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Review Article

Hylonome

Molecular regulation of calcium and bone metabolism through the vitamin D receptor

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1,25 dihydroxyvitamin D (1,25 D) is traditionally viewed as an endocrine hormone produced in the kidney whose function is to regulate calcium homeostasis by influencing intestinal calcium absorption, renal calcium reabsorption, and bone calcium resorption. These effects are mediated at the molecular level by a nuclear receptor of the steroid hormone receptor superfamily, the vitamin D receptor (VDR). Like the other members of the superfamily, the VDR is a ligand activated transcription factor; elevated levels of 1,25 D activate VDR-mediated transcriptional activation.

Transcriptional activation through the VDR is a multistep process that includes ligand binding to the receptor, heterodimerization to the retinoid X receptor (RXR), nuclear import through an importing mediated process, DNA binding, chromosomal remodeling, and recruitment of the basal transcription complex that includes RNA polymerase II (Figure 1). The gene promoter most sensitive to transcriptional activation by 1,25 D encodes a cytochrome P450 family member whose activity initiates the degradation of the hormone (CYP24). The biological activity of 1,25 D in a cell is strongly regulated by CYP24 activity. The CYP24 promoter contains multiple vitamin D responsive elements (VDREs) in the proximal promoter and additional VDREs acting as enhancer elements in the distal promoter. Phosphorylation events resulting from activation of signal transduction pathways can modulate 1,25 D action and VDR transcriptional activity on this promoter.

Studies on mice lacking the VDR demonstrate essential function of the VDR in the bone and intestine. In the growing animal the primary role of the VDR is to maintain high levels of intestinal calcium absorption; loss of VDR leads to hypocalcemia and rickets that can be prevented by by-passing active calcium absorption with a diet containing high levels of lactose and calcium. The targets of 1,25 D action in the intestine are the apical membrane calcium channel, TRPV6, the calcium binding protein, calbindin D9k, and the basolateral membrane pump, PMCA1b. Reduced levels of intestinal VDR (50% of normal) lead to intestinal resistance to 1,25 D and also suggest a role for VDR in the translational control of calbindin D9k.

The classical role of 1,25 D in bone biology has been the induction of osteoclast differentiation and stimulation of bone resorption leading to the release of calcium from bone

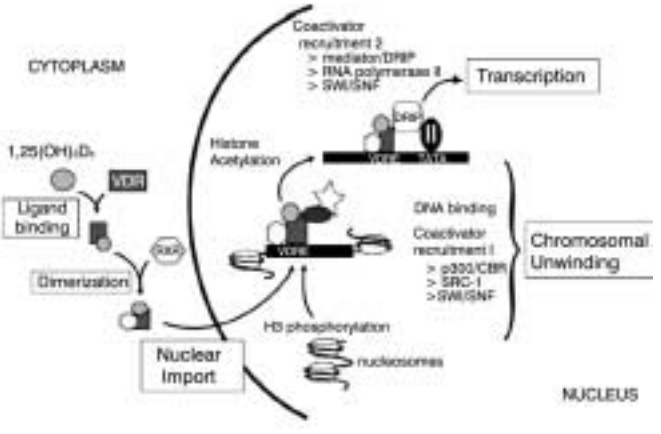

Figure 1. An overview of the steps necessary for transcriptional activation of genes by binding of 1,25 dihydroxyvitamin D ($1,25(OH)_2D_3$) to the vitamin D receptor (VDR). RXR= retinoid X receptor, VDRE= vitamin D response element; H3= histone H3; DRIP= VDR interacting proteins or mediator; SWI/SNF= ATP-dependent remodeling factors; SRC-1= steroid receptor co-activator 1; p300/CBP= histone acetyl transferase activity containing co-activators.

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in times of increased need. This is known to be mediated through a VDR mediated coupling of signaling between the osteoblast and osteoclast. In this paradigm, osteoclast differentiation is induced by activation of the Receptor for the Activation of NFk (RANK). The ligand for RANK (RANKL) is produced by osteoblasts and its gene is transcriptionally regulated by 1,25 D. In addition to this well characterized action, VDR knockout mice reveal that VDR has a role in the suppression of bone formation. When mineral homeostasis is normalized in VDR null mice, their bones show high rates of bone formation *in vivo*. In addition, cultured osteoblast precursors lacking the vitamin D receptor have higher osteogenic potential. This is likely due to the loss of the VDRs role as a suppressor of the osteoblast differentiation factor, Runx2. In contrast, transgenic mice with over-expression of VDR in mature osteoblasts have higher rates of bone formation. This demonstrates the complex nature of the role for VDR in the control of bone health.