Vitamin A signals offer clues to treating autoimmunity

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Distributed around the body, dendritic cells act as the security alarms of the immune system. After sensing the presence of intruders, dendritic cells can transmit the alarm to white blood cells or tell them to relax, depending on the signals they send out.

Researchers at the Emory Vaccine Center and Yerkes National Primate Research Center have discovered that dendritic cells can respond to the same compound, through two different receptors, by sending out both stimulatory and calming messages at once.

The compound is zymosan, a component of yeast cell walls. However, the finding could guide scientists in designing vaccines against many infectious agents since the calming receptor is known to respond to bacteria and viruses as well as yeast. In addition, silencing the calming receptor's messages might boost the immune system's ability to fight a chronic infection.

The results are published in the March 2009 issue of *Nature Medicine*.

The calming receptor, known as TLR2 (Toll-like receptor 2), uses vitamin A to transmit its signals, which provides an explanation for the connection between vitamin A deficiency and autoimmune diseases. Vitamin A deficiency has been linked to diseases such as rheumatoid arthritis, lupus and type I diabetes.

This "two signals at once" feature of the immune system can be viewed

as the result of an evolutionary tug of war, says senior author Bali Pulendran, PhD, professor of pathology and laboratory medicine at Emory University School of Medicine and Yerkes National Primate Research Center.

"The immune system has to provide a defense against infection, while avoiding the destruction of too much of the body along the way," he says. "At the same time, pathogens have evolved strategies to manipulate the immune system for their own purposes."

Working with Pulendran, postdoctoral fellow Santhakumar Manicassamy, PhD, examined which genes are turned on in dendritic cells by zymosan in cell culture. They were surprised to find that both zymosan and live Candida albicans, which causes yeast infections, turned on genes involved in converting vitamin A to its active form, retinoic acid.

"Others have seen that these genes are turned on constitutively in the gut, but seeing how they can be induced elsewhere is new," Pulendran says.

Manicassamy and colleagues found that dendritic cells use retinoic acid along with other chemical messengers to steer white blood cells into a regulatory mode, rather than an attack mode. For dendritic cells to do so, they need TLR2, since zymosan also activates another receptor called dectin-1, which sends out stimulatory signals.

The effects of zymosan and TLR2 can deter white blood cells from attacking nerve tissue in a mouse model of multiple sclerosis, the authors found.

In the model, mice are immunized against myelin, which forms a protective sheath around nerves. Injecting the mice with zymosan at the same time as immunization reduced the damage to their nerves.

More information: S. Manicassamy et al. TLR2-dependent induction of vitamin A metabolizing enzymes in dendritic cells promotes T regulatory responses and inhibits Th-17-mediated autoimmunity. *Nature Medicine*, March 2009.

Source: Emory University