Multiple sclerosis is remote controlled

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(Medical Xpress)—Autoimmune diseases are triggered by immune cells that attack the body's own tissue. In multiple sclerosis (MS) immune cells succeed in invading nervous tissue and sparking off a destructive inflammation there which can be accompanied by neurological deficits such as paralysis and somatosensory defects. A healthy brain is practically free from immune cells, because the nervous system is separated from the rest of the body via specialized blood vessels that prevent immune cells from entering it from the blood. Up to now it has been unclear how in MS immune cells can overcome this barrier and seemingly pass unhindered into the brain tissue. A research team, initially at the Max Planck Institute for Neurobiology in Martinsried, and later at the University of Göttingen, could now show that these disease-causing immune cells are programmed in the lung to be more motile and to efficiently break through blood vessel barriers.

Specialised immune cells, so-called T cells, are held to be the cause of MS. Even though nearly every healthy human harbours potentially disease-causing T cells in his or her immune system, only around 0.1% of the population actually develops a manifest MS. One of the reasons for this is that normally T cells are stopped from entering the brain by a virtually impermeable vascular barrier separating the central nervous 2/3 system from the blood circulation. "Earlier work in experimental MS research showed that when T cells are pre-activated outside nervous tissue they are very well able to pass into the brain and trigger MS-like symptoms there", explains Alexander Flügel, now head of the Department of Neuroimmunology and the Institute for Multiple Sclerosis, University Medical Center, Göttingen. "However, we wanted

to find out exactly where in the body these T cells are activated and exactly which properties enable them to overcome the blood–brain barrier."

Scientists working at the University Medical Center Göttingen initially discovered that disease-causing T cells cannot enter the brain immediately after activation but rather have to "learn" how to do so. During this learning process the T cells completely re-gear themselves. They stop dividing and throttle their production of proteins that foment inflammation. Instead they are programmed for migration: they become more motile, and specialized receptors appear on their surface membranes. These receptors are like little antennae that enable a T cell to orientate itself by picking up signals from its environment and to cleave to surfaces.

The Göttingen scientists discovered that the receptor Ninjurin 1, previously unknown to have any relevance to T cells, controls the ability of T cells to cleave to the inner side of the brain's blood vessels and thus is of great significance for the migration of T cells from the blood into the nervous tissue. Once the T cells arrive in the nervous tissue, this program goes into reverse: the immigrant T cells are reactivated and they produce inflammatory mediators that set the tissue-damaging autoimmune processes in motion typical to MS.

But where in the body are the T cells programmed for migration? The Göttingen scientists could also make new, unexpected discoveries on this question. They found out that activated T cells migrate directly from the circulation into the lung. Once in the lung tissue the cells move forward with increasing speed along its blood vessels and airways to reach the adjoining lymph nodes from where they re-enter the blood circulation and spleen and ultimately invade the nervous system. Curiously, when in the lung the T cells do not only creep along the outer surface of the bronchial tubes but also crawl briskly along the inner surfaces of the

airways where breathing air is circu-lated. Using a special microscopic technique the researchers could observe in living lung tissue the T cells using the bronchial tubes as a kind of highway. And indeed, when activated T cells are introduced directly into the airways they are able to set an autoimmune disease process in motion. It is also here in the lung where the first decisive steps take place towards programming the disease-causing T cells into a migratory mode.

The direct relevance of these results to the human disease MS lies in the possibility that infections of the respiratory tract and/or lung irritants, e.g. smoking, can trigger disease attacks. The scientists of this study discovered potentially autoaggressive T cells dwelling long-term in the lung as immunological memory cells. When stimulated locally, these "sleeping" cells became active: They migrated to the brain and triggered off an MS-type disease there.

The key role of the lung in activating and reprogramming disease-causing T cells could also be valid for other organ systems such as the gut or urinary tract, though perhaps less dramatically. Recent comprehensive genetic analyses could identify various genes in persons suffering from MS that made these persons more susceptible to the disease. "Interestingly, a significant number of these genes were the same as those found in the current study to be involved in the migratory programming of T cells", says Alexander Flügel. The aim of further studies will therefore be to find genes from the migratory programming that are suitable as therapeutic targets.

More information: Francesca Odoardi, et al. T cells become licensed in the lung to enter the central nervous system. *Nature* (2012) 488: 675-679, doi: 10.1038.nm.2629

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