# Integrins as Therapeutic Targets in Autoimmune Disease

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Cell adhesion refers to a molecular mechanism that is critical for normal development and maintenance of the nervous system. It is mediated by a wide variety of cell adhesion molecules, which have been subdivided into several families whose members share specific structure–function characteristics. Overall, it is the well-coordinated cooperation and cross-talk between cell adhesion molecules that ensures proper development and function of the nervous system. With that said, it is not surprising that there are nervous system diseases in which an increased expression of a cell adhesion molecule contributes to pathology and for which, consequently, an antibody directed specifically against the respective cell adhesion molecule may be converted into a therapeutic compound.

## Anti-Integrin antibodies are used for the treatment of multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by progressive demyelination and neurodegeneration in the CNS (see Chapter 39, 'Diseases Involving Myelin'). Despite the existence of therapeutic approaches aimed at reducing inflammation, no curative treatment is currently available for MS. Thus, the need for better and more specific therapeutics is evident.

A key event in the pathophysiology of MS, and thus a potential target for therapeutic intervention, is the increased migration of lymphocytes into the CNS via mechanisms involving cell adhesion (Engelhardt, 2008). Lymphocyte entry into the inflamed CNS is thought to occur primarily via the blood–brain barrier (BBB), a structure consisting of endothelial cells that form intercellular tight junctions and are surrounded by a continuous basement membrane as well as astroglial end-feet. Under physiological conditions, the BBB restricts passage of circulating cells

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and macromolecules. Thus, only limited numbers of lymphocytes enter the CNS as part of routine immunosurveillance (Ransohoff et al., 2003). Under neuroinflammatory conditions as they exist in MS, however, the expression of certain chemokines and cell adhesion molecules is upregulated, leading to the presence of additional trafficking signals and to the entrance of significantly increased numbers of lymphocytes into the CNS by the following multi-step process.

First, lymphocytes interact with endothelial cells in a transient manner, a process referred to as tethering. Next, so-called lymphocyte rolling reduces the velocity of the cells' movement and allows lymphocytes to recognize the presence of chemokines that are presented on the endothelial cell surface. Both tethering and rolling involve cell adhesion molecules of the selectin family. Interaction of chemokines with their respective receptors present on the lymphocytes' cell surfaces activates intracellular signaling that leads to inside-out integrin activation, firm lymphocyte adhesion and ultimately lymphocytes crossing through the BBB by a process called diapedesis.

In the process of lymphocyte entry into the inflamed CNS the integrin α4β1 was found to be crucial for both initial contact (tethering and rolling) and firm adhesion of lymphocytes to endothelial cells. Based on these findings, function blocking antibodies directed against the α4-integrin subunit were developed and found to inhibit inflammatory cell accumulation in the CNS in an animal model of MS (Yednock et al., 1992). For treatment of the human disease, a so-called humanized monoclonal antibody against the α4-integrin subunit was generated. In this humanized antibody, which is referred to as natalizumab and marketed as Tysabri, parts of high immunogenicity were eliminated to diminish recognition of the therapeutic and thus foreign antibody by the human immune system. Natalizumab provides the advantage of targeting a

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precise molecular mechanism and was thus tested in two large phase III clinical trials in which it was found to lead to significant improvement in clinical outcome for at least some types of MS patients. Despite growing evidence for potential complications due to adverse effects, natalizumab has been approved as the first immunospecific therapeutic for the treatment of certain forms of MS (Stuve et al., 2008).

The above-described example highlights the clinical relevance of research aimed at a better understanding of the role of cell adhesion molecules and the mechanisms they are involved in. In addition, it emphasizes the importance of continuing studies to further improve therapeutic strategies targeting cell adhesion mechanisms in general and in particular in MS.

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