New findings could help vaccine designers elicit long-term immunity

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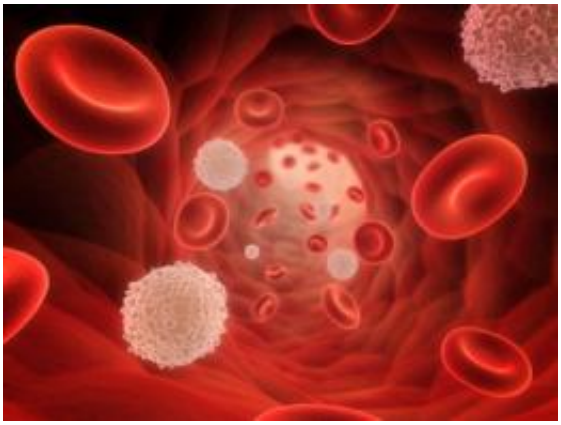

Red and white blood cells flow through a blood vessel. White blood cells known as memory T cells help the body react quickly to viruses or bacteria it has seen before.

After recovering from a cold or other infection, your body's immune system is primed to react quickly if the same agent tries to infect you. White blood cells called memory T cells specifically remember the virus or bacterium and patrol the body looking for it. Vaccines work on the same principle: Harmless fragments of a virus or bacterium provoke the immune system to generate memory T cells that can attack the real thing later on.

As time passes, however, this specific immunity can wear off. That's because not all memory T cells live long enough to foster long-term

immunity.

MIT biologists have now demonstrated the conditions that favor development of long-term memory T cells over short-term memory T cells, which can respond quickly but don't stick around for very long after the initial infection. That discovery could help vaccine designers better tailor their formulas to elicit long-term memory immunity, says Jianzhu Chen, MIT professor of biology and member of the David H. Koch Institute for Integrative Cancer Research.

Chen and Herman Eisen, emeritus professor of biology, are senior authors of a paper on the work that appeared in the *Proceedings of the National Academy of Sciences* the week of Dec. 13.

Memory

In the *PNAS* study, the MIT team looked at mice infected with influenza. In mice, as in humans, influenza virus stimulates T cells, whose job is to kill infected cells. Every T cell is programmed to recognize different foreign proteins (also called antigens) located on the surfaces of infected cells. When a T cell binds to the antigen, the T cell becomes activated and starts rapidly reproducing, creating an army of cells that can identify and destroy the invader.

Once the infection is eliminated, most of the activated T cells die off, but a few of them stick around, in case the virus comes back. These are short-term memory T cells. Because they have already battled the virus and reproduced many times, they survive only weeks or months after the initial infection. (T cells can only divide a certain number of times before they die.)

A set of long-term memory T cells also develops during infection. These cells are programmed differently, so they can persist for decades.

Recipients of the smallpox vaccine, for example, have been shown to still have T cells against the virus up to 70 years later, says Eisen.

T cell development

Until now, it has been unclear how these different cell types develop. In their new study, Eisen and Chen investigated the role three factors: T-cell location, the amount of antigen exposure, and length of exposure.

Scientists already knew that T cell contact with a large amount of virus provokes development of short-term memory T cells, says Eisen. Chen and colleagues discovered that large amounts of antigen also suppress development of long-term memory T cells. Those cells only develop when exposed to a small amount of the antigen, for a short period of time.

For example, if you have an infection in the respiratory tract, nearby T cells will be exposed to many viruses and become short-term memory cells. Those cells hang around the respiratory tract, ready to pounce quickly if the same virus re-infects you, but they eventually die off.

In more distant parts of the body, T cells are exposed to only small amounts of the virus, and some of those cells become long-term memory T cells specific to that virus. These maintain a low level of constant vigilance, in case the virus ever returns.

Ulrich von Andrian, professor of immunopathology at Harvard, says the new study's major contribution is its experimental support of existing theories. "It builds on ideas that have been around for a while, that were not rigorously tested by experiments, for the most part," says von Andrian, who was not part of the research team.

Vaccination

When developing vaccines, the goal is usually to generate a stable population of long-term memory T cells. This study suggests that the best way to do that is to give a small amount of antigen, and, for vaccines that require multiple injections, not to give them too frequently.

“The general rule of thumb is that you don’t want to give a large amount of antigen on a short-term basis,” says Chen. He adds that the amount of antigen for inducing a long-term memory T cells likely varies depending on the route of immunization and the form of antigen, and so the dosage for each vaccine will have to be determined through experiments.

He says the findings will likely not impact flu-vaccine design because existing dosages have already been optimized over many decades. However, the findings should be applicable to vaccines now under development for other diseases, such as HIV, tuberculosis and dengue fever, says Chen.

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