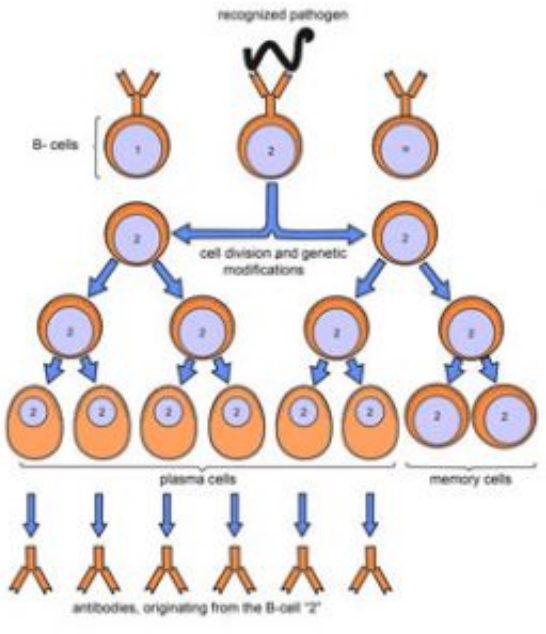
Antibodies in the brain

May 19 2008



Antibody development: A B-cell&acutes recognition of a target structure quickly leads to the production of numerous antibodies ready to attack this target. Memory cells ensure a quick response in case the target reappears at a later time. B-cells which don't recognize the target (here the cells 1 and n), don't produce antibodies. Image: Max Planck Institute of Neurobiology

Each of us carries an unbelievable multitude of antibodies, allowing us to survive the daily battle against pathogens. However, sometimes these antibodies go haywire and attack structures of their own body, for example nerve cells in patients with multiple sclerosis. The origin of these antibodies remained long unknown.

Scientists from the Max Planck Institutes of Neurobiology and Biochemistry and the University Hospital Großhadern (LMU) now developed a procedure, which allows allocating antibodies to their source cells. The method should promote the identification of attacked target structures of multiple sclerosis and other autoimmune- and inflammatory diseases.

With diversity against pathogens

There are thousands of pathogens, many of which alter their shape almost continuously in order to evade the defenses of the immune system. In case a pathogen does manage to breach the first level of rather unspecific barriers, T- and B-cells stand ready for a more specialized attack. To this end, B-cells produce the incredible amount of several billion different antibodies, each of which recognizes a different target structure. The formation of antibody-target complexes then enables other agents of the immune system to attack and destroy the so marked pathogen.

It is impossible for organism's immune system to know in advance which pathogens it will encounter throughout life. Therefore, antibody producing cells are created at random. The incredible variety of these B-cells arises through the combination of different genes and spontaneous mutations. In addition, once a B-cell recognizes a target structure it begins to "learn": the cell rapidly divides and changes the produced antibodies via mutations in such a way, that these bind even tighter to their target (figure).

Misguided immune system: the multiple sclerosis

Just as other highly complex systems, the immune system is not infallible. A by-product of the random genesis of B-cells is that some

cells will target structures of the own body. These cells are usually eliminated before they can do any harm. However, this control system fails in autoimmune diseases such as multiple sclerosis (MS), where the immune system attacks nerve cells in the brain and spinal cord. The liquid surrounding these nerve cells (the liquor) contains many antibodies in MS patients, and antibody occurrence in the liquor is used as one of the indicators for this disease.

Yet, where do these antibodies come from? Do they stem from the relatively few B-cells found in the liquor? Or do they have their origin, like other antibodies, in the blood or the lymphatic organs such as the spleen, the lymph nodes or the bone marrow? With such an origin, the antibodies would need to breach the blood-brain barrier in order to reach the liquor. Although these questions can essentially aid our understanding of multiple sclerosis, they remained long unaddressed.

Now, scientists of the Max Planck Institute of Neurobiology and their Munich colleagues succeeded in developing a procedure which allows the allocation of antibodies to their cells of origin. To achieve this, the scientists took advantage of the vast variety of B-cells. They isolated B-cells from the liquor and analyzed the genetic code of the DNA region responsible for the production of antibodies. This information then allowed the calculation of the size and weight of the respective antibody fragments produced by each analyzed B-cell.

Concurrently, the scientists extracted antibodies found in the liquor and analyzed the weight of their fragments. The comparison of the two datasets left no doubt: the antibodies found in the liquor are produced by the likewise present B-cells. Moreover, the high genetic variability in certain areas of the DNA showed that the liquor B-cells already made contact with their target structures in the nervous system.

A step in many directions

"The next step is now the assembly of the fragments into complete antibodies, which should allow us to identify their target structures in the nervous system" explains Klaus Dornmair, who supervised the study. So far, the targets of most antibodies are still unknown. The identification of target structures could eventually allow the removal of antibodies with the most detrimental effects, which in turn could mitigate multiple sclerosis effects. "An additional highlight of our new procedure is the fact that it's not restricted to multiple sclerosis analyses", reports Klaus Dornmair. The relatively quick and easy procedure should also allow the allocation of antibodies and B-cells in other inflammatory and autoimmune diseases and thus aid our understanding of underlying processes.

Citation: Birgit Obermeier, Reinhard Mentele, Joachim Malotka, Josef Kellermann, Tania Kümpfel, Hartmut Wekerle, Friedrich Lottspeich, Reinhard Hohlfeld, Klaus Dornmair, Matching of oligoclonal Ig transcriptomes and proteomes of cerebrospinal fluid in multiple sclerosis, *Nature Medicine*, 18. May 2008 (The study is part of the SFB 571: Autoimmune reactions: from manifestations and mechanisms to therapy)

Source: Max Planck Institute of Neurobiology