The molecular mechanisms of Vitamin D action

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The International Symposium on Vitamin D Deficiency
Abu Dhabi 2012

Learning Objectives

- **Upon completion of this educational activity, participants will be able to:**

  1. Examine the various roles of Vitamin D3 e.g. calcium/phosphorus uptake and transport, in immune function, in proliferation and growth, in cellular differentiation, and apoptosis.

  2. Explain the signaling pathways involved in Vitamin D action.

  3. Explain molecular mechanisms of Vitamin D action mediated via the Vitamin D receptor (VDR).

  4. Describe the structure and mechanistic action of VDR as a transcription factor regulating gene expression.

  5. Identify genes targeted by VDR in different cell types and their physiological function.

Learning Objectives

- **Upon completion of this educational activity, participants will be able to:**

  6. Explain the interaction/cross talk between Vitamin D mediated signaling pathways and other cytokine or growth factor medicated signaling pathways e.g. TGF-□, TNF-□, IGF-I, etc.

  7. Examine the role of Vitamin D signaling in health and disease using examples such as:

  a) pancreatic □-cell function and diabetes.

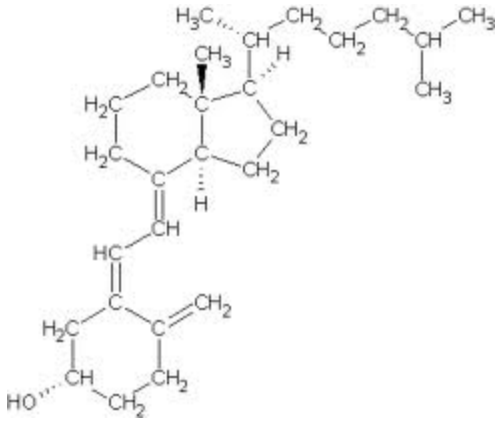
  b) apoptosis, tissue remodeling and cancer.

  c) vascular function and cardiovascular disease

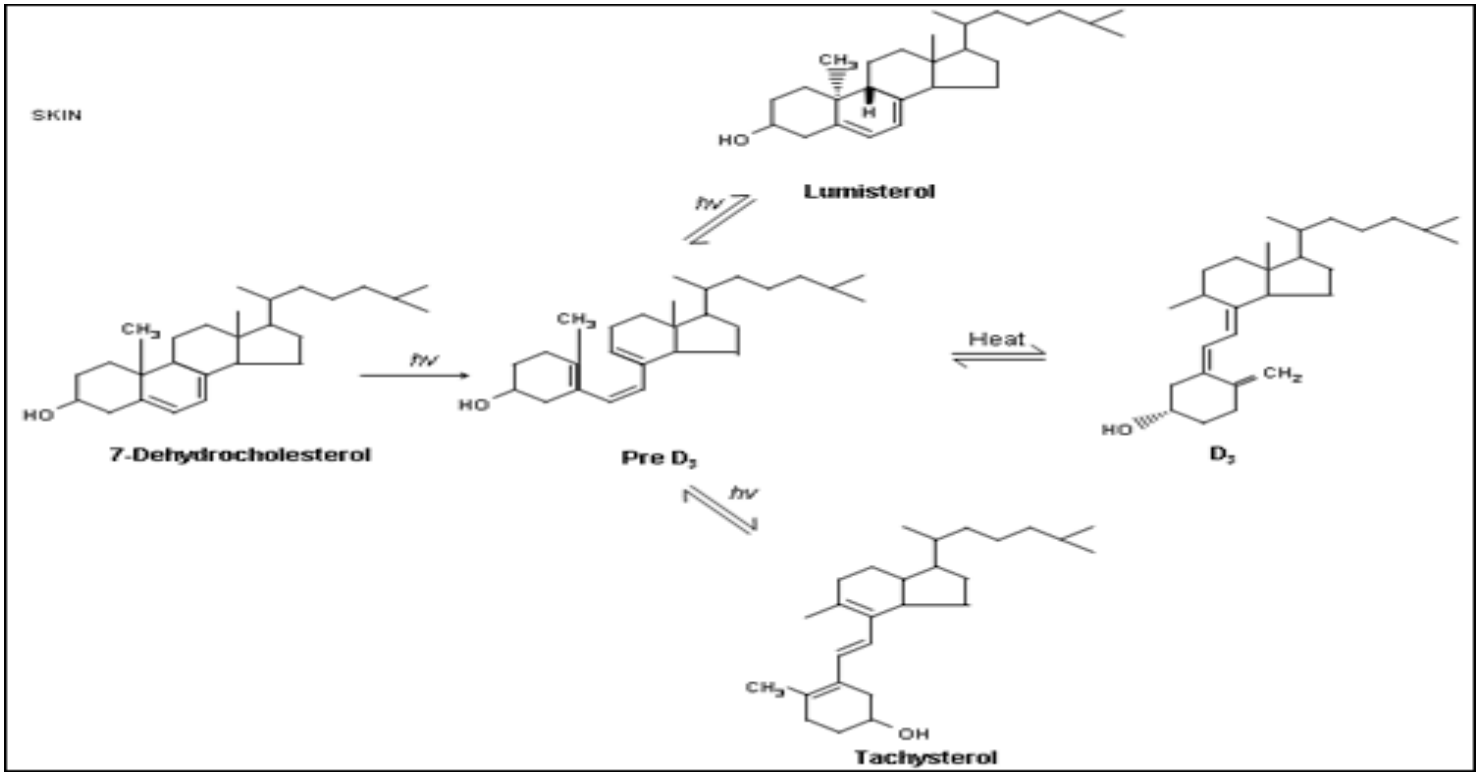
  8- Reflect upon the therapeutic role of pharmacological agents mimicking Vitamin D action or stimulating Vitamin D signaling pathways.

