No Antibodies Required For Immunity Against Some Viruses

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A new study turns the well established theory that antibodies are required for antiviral immunity upside down and reveals that an unexpected partnership between the specific and non-specific divisions of the immune system is critical for fighting some types of viral infections. The research, published online in the journal *Immunity* by Cell Press, may lead to a new understanding of the best way to help protect those exposed to potentially lethal viruses, such as the rabies virus.

The immune system has two main branches, innate immunity and adaptive immunity. Innate immunity is a first line of defense that relies on cells and mechanisms that provide non-specific immunity. The more sophisticated adaptive immunity, which counts antibody-producing B cells as part of its arsenal, is thought to play a major role in the specific response to viral infections in mammals. However, adaptive immune responses require time to become fully mobilized.

"Mice infected with vesicular stomatitis virus (VSV) can suffer fatal invasion of the central nervous system even when they have a high concentration of anti-VSV antibodies in their system," explains senior study author, Dr. Ulrich H. von Andrian, from Harvard Medical School. "This observation led us to revisit the contribution of adaptive immune responses to survival following VSV infection."

The research team studied VSV infection in mice that had B cells but did not produce antibodies. Unexpectedly, although the B cells themselves were essential, survival after VSV exposure did not require antibodies or other aspects of traditional adaptive immunity."We determined that the B cells produced a chemical needed to maintain innate immune cells called macrophages. The macrophages produced type I interferons, which were required to prevent fatal VSV invasion," says co-author Dr. Matteo Iannacone.

Taken together, the results show that the essential role of B cells against VSV does not require adaptive mechanisms, but is instead directly linked with the innate immune system. "Our findings contradict the current view that antibodies are absolutely required to survive infection with viruses like VSV, and establish an unexpected function for B cells as custodians of macrophages in antiviral immunity," concludes Dr. von Andrian. "It will be important to further dissect the role of antibodies and interferons in immunity against similar viruses that attack the nervous system, such as rabies, West Nile virus, and Encephalitis."

References:

Moseman et al.: "B Cell Maintenance of Subcapsular Sinus Macrophages Protects against a Fatal Viral Infection Independent of Adaptive Immunity."
Cell Press

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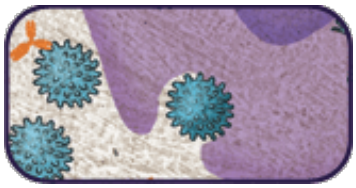
Vaccines

How Vaccines Work

The human immune system is a complex network of cells and organs that evolved to fight off infectious microbes. Much of the immune system's work is carried out by an army of various specialized cells, each type designed to fight disease in a particular way. The invading microbes first run into the vanguard of this army, which includes white blood cells called macrophages (literally, "big eaters"). The macrophages engulf as many of the microbes as they can.



View an illustration of immune cells responding to an invading virus.

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Antigens Sound the Alarm

How do the macrophages recognize the microbes? All cells and microbes wear a "uniform" made up of molecules that cover their surfaces. Each human cell displays unique marker molecules unique to you. Microbes display different marker molecules unique to them. The macrophages and other cells of your immune system use these markers to distinguish among the cells that are part of your body, harmless bacteria that reside in your body, and harmful invading microbes that need to be destroyed.

The molecules on a microbe that identify it as foreign and stimulate the immune system to attack it are called "antigens." Every microbe carries its own unique set of antigens, which are central to creating vaccines.

Macrophages digest most parts of the microbes but save the antigens and carry them back to the lymph nodes, bean-sized organs scattered throughout your body where immune system cells congregate. In these nodes, macrophages sound the alarm by "regurgitating" the antigens, displaying them on their surfaces so other cells, such as specialized defensive white blood cells called lymphocytes, can recognize them.

Lymphocytes Take Over

There are two major kinds of lymphocytes, T cells and B cells, and they do their own jobs in fighting off infection. T cells function either offensively or defensively. The offensive T cells don't attack the microbe directly, but they use chemical weapons to eliminate the human cells that have already been infected. Because they have been "programmed" by their exposure to the microbe's antigen, these cytotoxic T cells, also called killer T cells, can "sense" diseased cells that are harboring the microbe. The killer T cells latch onto these cells and release chemicals that destroy the infected cells and the microbes inside.

The defensive T cells, also called helper T cells, defend the body by secreting chemical signals that direct the activity of other immune system cells. Helper T cells assist in activating killer T cells, and helper T cells also stimulate and work closely with B cells. The work done by T cells is called the cellular or cell-mediated immune response.

B cells make and secrete extremely important molecular weapons called antibodies. Antibodies usually work by first grabbing onto the microbe's antigen, and then sticking to and coating the microbe. Antibodies and antigens fit together like pieces of a jigsaw puzzle—if their shapes are compatible, they bind to each other.

Each antibody can usually fit with only one antigen. The immune system keeps a supply of millions and possibly billions of different antibodies on hand to be prepared for any foreign invader. It does this by constantly creating millions of new B cells. About 50 million B cells circulate in each teaspoonful of human blood, and almost every B cell—through random genetic shuffling—produces a unique antibody that it displays on its surface.

When these B cells come into contact with their matching microbial antigen, they are stimulated to divide into many larger cells, called plasma cells, which secrete mass quantities of antibodies to bind to the microbe.

Antibodies in Action

The antibodies secreted by B cells circulate throughout the human body and attack the microbes that have not yet infected any cells but are lurking in the blood or the spaces between cells. When antibodies gather on the surface of a microbe, it becomes unable to function. Antibodies signal macrophages and other defensive cells to come eat the microbe. Antibodies also work with other defensive molecules that circulate in the blood, called complement proteins, to destroy microbes.

The work of B cells is called the humoral immune response, or simply the antibody response. The goal of most vaccines is to stimulate this response. In fact, many infectious microbes can be defeated by antibodies alone, without any help from killer T cells.

Clearing the Infection: Memory Cells and Natural Immunity

When T cells and antibodies begin to eliminate the microbe faster than it can reproduce, the immune system finally has the upper hand. Gradually, the virus disappears from the body.

After the body eliminates the disease, some microbe-fighting B cells and T cells are converted into memory cells. Memory B cells can quickly divide into plasma cells and make more antibody if needed. Memory T cells can divide and grow into a microbe-fighting army. If re-exposure to the infectious microbe occurs, the immune system will quickly recognize how to stop the infection.

How Vaccines Mimic Infection

Vaccines teach the immune system by mimicking a natural infection. For example, the yellow fever vaccine, first widely used in 1938, contains a weakened form of the virus that doesn't cause disease or reproduce very well. Human macrophages can't tell that the vaccine viruses are weakened, so they engulf the viruses as if they were dangerous. In the lymph nodes, the macrophages present yellow fever antigen to T cells and B cells.

A response from yellow-fever-specific T cells is activated. B cells secrete yellow fever antibodies. The weakened viruses in the vaccine are quicky eliminated. The mock infection is cleared, and humans are left with a supply of memory T and B cells for future protection against yellow fever.

back to top

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