of endothelium is an important mechanism of CAM turnover; increased shedding of L-selectin has been observed in response to a variety of NSAIDs.[34]

In vitro studies have examined the effect of corticosteroids on the endothelial expression of CAMs suggesting that these immunosuppressive drugs do reduce CAM expression directly.[35] This *in vivo* effect, however, may depend on a patient's overall corticosteroid-sensitive status.

2.2 Therapeutic Trials

The advent of immunotherapy has led to one study in humans that addressed the role of monoclonal antibody therapy directed against ICAM-1 in RA.[27] This study examined the use of murine anti–ICAM-1 monoclonal antibody in patients with resistant RA, who had not previously responded to conventional therapy; this may in itself have preselected a group unlikely to respond. 23 patients with refractory RA were given a 5-day course of treatment and 9 more patients were given a 1- or 2-day treatment course. 13 of the 23 patients receiving 5 days' therapy with this antibody demonstrated clinical improvement as measured by reductions in joint score, morning stiffness, global assessment by the physician and mean health assessment questionnaire (HAQ) score. The benefit was, however, only sustained in a few patients after 6 months. Immunologically, it was noted that there was a transient increase in the number of circulating T lymphocytes on day 5 of treatment, cutaneous anergy was noted in 6 patients and all patients developed human anti-mouse antibodies. The study authors concluded that treatment with anti-ICAM-1 monoclonal antibody is well tolerated and effected clinical improvement in some patients.[27]

Since these data were published the same authors have reported preliminary data on re-treatment of 8 RA patients with anti–ICAM-1, which resulted in a serum sickness–like reaction in 6 patients, and clinical response was not as effective second time around in some patients.[36] The adverse reaction is undoubtedly due to the formation of anti-mouse antibodies by the patients; however, the lack of efficacy of re-treatment is disappointing.

3. Conclusion

There is now a great deal of knowledge about the mechanisms of leucocyte arrest and adhesion to vascular endothelium, their egress into synovial membranes, and the subsequent changes in tissue cell interactions in the presence of active inflammation within this tissue. Knowledge of the mechanisms responsible for the process of leucocyte-endothelial binding, and the CAMs involved, has allowed the study of the effects of standard steroidal anti-inflammatories, DMARD therapy and novel immunotherapeutic agents directed against CAMs in RA.

Although immunotherapy has not resulted in a lasting solution and re-treatment has not been successful, there may still be a role for these agents to induce remission in RA. Furthermore, increasing knowledge of the effects of standard therapeutic agents such as sulfasalazine, methotrexate, sodium aurothiomalate and, more recently, cyclosporin will lead to a greater understanding of how these agents interfere with the inflammatory process.

Studies of combination therapy aimed at inducing remission followed by maintenance therapy with a single agent are now under way. It is hoped that, by targeting the cell adhesion molecules in RA, pharmaceutical intervention may be directed at the initial step in the inflammatory process and thus prevent its perpetuation at the earliest pathophysiological stage of the disease.

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References

1. Pincus T. Rheumatoid arthritis: disappointing long term outcomes despite successful clinical trials. J Clin Epidemiol 1988; 41: 1037-41
2. Harlan JM. Leukocyte-endothelial interactions. Blood 1994; 84 (7): 2068-101
3. Rothlein R, Dustin ML, Marlin SD, et al. A human intercellular adhesion molecule distinct from LFA-1. J Immunol 1986; 137: 1270-4
4. Osborn L, Hession C, Tizard R, et al. Direct expression cloning of vascular cell adhesion molecule-1, a cytokine induced endothelial protein that binds to lymphocytes. Cell 1989; 59: 1203-11
5. Springer TA. Adhesion receptors of the immune system. Nature 1990; 346: 425-34
6. Hale LP, Martin ME, McCollum DE, et al. Immunohistologic analysis of the distribution of cell adhesion molecules within the inflammatory synovial microenvironment. Arthritis Rheum 1989; 32: 22-30
7. Veale D, Yanni G, Rogers S, et al. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis compared with rheumatoid arthritis. Arthritis Rheum 1993; 36: 893-900
8. Johnson BA, Haines GK, Harlow LA, et al. Adhesion molecule expression in human synovial tissue. Arthritis Rheum 1993; 36: 137-46
9. Mulherin D, Veale D, Belch JJF, et al. Adhesion molecule expression in untreated inflammatory arthritis. Q J Med 1996; 89: 195-203
10. Gearing JH, Newman W. Circulating adhesion molecules in disease. Immunol Today 1993; 14: 506-12
11. Lawrence MB, Springer TA. Leukocytes roll on a selectin at physiologic flow rates: distinction from and prerequisite for adhesion through integrins. Cell 1991; 65: 859-73
12. Butcher EC. Leukocyte-endothelial cell recognition: three (or more) steps to specificity and diversity. Cell 1991; 67: 1033-6
13. Smith MEF, Thomas JA. Cellular expression of lymphocyte function associated antigens and the intercellular adhesion molecule-1 in normal tissue. J Clin Pathol 1990; 43: 893-900
14. Dustin ML, Rothlein R, Bhan AK, et al. Induction by IL-1 and interferon γ: tissue distribution, biochemistry and functions of a natural adherence molecule (ICAM-1). J Immunol 1986; 137: 245-54
15. Pober JS, Bevilacqua MP, Mendrick DL, et al. Two distinct monokines, interleukin 1 and tumor necrosis factor, each independently induce the biosynthesis and transient expression of the same antigen on the surface of cultured human vascular endothelial cells. J Immunol 1986; 36: 1680-7
16. Aoki S, Imai K, Yachi A. Soluble intercellular adhesion molecule-1 (ICAM-1) antigen in patients with rheumatoid arthritis. Scand J Immunol 1993; 38: 485-90
17. Diamond MS, Staunton DE, De Fougerolles AR, et al. ICAM-1 (CD54): a counter receptor for Mac-1 (CD11b/CD18). J Cell Biol 1990; 111: 3129-39
18. Wallis WJ, Beatty PG, Ochs HD, et al. Human monocyte adherence to cultured vascular endothelium: monoclonal antibody-defined mechanisms. J Immunol 1985; 135: 2323-30
19. Haskard DO, Cavender DE, Beatty P, et al. Cell adhesion to endothelial cells: mechanisms demonstrated by anti-LFA-1 monoclonal antibodies. J Immunol 1986; 137: 2901-6
20. Arnaout MA. Leukocyte adhesion molecules deficiency: its structural basis, pathophysiology and implications for modulating the inflammatory response. Immunol Rev 1990; 114: 145-79
21. Bevilacqua MP, Nelson RM. Selectins. J Clin Invest 1993; 91: 379-87
22. Veale D, Rogers S, FitzGerald O. Immunolocalization of adhesion molecules in psoriatic arthritis, psoriatic and normal skin. Br J Dermatol 1995; 132: 32-8
23. Groves RW, Allen MH, Haskard DO, et al. Endothelial leukocyte adhesion molecule-1 (ELAM-1) expression in cutaneous inflammation. Br J Dermatol 1991; 124: 117-23
24. Polley MJ, Phillips ML, Wayner EW, et al. CD62 and endothelial leukocyte adhesion molecule-1 (ELAM-1) recognise the