Vitamin D

- Several roles including :
  - Calcium/Phosphorous uptake and transport
  - Immune function
  - Proliferation and growth
  - Cellular differentiation
  - Apoptosis

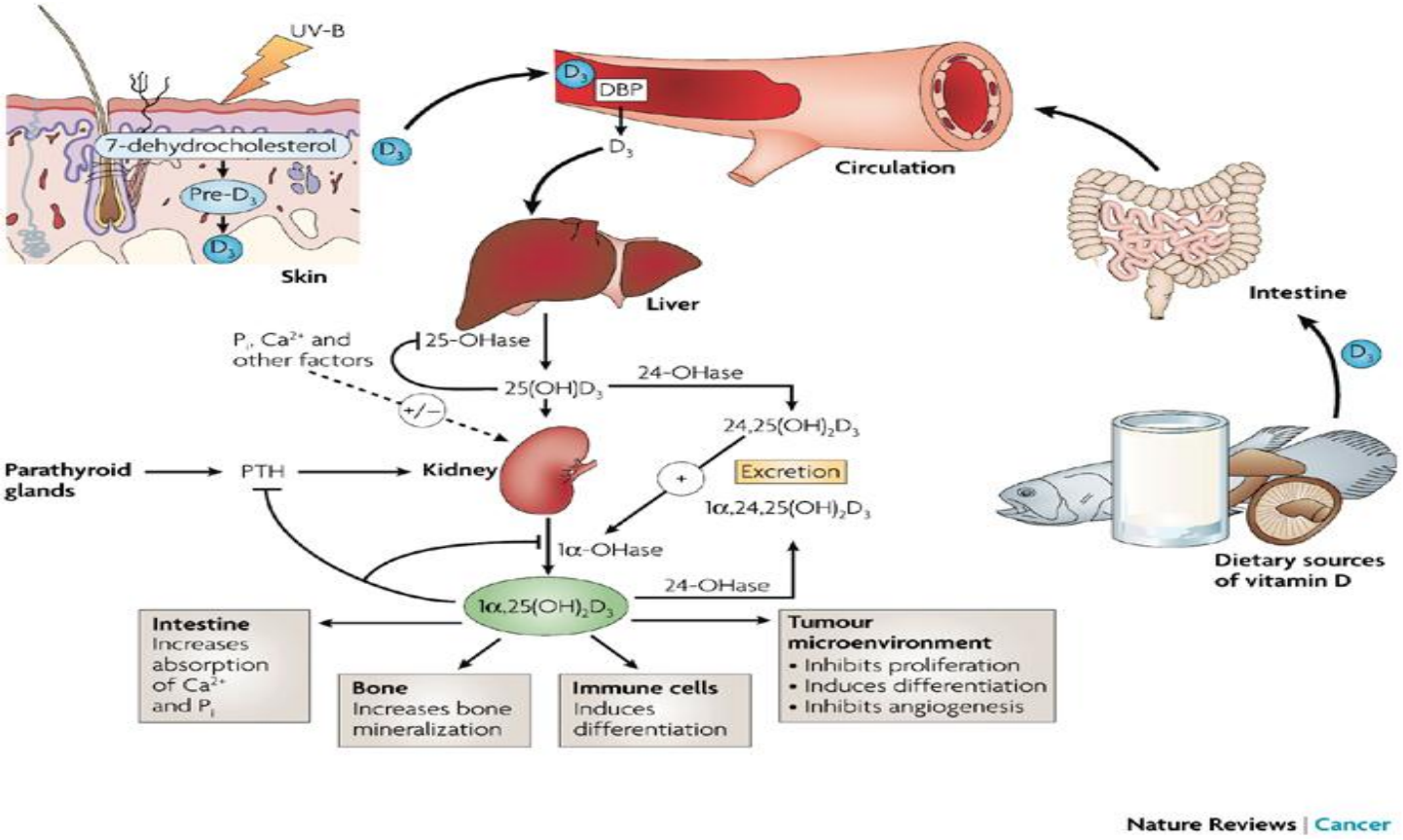


Vitamin D3 production in humans



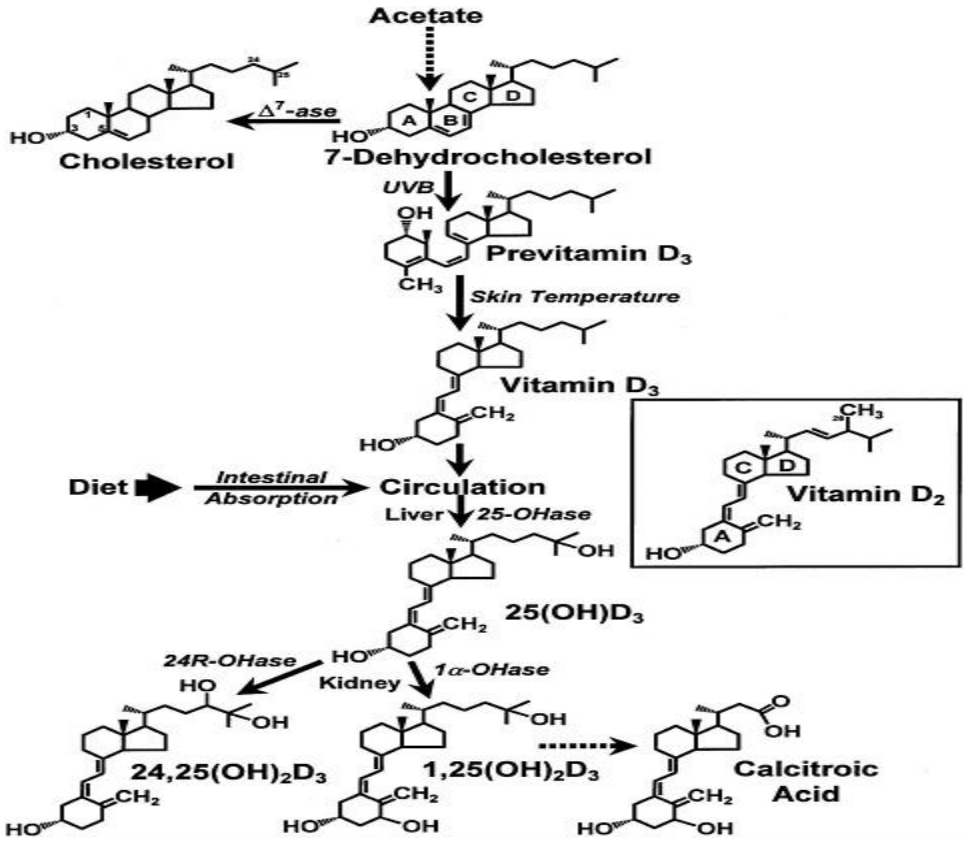
Production of 7-dehydrocholesterol in the epidermis of Humans.

