



THE OCULAR IMMUNOLOGY  
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## **Leukocyte Adhesion Molecules in Conjunctivitis**

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We analyzed the expression and cellular distribution of intercellular adhesion molecule-1 (ICAM 1), E-selectin (endothelial leukocyte adhesion molecule-1 (ELAM\_1), vascular cell adhesion molecule-1 (VCAM-1), very late antigen-4 (VLA-4), and lymphocyte function-associated antigen-1 (LFA-1) in diseased and in normal human conjunctiva, looking for any difference in expression of the adhesion molecules in conjunctival scarring diseases.

Monoclonal antibodies (mAbs) to VCAM-1, VLA-4, ICAM-1, LFA-1 and E-selectin were utilized for immunohistochemical staining of frozen sections of 38 cryopreserved human conjunctivae. The specimens were obtained from patients with ocular cicatricial pemphigoid (OCP), Stevens-Johnson syndrome (SJS), atopy, and normal individuals. An immunoperoxidase technique was used, and we found no expression of VCAM-1 or VLA-4 in any of the normal conjunctival samples; minimal expression of ICAM-1 and LFA-1 was noted in 3 normal individual's conjunctivae. E-selectin was present on the vascular endothelium of only one normal specimen.

In sharp contrast to these findings of normal conjunctiva, there was marked up regulation of all the cell adhesion molecules in the diseased conjunctival specimens. ICAM-1 and LVA-1 were strongly expressed on stromal cells, but not on epithelium. VLA-4 was also present on stromal cells, and VCAM-1 was present in stroma and on vascular endothelium. No E-selectin was noted. Six patients with atopy, 10 patients with Stevens-Johnson syndrome, and 14 patients with cicatricial pemphigoid exhibited these findings.

Kruskal-Wallice analysis of variants, conducted for each of 15 adhesion molecule-site combinations indicated, in 6 instances, statically significant differences in the expression of the adhesion molecule among the various patient groups: VCAM-1 in blood vessels; VLA-4 in stroma; ICAM-1 in blood vessels and in stroma; LFA-1 in blood vessels; and VLA-1 in stroma. For these 6 adhesion molecules-site combinations, pairwise comparisons of the various patient groups disclosed that all the patient groups differed from the conjunctiva of normal patients, and no significant difference in expression of molecules was observed for any comparison involving affected patients with each other (atopy with OCP, atopy with SJS, and OCP with SJS).

These results indicate that, at least as regards inflammatory disease in which immunoregulation is a key component, adhesion molecule expression is abnormally up regulated and is indiscriminant as regards to the specific disease which the patient has. E-selectin, which is exclusively expressed on vascular endothelial cells stimulated by interleukin-1 alpha (IL-1 a ), interleukin-1 beta (IL-b ), and tumor necrosis factor alpha (TNF-a ), participates in the initial capture of neutrophils from the circulation onto the vascular endothelium. Up regulation of E-selectin expression on vascular endothelial cells of our patients with atopy, SJS, and OCP indicate that blood vessel inflammation through pro-inflammatory cytokine involvement is present in each of these diseases. Blocking of E-selectin (a therapeutic strategy successful in a mouse model on endotoxin induced uveitis) may have some potential in the therapy of ocular autoimmune inflammatory diseases. Similarly, in the rat model of endotoxin induced uveitis, monoclonal antibodies directed against ICAM-1 and LFA-1 were effective in suppressing inflammation. The up regulation of these adhesion molecules in the conjunctiva of patients with autoimmune inflammatory conjunctivitis suggests that this too could conceivably be a therapeutic strategy that could be exploited in care of patients with autoimmune conjunctivitis.

VCAM-1 supports the adhesion of lymphocytes, monocytes, and eosinophils through an interaction with its counter-receptor VLA-4, the  $\alpha 4\beta 1$  integrin (CD49d/CD29). The marked expression of VLA-4 on the inflammatory infiltrate in the stroma of patients with autoimmune inflammatory disease, paralleling the expression of its ligand VCAM-1, indicates another potential target of intervention in autoimmune inflammatory conjunctivitis, and one which might be particularly appealing, since VLA-4 is not expressed on neutrophils and therefore therapy directed against this adhesion receptor might have the theoretical advantage of not interfering with neutrophil recruitment and defense against infection.