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Regulation of eukaryotic gene expression by vitamin A and D through nuclear receptors

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Natural derivatives of vitamin A and D are required for many physiological processes. The pleiotropic action of retinoids (vitamin A derivatives), which appear to play important roles in embryogenesis, cell growth and differentiation, and homeostasis, is mediated by interaction with two subfamilies of nuclear receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR). Each retinoid receptor subfamily consists of several receptor isoforms referred to as RARα, β, γ, and RXRα, β, γ. The classification of the RAR and RXR subfamilies are based on the differences in primary structure, sensitivity to retinoid ligands, and ability to regulate expression of different target genes. RARs bind both all-*trans*- and 9-*cis*-retinoic acid, wheras the second family RXRs appear specific for the 9-*cis* retinoic acid. RARs and RXRs are part of the steroid-thyroid hormone receptor superfamily that also includes receptors for estrogen and vitamin D. These receptors function as ligand-activated transcriptional factors that bind to specific response sequences on the target genes and thereby regulate the transcriptional expression of these genes. The RA response element, usually consisting of AGGTCA or like core motifs arranged as a direct repeat with 2- or 5-bp spacing were found in many genes such as phosphoenolpyruvate carboxykinase, apolipoprotein A1, laminin B1, and alcohol dehydrogenase 3 genes. For transactivation, RARs require interaction with RXRs, resulting in the formation of RAR-RXR heterodimers that recognize an RA response element. RXRs can also heterodimerize with several other nuclear hormone receptors, including thyroid hormone receptors, vitamin D receptor, and most likely other nuclear proteins. In addition, RXR can fuction as homodimers, in the presence of its ligand, 9-*cis*-retinoic acid.

Vitamin D_3 undergoes metabolic activation in liver and kidney to 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], the active form principally responsible for the regulation of calcium and phosphorus homeostasis in higher vertebrates. The biological response to [$1,25(OH)_2D_3$] in birds and mammals occurs through a complex series of events that are mediated by an intracellular receptor protein termed the vitamin D receptor (VDR). Vitamin D responsive elements (VDREs) were identified in several genes that are induced by [$1,25(OH)_2D_3$], namely, the osteocalcin, osteopontin, and calbindin D_{9k} . Generally, VDREs consist of an imperfect direct repeat of the hexanucleotide sequence, GGGTGA, separated by a 3-nucleotide space. Vitamin D receptors bind to the direct repeat motifs not as homodimers but as heteromeric complexes in association with other receptors of the superfamily or with other unidentified nuclear factors. The unusual homo- and heterodimerization capacity of RXR and vitamin D receptors not only greatly expands the repertoire of regulatory diversity and specificity of the nuclear hormone receptors but also allows receptors and their ligands to serve as important regulators in the interaction of the ligands and other signaling transduction pathways.