Immune cells hold clues to vitamin D absorption, study suggests

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Vitamin D plays an integral role in regulating immune function, and Penn State researchers have identified immune cells in mice that can be differentiated by whether or not they have vitamin D receptors—a

finding that could lead to a better understanding of the link between vitamin D status and autoimmune diseases such as ulcerative colitis, Crohn's disease and multiple sclerosis.

In laboratory studies, Margherita Cantorna, distinguished professor of molecular immunology in the College of Agricultural Sciences, and Juhi Arora, former pathobiology doctoral student in the Cantorna lab, used flow cytometry, a lab test that analyzes characteristics of cells or particles, to perform highly sensitive assays or analyses to determine the composition of substances. These assays categorized particular immune cells based on whether or not they express the vitamin D receptor. Immune cells include cells such as monocytes, T cells and B cells—all of which perform critical roles in the immune system, protecting the body from infection.

"It's tricky with immune cells," Cantorna said. "They express vitamin D receptors, but at very low levels compared to cells in other tissues—epithelial cells and cells in the kidney, for example. To detect vitamin D receptors in immune cells, you need more sensitive assays. To make identification even more challenging, most of the data show that the resting immune system has very low levels of the vitamin D receptor. Only a couple of days after an infection did immune cells actually express the vitamin D receptor. So receptor expression was regulated by the presence of an infection."

Interest in vitamin D as an immune system regulator goes back to the 1980s when researchers first identified receptors for vitamin D in cells in the immune system, Cantorna noted.

"Since 1983, it has been known that immune cells such as monocytes and activated T and B cells expressed the vitamin D receptor and are, therefore, vitamin D targets," she said. "We set out to understand more about the mechanisms that regulate the immune system—how vitamin D

affects these cells whose job it is to turn the immune response on and off."

The body needs vitamin D to help absorb calcium from the intestines—calcium that is needed for bone health and strength. Vitamin D can come from food, sunlight exposure to the skin and supplements. After vitamin D is absorbed through the skin or acquired from food or supplements, it gets stored in the body's fat cells, where it remains inactive until it's needed. When the body needs vitamin D, the liver and kidneys, through a process called hydroxylation, turn the stored vitamin D into the active form that binds to receptors.

How much active vitamin D the body makes is a tightly controlled process, Cantorna said. This regulation of vitamin D is critical for health: Vitamin D deficiency can cause weak bones and muscles, and too much vitamin D can lead to calcium buildup in the blood, which causes problems such as nausea and high blood pressure.

Through their research, Cantorna and her graduate students discovered that vitamin D acts as a "fine tuner" when regulating immunity. She explained that the immune system's job is to recognize a threat—that is, an infection—ramp up to fight the infection, and once the infection is gone, come back down.

"We learned by studying various infections in mice that vitamin D seems to help the immune system turn off after the infection is gone," she said. "And that's critical for recovery from infection because many infections' lethality results from too much immune response—the inflammation caused by the infection lasts longer and is more severe if the immune response goes unchecked. This discovery that vitamin D plays a subtle yet critical role in controlling immune response advanced our understanding of the role of vitamin D as a regulator of immunity."

In their recent paper, published in *The Journal of Steroid Biochemistry and Molecular Biology*, the researchers report that in the mouse tissues they examined, some immune cells are insensitive to vitamin D—do not have vitamin D receptors—and other immune cell populations are almost all sensitive to vitamin D because they have vitamin D receptors. Most immune cell populations fall somewhere in the middle.

"This suggests that vitamin D is regulating immune response by targeting some cells but not others," Cantorna said.

This finding has treatment implications for humans with a vitamin D deficiency: The presence of fewer immune cells that express the vitamin D receptor suggests an inability or reduced ability to respond to vitamin D supplements.

Cantorna said she wants to explore these contrasting immune cells and determine what might cause the difference in them.

"We're also interested in tweaking those cells—or finding out if that's possible," she said. "What signals could increase vitamin D receptor expression in tissues and cells where we want to see the benefits of vitamin D? That knowledge will help advance us on the path of understanding the nuances of vitamin D as a regulator of immunity."

More information: Margherita T. Cantorna et al, Two lineages of immune cells that differentially express the vitamin D receptor, *The Journal of Steroid Biochemistry and Molecular Biology* (2023). DOI: 10.1016/j.jsbmb.2023.106253

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