New origin found for a critical immune response

March 1 2009

An immune system response that is critical to the first stages of fighting off viruses and harmful bacteria comes from an entirely different direction than most scientists had thought, according to a finding by researchers at the Duke University Medical Center.

"This finding will have important implications in vaccine science and autoimmune disease therapy development," said Michael Gunn, M.D., an immunologist and cardiologist at Duke and senior author of the study published in *Nature Immunology*.

Type 1 helper (TH1) T cell immune responses are critical for the control of viruses and certain bacteria. Immunologists have generally believed that TH1 responses are induced by rare immune cells, called dendritic cells. When activated by infection or vaccination, the dendritic cells were thought to move from peripheral tissues into lymph nodes to stimulate T cell responses.

The Duke researchers found, however, that the dendritic cells that stimulate TH1 responses didn't come from peripheral tissues, but rather arose from monocytes, a common cell type in the blood, that moved directly into lymph nodes after infection.

"The result speaks to the most basic principles of immune response to pathogens," Gunn said. "It may also explain the poor results we have seen in attempts to develop effective dendritic-cell vaccines."

Gunn previously had identified a particular protein, known as a chemokine, that stimulates the migration of activated dendritic cells from peripheral tissues to lymph nodes. The Duke researchers generated a TH1 response in laboratory mice that lacked this chemokine with influenza viruses.

"We really thought the mice would not be able to generate much of an immune response at all," Gunn said, because they wouldn't be able to mobilize dendritic cells. "The mice, however, had increased TH1 responses. We knew we had to find what was really causing the response."

One scientist who knew about these findings told Gunn the Duke group would "never figure this out" because their findings were so unconventional.

To solve the mystery, the Duke team studied several different types of mice, which were missing other chemokines or chemokine receptors. They found that mice without the Ccr2 chemokine receptor that controls the migration of inflammatory monocytes had much lower accumulation of monocyte-derived dendritic cells and TH1 responses.

The scientists concluded that there is a blood-derived lymph node dendritic cell type that has a key role in developing acute T-cell responses. "For so long, dendritic cells from tissues were the obvious answer," Gunn said. "We found out that that's not always the case."

The team now plans to look at the blood-derived dendritic cells under different conditions to see if they may have other activities. "We observed the activity of these cells after TH1-inducing stimuli, like influenza," Gunn said. "Next we'd like to study other types of immune stimuli to see how the cells respond."

Understanding how dendritic cells stimulate different types of immune response would open the door to enhancing or inhibiting these responses, a major goal of immunologists trying to prevent infections or control autoimmune disease, Gunn said.

Source: Duke University Medical Center