Scientists Develop Novel Vaccine Concept

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Creating vaccines to protect people against viral diseases like AIDS, cervical cancer and infectious hepatitis is a delicate balancing act: If the immune system's response to the vaccine is too strong, toxic side effects can kill the patient. If it's not strong enough, the virus will spread faster than the immune system can kill it.

A new vaccine design strategy developed by scientists at The Wistar Institute Vaccine Center could be the answer. The secret is using a herpes simplex protein called glycoprotein D to block a specific receptor molecule on antigen-presenting cells, or APCs. These sentinel cells monitor the body for foreign antigens – molecules that can stimulate an immune response – from invading viruses.

When they detect viral antigens, APCs signal the body's immune system to activate T cells to attack and destroy cells infected with the virus. At the same time, they also send inhibitory signals to prevent overreaction by the immune system. One of thee inhibitory signals is blocked by glycoprotein D from herpes virus.

In a study that will be published February 6 in *Nature Medicine* and is available online, Wistar scientists showed that vectors, which are vaccine delivery systems, made by fusing the glycoprotein D with genes from target antigens increase the immune system's response to those antigens in cell cultures and laboratory mice. The researchers used antigens from HIV, the virus that causes AIDS, and from HPV-16, a human papilloma virus that causes cervical cancer.

Hildegund C.J. Ertl, M.D., director of The Wistar Institute Vaccine Center and senior author of the study, says using glycoprotein D to deliver antigens has a major advantage over other vaccine approaches. “It allows us to lower the dose but still get a stronger immune response,” she says.

Glycoprotein D is part of the herpes viral envelope and is expressed on the surface of cells infected with the herpes simplex virus. Glycoprotein D binds to a receptor molecule called HVEM (herpes virus entry mediator) on antigen-presenting cells. By locking onto the HVEM receptor, glycoprotein D prevents HVEM from binding to another molecule called BTLA on T and B lymphocytes – white blood cells that attack disease-causing pathogens.

Binding between HVEM and BTLA is the first step in an inhibitory signaling pathway that reduces the immune system’s response to the presence of a virus. Blocking this inhibitory pathway allows the body to mount a stronger immune response by generating more antigen-specific CD8+ T cells to attack cells infected with the virus.

The researchers found that fusing HIV and HPV antigens to glycoprotein D enhances the immune response to those antigens. Mice injected with vaccines that included antigens fused to glycoprotein D generated more virus-killing CD8+ T cells than mice injected with the same vaccines and antigens, but without the glycoprotein D carrier protein.

Researchers also inoculated identical strains of laboratory mice with vaccines containing genes for the cancer-causing proteins E7, E6 and E5 from the HPV-16 virus. One group of animals received HPV-16 genes spliced into the genetic code for glycoprotein D; another group received the same antigens without glycoprotein D. Ten to 14 days later, both groups of animals were injected with a fast-growing tumor cell line that normally generates extensive tumors in mice within 14 days.

Mice that received vaccines with the glycoprotein D-antigen combination were fully protected against cancer, says Wistar's Marcio Lasaro, Ph.D., lead author of the study. However, mice inoculated with vaccines containing the same HPV-16 genes, but without glycoprotein D, developed tumors after being inoculated with the same tumor cell line.

"It's important to point out that the molecules we targeted in mice are similar to those in humans, and all the basic in-vitro studies in the paper were done with human molecules, making it likely that the method will also work in people," Lasaro says.

Ertl says the ability of the glycoprotein D carrier protein to enhance the immune response could be particularly important to the development of a long-sought vaccine for AIDS. "The problem with HIV vaccines is that they might look good in mice and primates, but comparable doses in humans are too toxic," she says. "If you lower the dose to avoid toxic side effects, you don't get the immune response you need." She believes that using glycoprotein D may solve that problem.

Ertl and her colleagues are planning future studies to further elucidate the mechanism behind the carrier protein's effectiveness. If studies in research animals continue to be positive, they hope to conduct human clinical studies with HIV and HPV vaccines currently under development at The Wistar Institute Vaccine Center.

The Wistar Institute has filed for patent protection on the glycoprotein D carrier protein technology.

Source: The Wistar Institute