Biochemical pathways of Vitamin D3 metabolism in the human body



Deeb K et al 2007

Vitamin D Hydroxylation



The photochemical, thermal, and metabolic pathways for vitamin D_3 activation to biologically active molecule

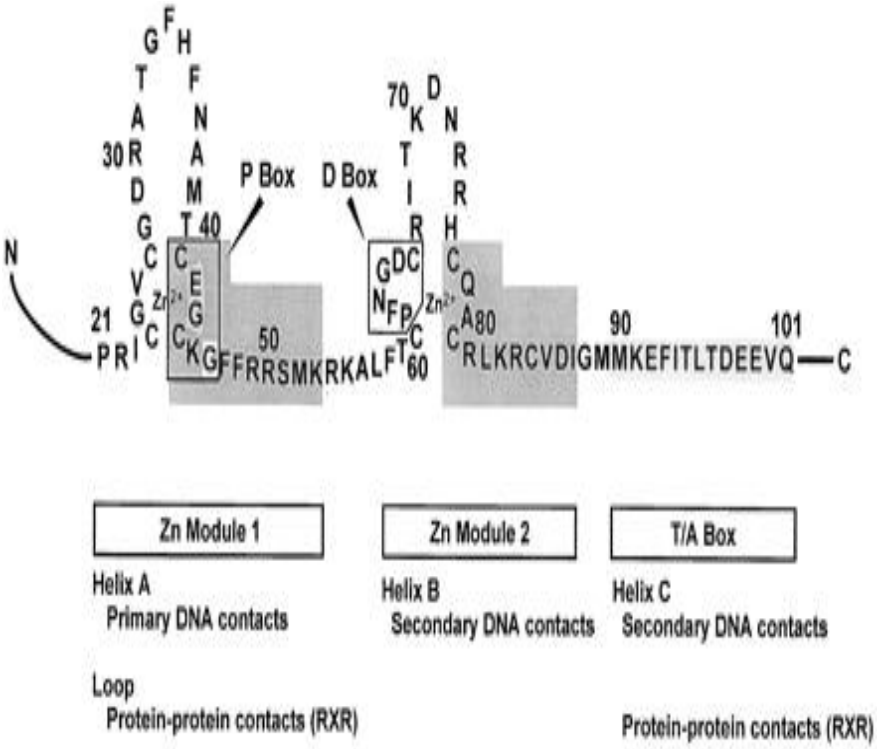
Holick MF. 1996

The Vitamin D Receptor (VDR)

- Protein produced by gene 12q12-q14
- The Vitamin D Receptor is a 423-residue long protein composed of two domains:
  - DNA binding domain (DBD)
  - ligand binding domain (LBD)

