Chapter A9

ENDOTHELIAL CELLS AND ADHESION MOLECULES IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Abstract: Under normal circumstances, entry of immune system cells into the central nervous system (CNS) is restricted by the blood-CNS barrier. However, with activation, cells of the immune system undergo changes that allow for an immune response within the CNS. The animal model, experimental autoimmune encephalomyelitis (EAE), is an important tool by which to investigate these processes. Using EAE, it has been shown that the establishment of an immune response in the CNS involves activation not only of the infiltrating inflammatory cells, but also of the CNS endothelial cells. Receptor-ligand interactions between CNS-EC and invading immune cells involved in EAE are multi-factorial. Particularly critical interactions occur between cell surface selectins on leukocytes and addressins on CNS-EC, and between integrins on leukocytes and their ligands on CNS-EC and other CNS cells. These interactions are good targets for potential therapies of MS, the human disease for which EAE is a model.

Key words: EAE, Endothelial Cells, Adhesion Molecules

1. INTRODUCTION

Experimental Autoimmune Encephalomyelitis (EAE) is an autoimmune demyelinating disease of the central nervous system (CNS) that results from the infiltration of neuroantigen-specific T cells into the CNS. These T cells in turn initiate a cell- and humoral-mediated inflammatory response that leads to the destruction of the myelin sheath, resulting in histopathology and clinical signs similar to those observed in multiple sclerosis.

Under normal circumstances, entry of immune system cells (e.g. T cells, B cells, monocytes, polymorphonuclear cells--PMNs) into the CNS is
restricted by the blood-CNS or blood-brain barrier (BBB; discussed elsewhere in this volume). However, upon cell activation, T cells of any antigen specificity are able to cross the BBB and enter the CNS. During immune surveillance, only those T cells specific for neuroantigen remain for an extended period of time (1). Although unproven, it is presumed that cellular activation enhances migration across the BBB by cell types other than T cells as well.

With immune activation, blood vessel endothelial cells (EC) and antigen-specific T cells undergo morphologic and phenotypic changes, allowing for the migration of T cells from the peripheral blood into tissues at the site of an immune response. These processes of cell activation and migration have been the subjects of much investigation. In many ways, migration of T cells across the BBB into the CNS is similar to T cell migration into other anatomic sites. However, there are differences unique to the CNS. Here we will discuss the role of CNS-EC and the adhesion molecules involved in the immunopathogenesis of EAE.

2. INFLAMMATORY CELL MIGRATION IN EAE

EAE lesions are comprised of T cells, monocytes/macrophages, occasional B cells and plasma cells, and reactive glial cells. During early clinical EAE, PMNs are also observed. Migration of inflammatory cells from the peripheral circulation into the CNS is normally highly restricted.

2.1 T Cell migration

Migration of inflammatory cells from blood into tissues is a multi-step process (2; Figure 1). While this model was first derived from studies of monocyte and neutrophil migration, most of the current data, especially as it pertains to migration of cells across the BBB, comes from studies of T cell migration. Activated lymphocytes are far better able to adhere to EC and to migrate across them than are resting T cells. Upon interaction with antigen (Ag), T cells express active forms of a variety of cell surface molecules including chemokine receptors and adhesion molecules. Similarly, chemokine and adhesion molecule expression is induced in EC at the site of an inflammatory response. Expression is induced by cytokines produced by inflammatory cells. Invading inflammatory cells and intrinsic CNS cells at the site of the immune response produce chemokines, small negatively charged chemoattractant molecules (reviewed elsewhere in this volume), which bind to receptors expressed by inflammatory cells. Chemokines also interact with extracellular matrix via electrostatic interactions to form a