

Abstract

J Nutr Biochem. 2007 Aug;18(8):497-508.

Vitamin A regulation of gene expression: molecular mechanism of a prototype gene.

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BACKGROUND: Vitamin A regulation of gene expression is a well-characterized example of direct nutrient regulation of gene expression. The downstream metabolites of retinol, all-trans and 9-cis retinoic acids are the bioactive components that bind and activate their cognate nuclear receptors to regulate target genes.

SUMMARY OF FINDINGS: There are multiple retinoid receptor subtypes that are encoded by separate genes and each subtype has different isoforms. These receptors are Class II members of the thyroid/retinoid/vitamin D superfamily of nuclear receptors. The characterization of the retinoid receptors and the DNA response elements of target genes that bind these receptors have vastly expanded our knowledge of the mechanism of retinoid regulation of target genes. The basic regulatory mechanism of retinoids interacting with their cognate receptors is further complicated by the interaction of coactivators and corepressors, nuclear proteins that are involved in activation or repression of transcription, respectively. Most of these coregulators are involved in modifying chromatin and nucleosome structure such that chromatin is relaxed or condensed, and in bridging between the upstream enhancer domains and the transcription preinitiation complex. Retinoid regulation of the rate of transcription of target genes and the duration of the retinoid response is further complicated by covalent modification of the retinoid receptors by phosphorylation involved in coactivator association and ubiquitinylation involved in the degradation of retinoid receptors.

DISCUSSION: This review presents a prototype retinoid responsive gene that encodes the phosphoenolpyruvate carboxykinase (PEPCK) gene as an example of a specific mechanism of retinoid regulation of a metabolic gene. The retinoid response elements and overall mechanism of retinoid regulation of the PEPCK gene have been well documented by both in vitro and in vivo methods.

CONCLUSION: We provide detailed information on the specific nuclear receptors, coactivators and chromatin modification events that occur when vitamin A is deficient and, therefore, retinoids are not available to activate the nuclear retinoid-signaling cascade.

PMID: 17320364