

The “Immune” in Autoimmune Encephalitis: The Role of T and B Cells

The Immune System: An Explainer

When we catch a cold, get an infection, or otherwise become sick, our bodies use a natural defense mechanism called the immune system to fight off what’s attacking us. The immune system has two ways of responding¹. The first, called innate immunity, involves physical and chemical barriers like the skin and saliva, as well as many different types of cells that “eat” and destroy whatever is causing the trouble. While this innate response happens very quickly, then downside is that it’s not very specific, and the immune cells can damage healthy parts of the body while trying to gobble up the foreign invaders. In order to specifically target particular offenders, the body uses its second way of responding: the adaptive immune system. This response can take days or weeks to develop, but is also able to remember what the foreign invader looked like, so if it attacks again a targeted reaction can occur faster than the first time. To acquire this immunity against a particular foreign substance, the body uses two types of cells that act in different ways: T cells (which develop in an organ called the thymus, that’s where the “T” comes from) and B cells (which mature in the bone marrow, hence the “B”).

These two cell types are able to attack so specifically because each one recognizes a particular structure, called an antigen, on a foreign substance. For instance, one T cell might recognize a certain part of an influenza virus, while another could recognize a specific part of a bacterium; the same situation also holds true for B cells. The T and B cells travel around between different lymphoid tissues (organs like the spleen, tonsils, and lymph nodes, the last which are spread throughout the body) until they encounter their particular antigen. Once activated by their antigen, the T and B cells leave the lymph tissues and work in different ways to fight off the foreign invader (Figure 1).

T cells come in many varieties, but the two major types are cytotoxic and helper. Cytotoxic T cells (sometimes referred to as CD8+ T cells due to a particular identifier on their surface) travel to the disease site to search for cells that also bear the antigen that activated them, and destroy them. Helper T cells (sometimes referred to as CD4+ T cells), as the name might suggest, help activate other parts of the immune system. There are many subtypes of helper T cells that activate different types of responses; for instance, some promote the cytotoxic T cell response, while others activate B cells. Another kind of CD4+ T cell called regulatory cells actually tells the immune system not to attack².

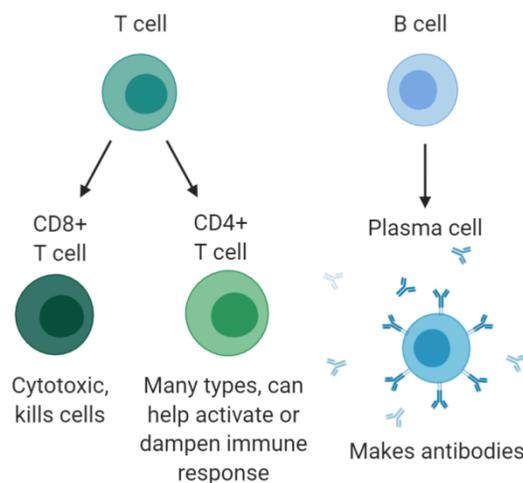


Figure 1: Types of T and B cells

Unlike T cells, B cells do not destroy their target. Instead, once they are activated by their antigen and T helper cells, they mature into plasma cells that produce antibodies, proteins that recognize the same antigen as the B cell. These antibodies essentially enhance the innate immune system and act in several ways, including neutralizing toxins, signaling to other immune cells that a cell should be attacked and destroyed, or activating complement. Complement is a group of proteins (not cells) that make up yet another arm of the immune system. These complement proteins can recruit immune cells or directly kill foreign cells themselves¹.

T and B Cells in Autoimmune Encephalitis

So what happens in autoimmune encephalitis (AE)? In this and other autoimmune diseases, the body mistakenly recognizes part of itself as a foreign invader and mounts an attack. Scientists believe that AE starts when a tumor or virus causes proteins from neurons to be exposed to the immune system. The proteins get picked up by immune cells outside the brain that go on to activate T and B cells in lymphoid tissue. These activated cells then make their way into the brain where they cause AE^{3,4}. Which cells are responsible for causing the disease depends on what antigen set off the immune response.

In cases where the antigen comes from inside a cell, cytotoxic T cells are the culprits. When proteins from inside neurons like Hu, Yo, or Ma2 are the antigens, that usually indicates that the immune system first encountered the proteins in a cancerous tumor, which can express proteins from all sorts of cell types (this cancer association is why these antibodies and diseases are called “onconeural,” or “paraneoplastic”). Cytotoxic T cells fighting the tumor can make their way into the brain and kill neurons⁵. This cell death is likely part of the reason why patients with these diseases have poor recovery. Antibodies from B cells that have matured into plasma cells can also be produced in response to the tumor, but they do not contribute to AE symptoms⁶.

Antibodies *do* have a strong role in producing AE symptoms when the antigen comes from the outside surface of a neuron, like the NMDA receptor for instance. These antibodies can still be formed in reaction to a tumor, but this is less common. Research on NMDAR encephalitis in particular has revealed the presence of B cells and antibody-secreting plasma cells in the brain^{7,8}. Because the antibodies have access to the surface proteins they target, they can bind to them and interfere with their function. In the case of NMDAR encephalitis, it’s thought that the antibodies cause the receptors, which normally are exposed to the outside of the cell, to be taken back inside so that they can’t function properly. Once the antibodies are gone the receptors can return to the cell surface, reversing many of the symptoms⁹. Unlike diseases in which the antibodies target intracellular proteins, in NMDAR encephalitis there are few to no cytotoxic T cells in the brain or neuronal death^{5,7,8}. But while there are little to no cytotoxic T cells, there have been reports of helper T cells around blood vessels in the brain, including one type called Th17 that act to enhance the immune response¹⁰.

In other cases of encephalitis with antibodies against a cell surface protein, such as LGI1, CASPR2, or GABA receptors, the precise immune reaction is less certain and in some ways seems to be a little different from NMDAR encephalitis. B cells and plasma cells are still found in the brain, and antibodies also play a major role in causing symptoms^{5,11}. For instance, antibodies against the GABA_B receptor block it from functioning, while antibodies against LGI1 can disrupt interactions between proteins and lead to a decrease in AMPA receptors¹². The involvement of T cells is unclear and may vary depending on the disease-causing antibody. For example, cytotoxic and helper T cells have been found in the brain of anti-GABA_B receptor patients¹¹, while few T cells were found in anti-VGKC-complex patients⁵. In addition, scientists sometimes observe signs of complement, the protein arm of the immune system that can kill cells^{5,6}. In line with the presence of cytotoxic T cells and complement, neuronal loss is sometimes reported^{5,13}.

Overall, the type of immune response the body produces appears to be dependent on the specific antigen. In general, diseases with antibodies that target intracellular proteins like Hu, Yo, or Ma2 involve cytotoxic T cells that kill neurons. In contrast, diseases with antibodies that target cell surface proteins like NMDAR, LGI1, and GABA_B involve B cells in symptom production. In this second category, the role of T cells and complement may vary depending on the particular antigen.

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