Hum Mol Genet. 2015 Jun 1;24(11):3206-19. doi: 10.1093/hmg/ddv072. Epub 2015 Feb 20.

A genetic dissection of intestinal fat-soluble vitamin and carotenoid absorption.

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Abstract

Carotenoids are currently investigated regarding their potential to lower the risk of chronic disease and to combat vitamin A deficiency. Surprisingly, responses to dietary supplementation with these compounds are quite variable between individuals. Genome-wide studies have associated common genetic polymorphisms in the BCO1 gene with this variability. The BCO1 gene encodes an enzyme that is expressed in the intestine and converts provitamin A carotenoids to vitamin A-aldehyde. However, it is not clear how this enzyme can impact the bioavailability and metabolism of other carotenoids such as xanthophyll. We here provide evidence that BCO1 is a key component of a regulatory network that controls the absorption of carotenoids and fat-soluble vitamins. In this process, conversion of β-carotene to vitamin A by BCO1 induces via retinoid signaling the expression of the intestinal homeobox transcription factor ISX. Subsequently, ISX binds to conserved DNA-binding motifs upstream of the BCO1 and SCARB1 genes. SCARB1 encodes a membrane protein that facilitates absorption of fat-soluble vitamins and carotenoids. In keeping with its role as a transcriptional repressor, SCARB1 protein levels are significantly increased in the intestine of ISX-deficient mice. This increase results in augmented absorption and tissue accumulation of xanthophyll carotenoids and tocopherols. Our study shows that fat-soluble vitamin and carotenoid absorption is controlled by a BCO1-dependent negative feedback regulation. Thus, our findings provide a molecular framework for the controversial relationship between genetics and fat-soluble vitamin status in the human population.

PMID: 25701869 PMCID: PMC4424956 DOI: 10.1093/hmg/ddv072