Medical Xpress

Vaccine study reveals link between immunity and cells' starvation response

December 5 2013

One of the most effective vaccines in history has been the yellow fever vaccine, which was developed in the 1930s and has been administered to more than 500 million people.

Scientists at Emory Vaccine Center studying immune responses to the yellow fever vaccine have identified a gene whose activation in key immune cells is a sign of a robust response. The gene, called GCN2, encodes a protein involved in sensing amino acid starvation and regulates the process of autophagy, a response to starvation or stress within cells.

The findings highlight a link between antiviral defenses and an ancient way that cells adapt to scarcity, and could help researchers develop vaccines against challenging viruses such as HIV or dengue. The results suggest that vaccine additives (called adjuvants) that are effective in stimulating GCN2 and autophagy would be especially potent in stimulating long-lasting immunity.

The results are scheduled for publication Thursday by the journal *Science*.

"This is an example of taking a system-wide approach to studying vaccine responses, and how it can reveal new insights about the functioning of the immune system," says senior author Bali Pulendran, PhD. "We were not thinking about the stress response pathway and immunity until our analysis pointed us in that direction."

Pulendran is Charles Howard Candler professor of pathology and laboratory medicine at Emory University School of Medicine and a researcher at Yerkes National Primate Research Center. The co-first authors of the paper are postdoctoral fellows Ravesh Ravindran, PhD and Noor Khan, PhD.

A single dose of the live attenuated viral yellow fever vaccine can protect against disease-causing forms of the virus for decades. Investigators led by Pulendran have been dissecting immune responses to the yellow fever vaccine, taking a genome-wide "systems biology" approach.

They started by looking at all the genes that are turned on a few days after human volunteers were vaccinated against yellow fever and asked: which genes' activations are the signatures of especially strong immune responses later? In particular, Pulendran and his colleagues looked for responses by CD8 "killer" T cells, which are important for eliminating virally-infected cells from the body.

One gene that stuck out was GCN2, because it was induced quickly after vaccination and was a sign that the immune system would later respond with lots of CD8 T cells.

GCN2 was known to be a sensor inside cells that detects low levels of amino acids, the building blocks for proteins. GCN2 regulates the process of autophagy, in which cells respond to starvation or stress by ceasing growth and beginning to digest themselves.

In the *Science* paper, Pulendran and his colleagues show that GCN2's function is especially critical in dendritic cells, whose job is to "present" information about viruses and other pathogens to the rest of the immune system. Dendritic cells lacking GCN2 are less able to activate CD8 T cells, they found.

Mice that lacked GCN2 had impaired responses to yellow fever vaccine and to inhaled influenza vaccine, the researchers found.

They also found that infection with yellow fever leads to a depletion of amino acids within dendritic cells. When viruses infect dendritic cells, it appears that the viruses start using up the building materials on hand. This tips the dendritic cells into autophagy and raising an alarm with the rest of the immune system, Pulendran says.

"This may have evolved as a mechanism of pathogen sensing that is capable of detecting the footprints of a pathogen, such as depleted amino acids in a local microenvironment," he says.

More information: "Vaccine Activation of the Nutrient Sensor GCN2 in Dendritic Cells Enhances Antigen Presentation" *Science*, 2013.

Review on history of yellow fever vaccine: www.nature.com/nri/journal/v9/n10/abs/nri2629.html

Provided by Emory University