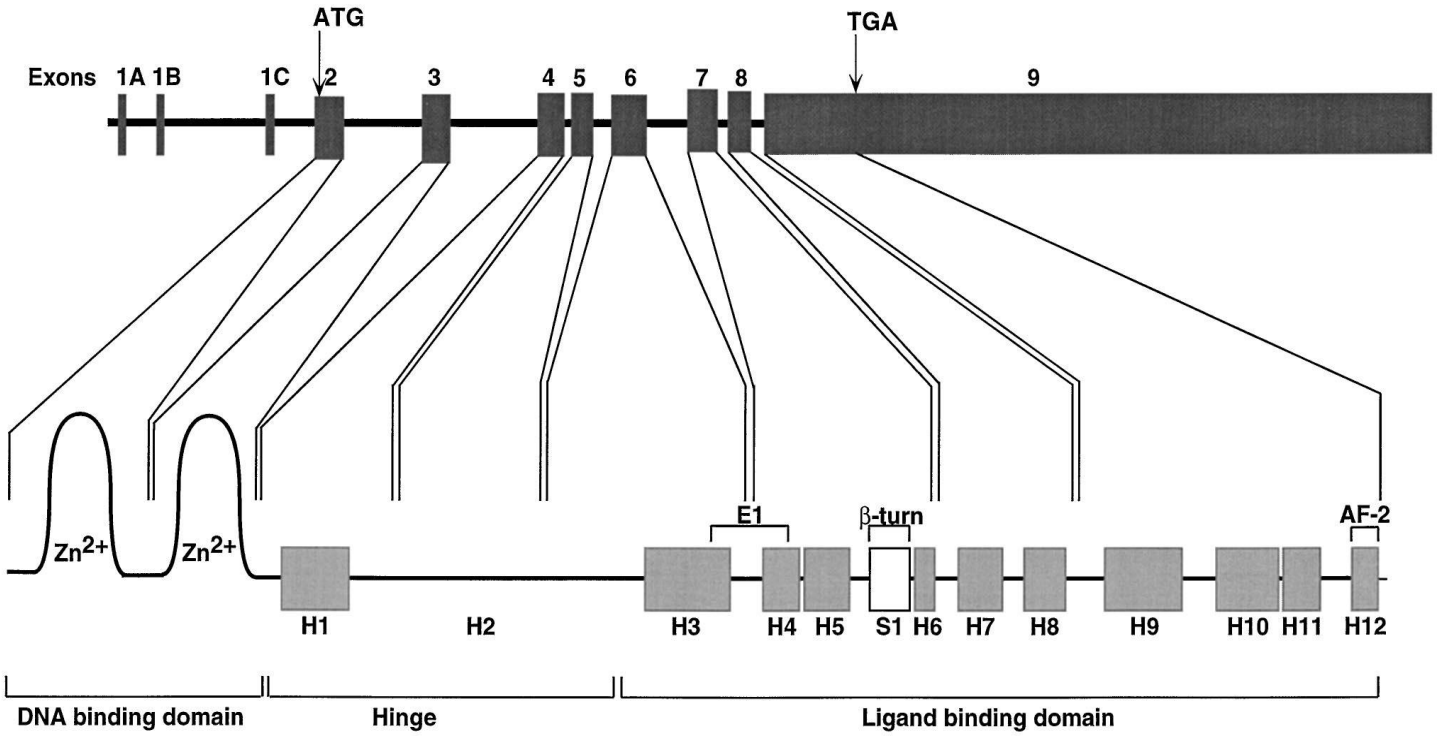
- The VDR belongs to the nuclear receptor (NR) superfamily including receptors for the steroid, retinoid and thyroid hormones.

- DNA binding domains (DBD) of these receptors are generally highly conserved however ligand binding domains (LBD) exhibit limited similarity.