same carbohydrate ligand, sialyl-Lewis x. Proc Nat Acad Sci U S A 1991; 88: 6224-8
25. Veale DJ, Maple C, Kirk G, et al. Soluble cell adhesion molecule levels in rheumatoid arthritis in response to sulphasalazine therapy [abstract]. Arthritis Rheum 1995; 37 (S370): 1299
26. Veale DJ, Kirk G, McLaren M, et al. Scleroderma skin score correlates with change in soluble ICAM-1 levels in response to endothelial stimulation [abstract]. Arthritis Rheum 1994; 37 (S259): 596
27. Kavanaugh AF, Davis LS, Nichols LA, et al. Treatment of refractory rheumatoid arthritis with a monoclonal antibody to intercellular adhesion molecule-1. Arthritis Rheum 1994; 37: 992-9
28. Corkill MM, Kirkham BW, Haskard DO, et al. Gold treatment of rheumatoid arthritis decreases synovial expression of the endothelial leukocyte adhesion receptor ELAM-1. J Rheumatol 1991; 189 (10): 1453-60
29. Cronstein BN, Van de Stowe M, Druska L, et al. Nonsteroidal antiinflammatory agents inhibit stimulated neutrophil adhesion to endothelium: adenosine dependent and independent mechanisms. Inflammation 1994; 18 (3): 323-35
30. Kyan-Aung U, Lee TH, Haskard DO. The inhibitory effect of tenidap on leucocyte-endothelial cell adhesion. J Rheumatol 1993; 20 (6): 1014-9
31. Boschelli DH, Kramer JB, Khatana SS, et al. Inhibition of E-selectin-, ICAM-1-, and VCAM-1-mediated cell adhesion by benzo[b]thiophene-, benzofuran-, indole-, and naphthalene-2-carboxamides: identification of PD144795 as an anti-inflammatory agent. J Med Chem 1995; 38 (22): 4597-614
32. Bator JM, Weitzberg M, Burch RM. N-[9H-(2,7-dimethyl-fluorenyl-9-methoxy)carbonyl]-L-leucine, NPC15669, prevents neutrophil adherence to endothelium and inhibits CD11b/CD18 upregulation. Immunopharmacology 1992; 23 (2): 139-49
33. Wolle J, Ferguson F, Keshava C, et al. Inhibition of tumour necrosis factor induced human aortic endothelial cell adhesion molecule gene expression by an alkoxybenzo[b]thiophene-2-carboxamide. Biochem Biophys Res Comm 1995; 214 (1): 6-10
34. Diaz-Gonzalez F, Campanero MR, Mollinedo F, et al. Prevention of *in vitro* neutrophil-endothelial attachment through shedding of L-selectin by nonsteroidal antiinflammatory drugs. J Clin Invest 1995; 95 (4): 1756-65
35. Pitzalis C, Pipitone N, Lee A, et al. Corticosteroid (C) inhibition of T cell adhesion molecule expression *in vivo* depends on C-resistant/C-sensitive status [abstract]. Arthritis Rheum 1995; 38 (S288): 812
36. Kavanaugh AF, Davis LS, Nichols LA, et al. Retreatment of rheumatoid arthritis patients with an anti-ICAM-1 monoclonal [abstract]. Arthritis Rheum 1995; 38 (S280): 765

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