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The Enemy Within

Clues to the development of autoimmune reactions that lead to multiple sclerosis

The clinical symptoms of multiple sclerosis – paralysis and vision disorders – stem from misled immune responses against the cell sheath insulating the nerve fibers. First clues to the mechanisms underlying such destructive "autoimmune" reactions are described by Privatdozent Dr. Bruno Kyewski, Division of Cellular Immunology of the Deutsches Krebsforschungszentrum, and Dr. Ludger Klein, Dana Faber Cancer Institute, Boston, together with their collaboration partners, in the latest issue of the science journal Nature Medicine*.

As a model system for investigating the molecular causes of this reaction scientists use a disease comparable to multiple sclerosis: experimental autoimmune encephalomyelitis (EAE). EAE can be triggered in certain inbred strains of mice by injecting specific proteins extracted from nerve cells. Among the targets of the self-destructive immune attacks in EAE is a protein called PLP, which is an important component of the insulating sheath of the nerves.

The researchers have studied the production of PLP in the thymus, an organ where immune cells learn to distinguish between "self" and "nonself". Immune cells directed against the body's own structures are sorted out here to prevent them from doing harm. Cells that have passed through this "school" of the immune system are tolerant of all those self proteins which they have encountered here. However, as the immunologists from Heidelberg have discovered, PLP is produced in the thymus in a shortened version, lacking 35 building blocks of the protein.

Now, what distinguishes EAE-susceptible mice from others not developing this autoimmune reaction? Due to their genetic constitution, EAE-resistant animals do not mount an immune response against the 35 PLP building blocks missing in the thymus. Immune cells attacking other regions of the protein are eliminated anyway. In contrast, in the EAE-susceptible strain scientists have found numerous immune cells targeting exactly the region of the PLP protein which is not produced by the thymus tissue. As the cells do not encounter this target structure in the thymus, the tolerance mechanism fails: They escape elimination and, on their patrols through the body, can cause disastrous damage to the nerve fibers.

According to the authors, a similar mechanism could explain why some people are afflicted by multiple sclerosis. Since only a short variant of PLP is produced in the human thymus, too, our immune system likely cannot acquire complete tolerance for this protein either.

*Klein, L., Klugmann, M., Nave, K.-A., Tuohy, V.K. & Kyewski, B. Shaping of the autoreactive T-cell repertoire by a splice variant of self protein expressed in thymic epithelial cells. Nature Medicine, 6:56 (2000)

The task of the Deutsches Krebsforschungszentrum in Heidelberg (German Cancer Research Center, DKFZ) is to systematically investigate the mechanisms of cancer development and to identify cancer risk factors. The results of this basic research are expected to lead to new approaches in the prevention, diagnosis and treatment of cancer. The Center is financed to 90 percent by the Federal Ministry of Education and Research and to 10 percent by the State of Baden-Wuerttemberg. It is a member of the Helmholtz Association of National Research Centers (Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V.).

This press release is available at www.dkfz.de/pressemitteilungen

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