Protein regulates vitamin A metabolic pathways, prevents inflammation

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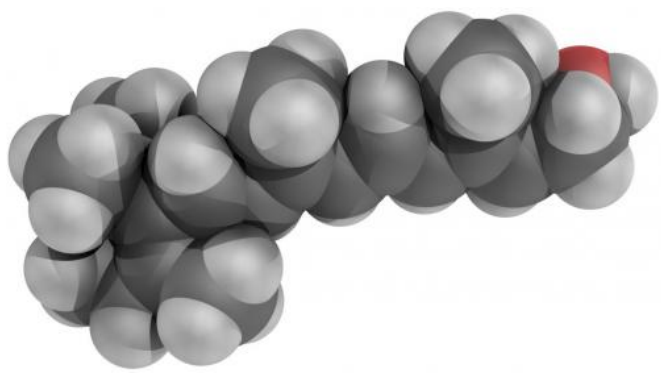

Retinol or Vitamin A 3D space model (balls model). Credit: YassineMrabet, Wikipedia.

A team of researchers from Case Western Reserve University School of Medicine have discovered how uncontrolled vitamin A metabolism in the gut can cause harmful inflammation. The discovery links diet to inflammatory diseases, like Crohn's disease and inflammatory bowel syndromes, and could inform nutritional interventions.

In the *Proceedings of the National Academy of Sciences*, the researchers described a branching point in the metabolic pathway for vitamin A that hinges on a single protein, called ISX. The pathway starts with beta-carotene—the pigmented nutrient that gives sweet potatoes and carrots their color. Beta-carotene forms vitamin A in the small intestine. From there, the majority of vitamin A is transported to other tissues to support healthy vision and other functions. Some vitamin A is also used to produce a growth factor for immune cells in the gut. By studying mice genetically modified to lack ISX, the researchers found ISX helps the body balance this process.

The study showed ISX turns on and off genes involved in the pathway based on beta-carotene availability. The protein helps the small intestine shuttle in the right amount of beta-carotene for the body's vitamin A needs, similar to a gatekeeper at a drawbridge. Nearby immune cells rely on this control mechanism to properly respond to foods entering the small intestine. This maintains an effective barrier against potential foodborne threats. The researchers found that when ISX is absent, immune cells in the small intestine can overreact to beta-carotene-rich diets. Their findings suggest ISX is a key mediator between diet and gut immunity.

Johannes von Lintig, PhD, associate professor of pharmacology at Case Western Reserve School of Medicine, led the study alongside colleagues from the department of pharmacology and the department of molecular biology and microbiology.

"Vitamin A exists in the diet as beta-carotene, which is enzymatically converted by cells lining the intestine. The content of beta-carotene in natural foods is variable and subject to seasonal fluctuations," said Ni Made Airanthi (Ila) Widjaja-Adhi, PhD, lead author of the study and post-doctoral fellow with von Lintig and Marcin Golczak, PhD, co-author and assistant professor of pharmacology at Case Western Reserve School of Medicine. "We describe in this study a mechanism for coping with this fluctuation, to maintain immunity at the intestinal barrier."

The researchers discovered removing ISX ramps up gene expression 200-fold for the enzyme (Bco1) that converts dietary beta-carotene to vitamin A. Because of this, mice without ISX overproduced vitamin A, and began converting it into retinoic acid—a molecule that regulates the activity of many genes, including genes essential for immunity. This caused localized swelling—inflammation—as immune cells flooded the area and reproduced. Such severe inflammation made mice lacking ISX immunocompromised, and the inflammation spread to the nearby pancreas.

Mice without ISX couldn't control their vitamin A levels. They overproduced vitamin A and drew too many immune cells to the small intestine. "Too much vitamin A can promote inflammatory disease," von Lintig concluded. "In future studies, the ISX-deficient mouse will be a versatile model to study the molecular details of the intriguing interplay between diet and gastrointestinal immunity."

The study positions ISX at an important control point in vitamin A metabolism. According to von Lintig, ISX may also drive the crosstalk between diet and gut immunity in humans. "Genetic mutations in the ISX gene have been associated with inflammatory disorders such as Crohn's disease. A better understanding of the molecular factors that control gut immunity will aid the development of nutritional intervention strategies to improve health."

More information: Made Airanthi K. Widjaja-Adhi et al, Transcription factor ISX mediates the cross talk between diet and immunity, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1714963114

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