

## How immune cells cross the blood-brain barrier

The search for specific therapies for multiple sclerosis has prompted an international research group to investigate how immune cells can cross the blood-brain barrier and trigger inflammatory processes in nerve tissue. The results obtained by the Center for Brain Research in Vienna show that the development of this inflammatory disease is dominated by two types of immune cells which represent an important basis for more specific therapies.



Training exercises for multiple sclerosis patients at health center. Source: Shutterstock.com

Multiple sclerosis (MS) is the most common neurological disease in young adults in

Western Europe and the United States. About one in a thousand individuals suffers from this chronic inflammation of the central nervous system, which is scattered in the brain and spinal cord. While effective therapies already exist, which slow down the course of the disease and can keep existing centres of inflammation in check for a long time, these drugs have a wide-ranging impact on the immune system and thus come with undesirable side effects. In the international research association MELTRA BBB, specialized research groups are jointly investigating which immune cells can penetrate the brain and trigger inflammation and how they do it. At the interface between blood vessels and nerve tissue, the “blood-brain barrier” normally prevents white blood cells and proteins from passing through.

As part of its multilateral activities in an ERA-Net cooperation, the Austrian Science Fund FWF supported this integrated MS research from 2015 to 2018 by funding the neuropathological testing of experimental results at the Center for Brain Research at the Medical University of Vienna. According to Hans Lassmann, the principal investigator, this is the central question that needs to be answered in this context: “Does the explanatory mechanism which colleagues identified in mice during laboratory experiments hold significance for the development of MS disease foci in humans?” The neuropathologist, who has been researching multiple sclerosis for four decades, defines the goal as “developing therapies that intervene in the MS-specific inflammatory process but allow the rest of the immune system to function”.

## **Protective shield for the brain**

Our brain is using up an extreme amount of energy and it is richly perfused with blood vessels. The blood-brain barrier isolates the central nervous system (i.e. brain and spinal cord) and prevents the intrusion of substances that circulate in the body but are not wanted in the control centre. This barrier is formed by the walls of the blood vessels in the brain and spinal cord that are less permeable there than they are in other organs. These so-called endothelial cells are closer together and have only very selective trafficking mechanisms. White blood cells, specifically T lymphocytes and B lymphocytes, can only pass to a minor extent if required for immune defence. To this end they have to be equipped with special molecules that dock on with great precision at a few checkpoints within this tissue barrier. While existing MS therapies focus on T cells of the CD4+ subtype, new data show that CD8+ T cells and B cells play an important role in MS.

## **Coordinated research processes**

The research groups involved in this endeavour are closely interconnected, almost mirroring the closely-knit tissue of the blood-brain barrier. A group in Montreal (Canada), for instance, focused on the identification of specific form-fitting molecules that dock at the checkpoints of the blood-brain barrier. In Toulouse (France), the path of CD8<sup>+</sup> T cells into the brain of mice was studied in experiments. The task of the Vienna-based neuropathologists, on the other hand, was to determine the pathological changes in the nervous tissue resulting from the laboratory experiments using traditional and modern methods – from successive staining of tissue sections with various antibodies to RNA extraction. This was the best way to determine which cell types were involved and what substances might be released at different stages of the disease. Tissue samples from laboratory mice were also compared with human MS samples from the extensive pathology archive. Experienced pathologists can draw conclusions about dynamic processes on the basis of static situations. In this way, they can ultimately show whether the supposed mechanism also takes place in the human body, which would make it relevant for clinical follow-up studies.

### **CD8<sup>+</sup> going postal in nervous tissue**

In the presence of MS, subtype CD8<sup>+</sup> T cells have been shown to stray from their usual role in immune defence. Such cells, for instance after having successfully fended off a virus infection, may stay in the tissue as an immunological memory, remaining dormant until a new infection occurs. However, in fresh foci of inflammation in multiple sclerosis they change into activated mode, which further advances the inflammation. The researchers also investigated the role of B cells, which are thought to play an important role in nerve tissue damage. Both cell types are now being intensively researched in order to be able to use them subsequently for the development of more specific anti-inflammatory drugs.

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### **Personal details**

**Hans Lassmann** is Professor of Neuroimmunology at the Medical University of Vienna and heads the Department of Neuroimmunology at the Center for Brain Research. In 1977 he did postdoc research at the New York State Institute for Basic Research in Developmental Disabilities (USA), where he also began to focus on multiple sclerosis.

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## Publications

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Kuhlmann T, Ludwin S, Prat A, Antel J, Brück W, Lassmann H.: An updated histological classification system for multiple sclerosis lesions, in: Acta Neuropathologica 2017 10.1007/s00401-016-1653-y; <http://doi.org/f9m72m>