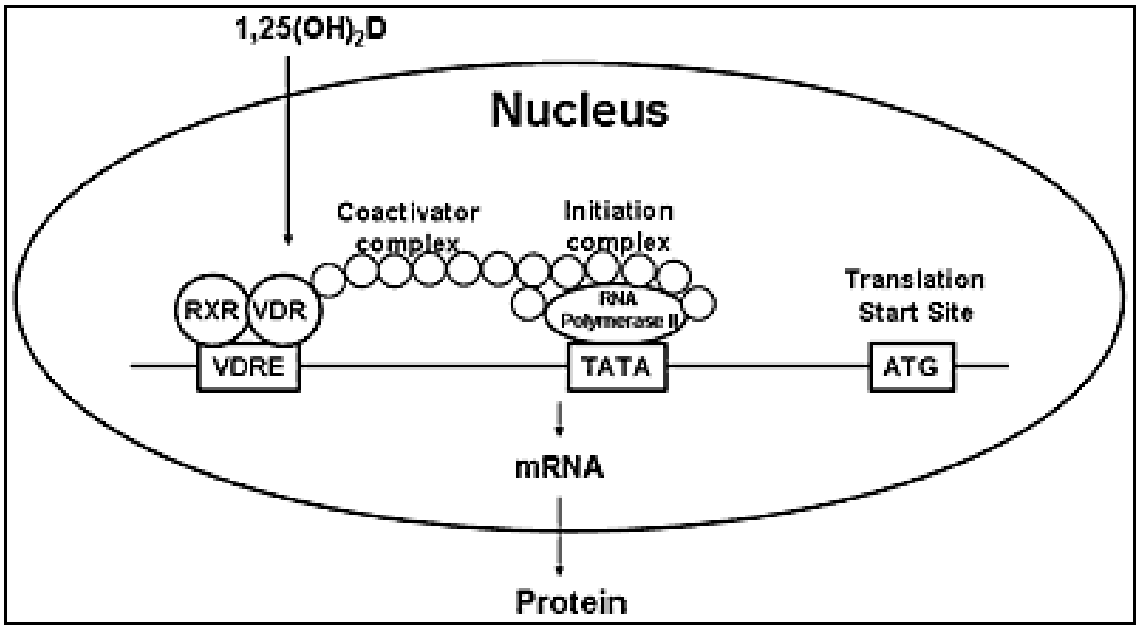
Binding Domains for VDR

The Vitamin D Receptor (VDR)



Binding Domains for VDR
Three mRNA isoforms exist for VDR.

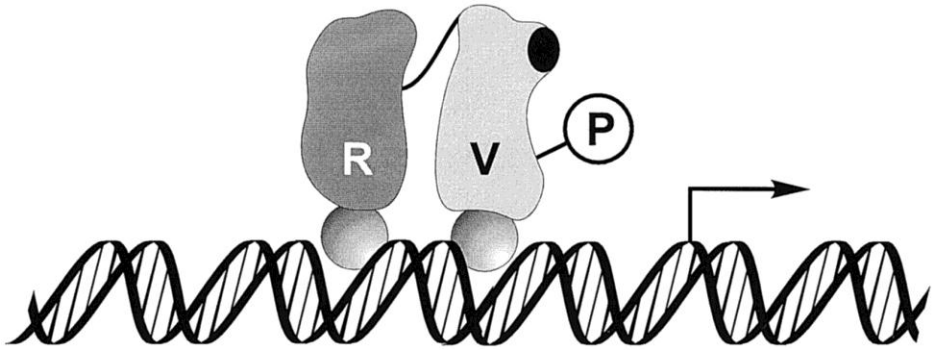
1,25(OH)2D- regulated gene transcription



1,25(OH)2D enters the target cell and binds to its receptor, VDR. The VDR heterodimerizes with the retinoid X receptor (RXR). The dimer VDR/RXR binds onto the vitamin D response element (VDRE)

Bickle et al. 2009

Model of the RXR/VDR heterodimer bound to a consensus VDRE. RXR (R) and VDR (V) are illustrated bound to a directly repeated VDRE located upstream of the start site of transcription.

