CELL ADHESION MOLECULES: AN OVERVIEW

One of the areas of biomedical sciences that has advanced significantly in the last decade is that concerning the interactions between immune cells and those that occur between leucocytes and endothelial cells. These cell interactions are mainly mediated by cell adhesion receptors, a heterogeneous and wide array of membrane molecules that have been classified by structural homology into three main families: selectin, integrin and immunoglobulin superfamilies [1,2]. The adhesion phenomena mediated by these molecules have an important role in many physiological and pathological conditions, such as lymphocyte homing, the immune response, inflammation, cell-mediated cytotoxicity, metastasis or thrombosis [2-4]. Thus, to gain insight into the pathogenic mechanisms of many rheumatic diseases, it is necessary to have an adequate knowledge of these adhesion receptors.

Selectins are a family of three highly homologous glycoproteins that are expressed by leucocytes (L-selectin), platelets (P-selectin) and endothelium (P- and E-selectin). These cell adhesion molecules (CAM) mainly bind to carbohydrate determinants found in leucocytes (sialyl Lewis X, CLA/HECA-452, CD15, CD66) and endothelial cells (SLE, SLE*). In addition, protein ligands for selectins have been identified in both leucocytes (PSGL-1) and endothelial cells (EC) from high endothelial venules (MadCAM-1, GlyCAM-1, CD34). On the other hand, integrins are heterodimeric CAM that mainly belong to four subfamilies (β1, β2, β3 and β7), each one with a common β chain. β1 integrins (also denominated VLA antigens) are widely expressed, with the exception of neutrophils, and bind to extracellular matrix proteins (collagen, fibronectin) and to a CAM expressed by endothelium (VCAM-1). The β2 leucocyte integrins have a common β chain (CD18) and one of three α subunits (CD11a, b and c). These three integrins are mainly expressed by bone marrow-derived cells (neutrophils, monocytes, natural killer (NK) cells), but T and B lymphocytes usually only express CD18/CD11a (LFA-1). Leucocyte integrins bind to the intercellular adhesion molecules-1 and -2 (ICAM-1 and -2), which are expressed on leucocytes, endothelium and other cells, as well as to ICAM-3, which is found only in leucocytes. The only well-characterized member of the β7 subfamily is the heterodimer α4β7 that is expressed by some lymphocyte subsets, and is able to bind to both VCAM-1 and MadCAM-1.

The CAM that belong to the immunoglobulin superfamily are characterized by the presence of one or several extracellular domains that are homologous to those found in antigen receptors of lymphocytes (mlg, TCR). Many members of this family are expressed on leucocytes and/or EC, such as CD2 (LFA-2), CD58 (LFA-3), ICAM-1 (CD54), ICAM-2 (CD102), ICAM-3 (CD50), VCAM-1 (CD106), PECAM (CD31) and MadCAM-1. These CAM interact among them (e.g. CD2/CD58, CD31/CD31), or with other adhesion receptors of the selectin (e.g. L-selectin/MadCAM-1) or integrin (e.g. LFA-1/ICAM-1, -2, -3; VCAM-1/α4β1, α4β7) families.

CAM mediate the interaction between leucocytes and EC, a phenomenon that has a key role in the pathophysiology of inflammation. The migration of inflammatory cells from the bloodstream involves a cascade of leucocyte/EC interactions that it is initiated by the rolling of leucocytes on EC (mainly mediated by selectins and their ligands), followed by the firm adhesion of leucocytes to endothelium (mediated by LFA-1/ICAMs and α4β1, 7/VCAM-1 interactions) and that ends with the extravasation (mediated by interactions in which CD31, integrins and extracellular matrix proteins are involved) of inflammatory cells.

New interesting data have arisen in recent years in the field of CAM. The role of CAM in the recirculation of lymphoid cells has been further elucidated and several peripheral node addressins (CAM expressed by EC that are involved in lymphocyte homing) have been clearly identified (GlyCAM-1, CD34, etc.). VAP-1 is another addressin, and it is very feasible that this molecule directs the trafficking of lymphoid cells to synovium, as well as to mucosal lymphoid tissues [5]. On the other hand, the role of CAM in the synovial infiltration by inflammatory cells has also been studied. Selectins, integrins and Ig superfamily CAM appear to be involved in the pathogenesis of synovial inflammation, either acute or chronic [6-10].

The experimental disruption of genes (knock out) encoding for CAM has proved to be a useful approach to define the precise function of these rather than redundant molecules. The targeting of L- and P-selectin genes in mice has recently demonstrated the key role of these molecules in both acute (thioglycollate-induced peritonitis) or chronic (delayed type hypersensitivity reactions) experimental inflammatory phenomena [11]. Similar valuable data have arisen from CD18- and ICAM-1-deficient animals. Furthermore, the congenital deficiencies of β2 integrins and ligands of selectins have been described in humans. Patients with these diseases have a marked impairment in the extravasation of neutrophils and, consequently, a defective inflammatory response. Interestingly, leucocytes from these patients are capable of extravasating to certain inflammatory foci, a phenomenon that strongly suggested the existence of alternative adhesion pathways. In fact, it has recently been demonstrated that α4β1 and α4β7 integrins are capable of sustaining the rolling of lymphocytes along EC [12], an adhesion step that was thought to be exclusively mediated by...
selectins. Additional 'non-classical' alternative adhesion pathways may be described in the forthcoming years.

Under this point of view, anti-adhesive therapy appears to be a plausible approach for the control of inflammation and immune-mediated tissue damage. Many reports on the therapeutic effect of anti-CAM monoclonal antibodies in animal models of inflammation have appeared in the past years. Phase I clinical trials with several anti-CAM monoclonal antibodies have shown the therapeutic potential of this approach. However, the high cost and side-effects of monoclonal antibody therapy (serum sickness, immunosuppression) seem to preclude its generalized use in chronic inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus. A more rational approach may be achieved by the use of soluble ligands capable of blocking and binding CAM. In fact, it has been shown that synthetic peptides and peptide analogues that resemble cell ligands are capable of blocking either ICAM-1, LFA-1 or selectins, with an efficient interference with experimental inflammatory phenomena [2]. Interestingly, it has recently been described that several NSAIDs, such as indomethacin, ketoprofen or diclofenac, are capable of preventing the leucocyte/EC interaction through the induction of L-selectin loss by the former cells [13]. New NSAIDs could have a stronger effect on the expression and function of leucocyte CAM [14]. The discovery of new substances with a potent effect on CAM expression and function will constitute a valuable advance in the control of many rheumatic diseases. Rheumatologists should be aware of the advances in this interesting area.

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REFERENCES

NEEDLE ARTHROSCOPY

Over two decades ago rheumatologists showed considerable interest in arthroscopy as a means of directly visualizing the synovium, obtaining biopsies and relating the observed changes to clinical, laboratory and radiological measures of disease activity in established rheumatoid arthritis (RA) [1–3]. However, the results were inconclusive and sometimes contradictory. This, together with the additional costs involved, the inconvenience of general anaesthesia and operating theatre use, the scarcity of training opportunities and insufficient collaboration with orthopaedic surgeons, resulted in a failure by rheumatologists to adopt routine arthroscopy.

When synovial tissue is required for diagnostic or research purposes many rheumatologists rely on the closed needle technique [4]. However, it can be argued that there is a lack of specificity and sensitivity associated with this method [5, 6]. First, it is restricted in clinical practice to knee synovitis and second, the operator is unable to visually select the biopsy site.