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Vitamin A may help boost immune system to fight tuberculosis

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Tuberculosis is a major global problem, affecting 2 billion people worldwide and causing an estimated 2 million deaths annually. Western countries are once again tackling the disease, with recent outbreaks in Los Angeles and London.

The rise of drug-resistant TB, called a "ticking time bomb" by the World Health Organization, and the high cost of fighting the disease highlight the need for new approaches to treatment.

In findings published in the March 1 issue of the *Journal of Immunology*, UCLA researchers investigating the role of nutrients in helping the immune system fight against major infections show that vitamin A may play an important role combating TB.

The UCLA team describes for the first time the mechanism by which vitamin A and a specific gene assist the immune system by reducing the level of cholesterol in cells infected with TB. This is important because cholesterol can be used by TB bacteria for nutrition and other needs, the researchers said.

"If we can reduce the amount of cholesterol in a cell infected with tuberculosis, we may be able to aid the immune system in better responding to the infection," said senior author Philip Liu, an assistant professor of medicine in the divisions of dermatology and orthopedic surgery at UCLA's David Geffen School of Medicine and Orthopaedic Hospital Research Center. "Understanding how nutrients like vitamin A

are utilized by our immune system to fight infections may provide new treatment approaches."

Although vitamin A circulates in the body in an inactive form known as retinol, it's the active form of the nutrient—all-trans reinoic acid—that is responsible for activating the immune system.

To investigate the role of this active form of vitamin A in immune defense, the UCLA team first compared its effects on cells to the effects of a similar nutrient, vitamin D, which the group had previously studied. The researchers thought the two vitamins might use the same mechanism to aid the immune system, but this wasn't the case. They found that when the vitamins were added to human blood cells infected with tuberculosis, only vitamin A decreased the cells' cholesterol levels.

The researchers also discovered that the action of vitamin A was dependent on the expression of a gene called NPC2. Further experiments in the lab showed that even if an infected blood cell was stimulated with vitamin A, it would not be able to fight the tuberculosis bacteria if the cell couldn't express the NPC2 gene.

"We were very surprised that this particular gene was involved, since it has traditionally been associated with cholesterol transport and not immune defense," said co-first author Elliot Kim, who was a research technician in Liu's lab at the time of the study and is currently a graduate student in the department of microbiology, immunology and molecular genetics at the Geffen School.

However, once the team took a closer look at the actions taking place in the cells, it made sense.

Cholesterol is stored in lysosomes, compartments in a cell that also play an integral role in fighting infections. If the lysomome is full of

cholesterol, it supplies the bacteria with needed nutrition instead of killing it.

Vitamin A induces the cell to express NPC2, which helps the cell effectively remove cholesterol from the lysosomes so the bacteria can't access it. This allows the lysomomes to once again become effective in killing the bacteria.

When activated correctly, lysomomes fuse with the area of the cell containing the bacteria and dump antimicrobial material onto the bacteria to kill it, similar to a helicopter dropping water and retardant on a forest fire.

"The cells need vitamin A to trigger this defense process and NPC2 to carry it out," said co-first author Matthew Wheelwright, a medical and doctoral student at the University of Minnesota who was an undergraduate research assistant in Liu's lab when the research was conducted. "We may be able to target these pathways that regulate cholesterol within a cell to help the immune system respond to infection."

The next stage of research will focus on better understanding how the immune system takes retinol, the inactive form of vitamin A, and creates all-trans retinoic acid, the form of the nutrient that can activate the infected cells against the tuberculosis bacteria.

The UCLA team notes that this is an early study and that more research needs to be done before recommending vitamin A supplementation to combat tuberculosis or other infections.

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