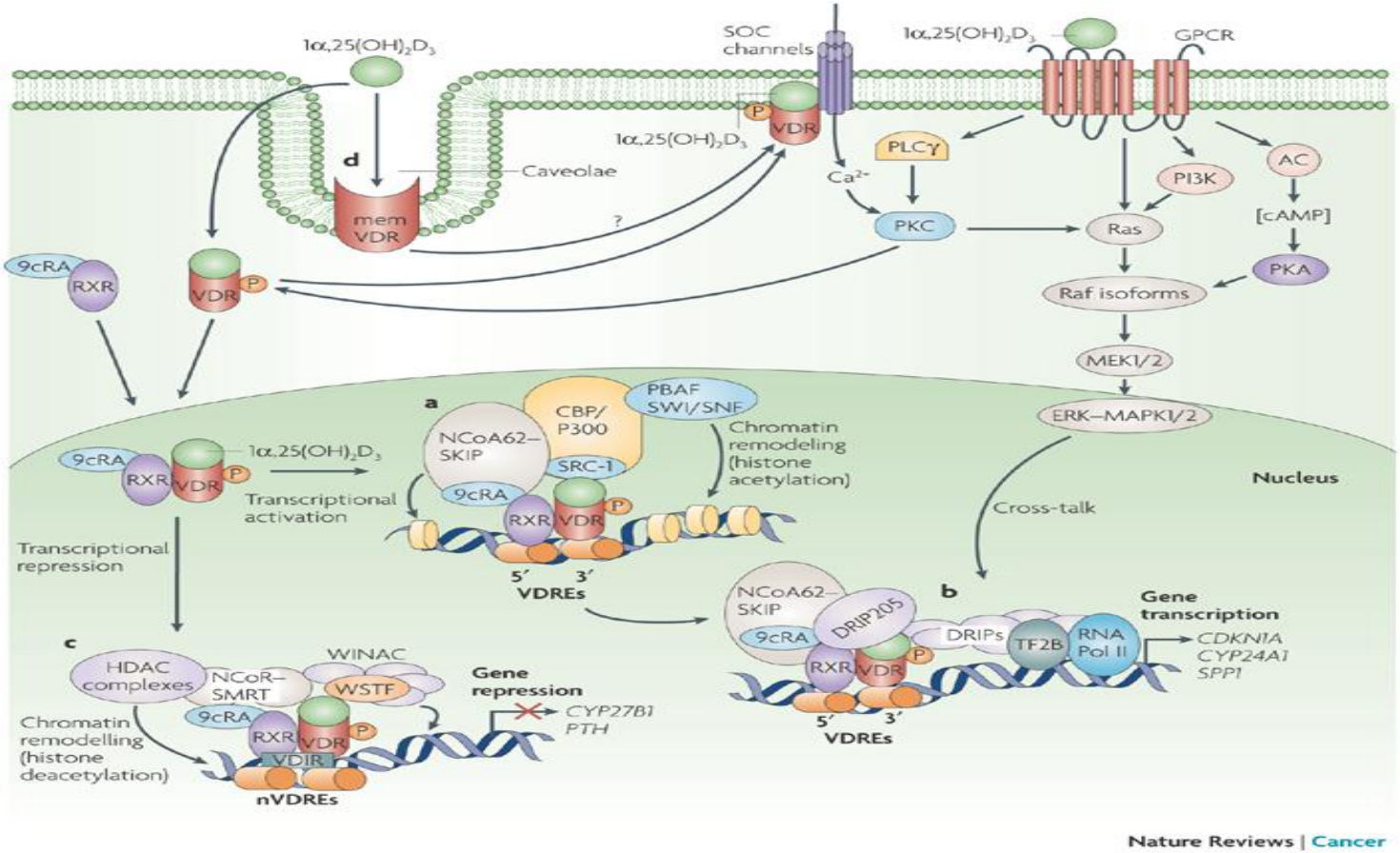


GGGTGA 3 GGGGCA	Human Osteocalcin
GGTTCA 3 GGTTCA	Mouse Osteopontin
ATTGTA 3 AGGGCG AGGTCA 3 GGTGTG	Human 24-Hydroxylase
AGGGAG 3 GGTTCA	Human p21

Malloy P J et al. Endocrine Reviews 1999;20:156-188

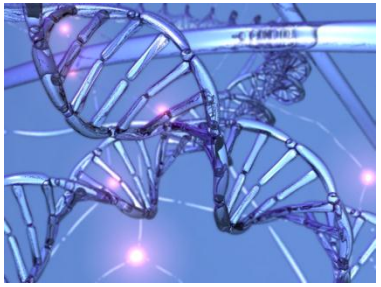
ENDOCRINE REVIEWS

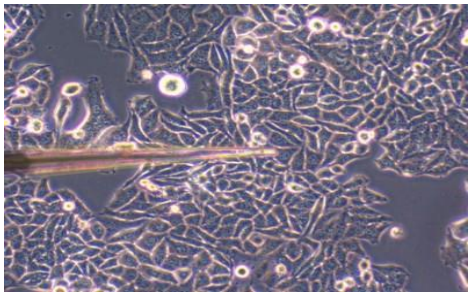
Signalling Pathways in Vitamin D action



Nature Reviews | Cancer

Deeb K et al 2007

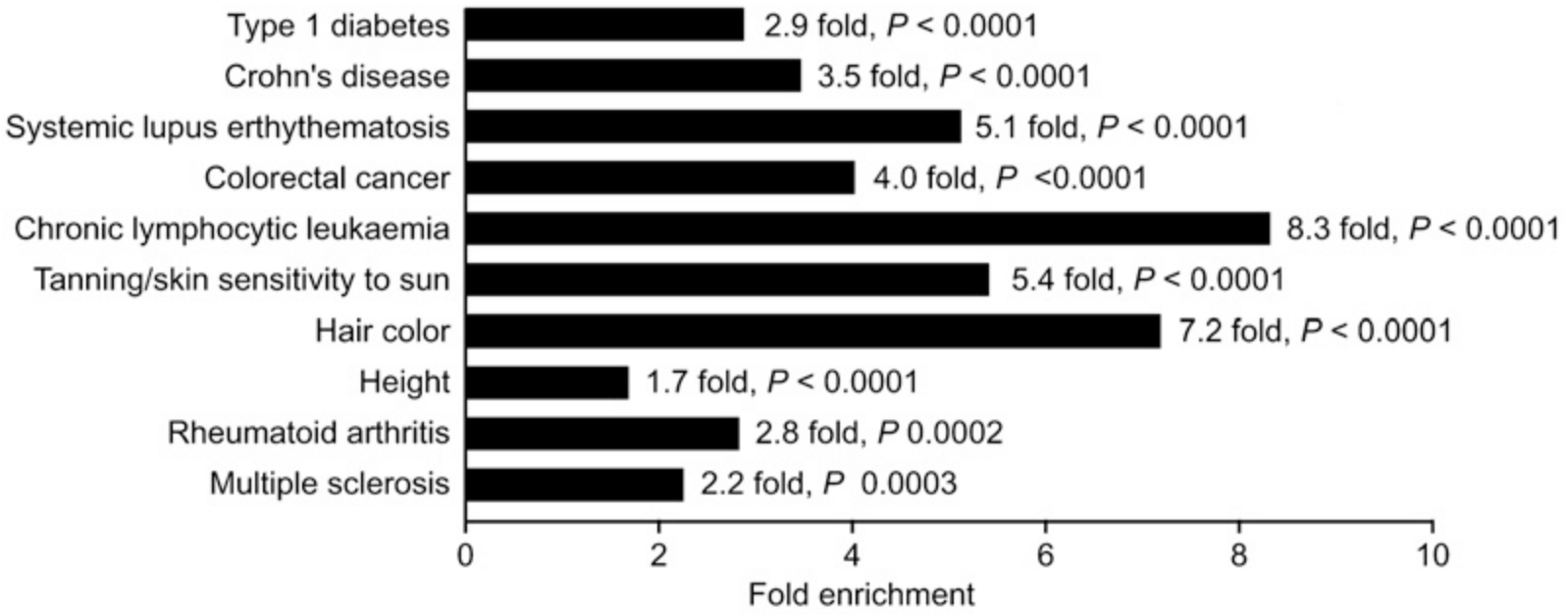




Human Genome Wide Association Scan and In Vitro studies

- 2776 genomic positions occupied by the VDR
- 229 genes with significant changes upon *in vitro* stimulation with Vitamin D3
- Motifs used between 5 and 30 bp long.
- Regions identified include: intergenic, intronic, upstream, downstream and UTR regions.

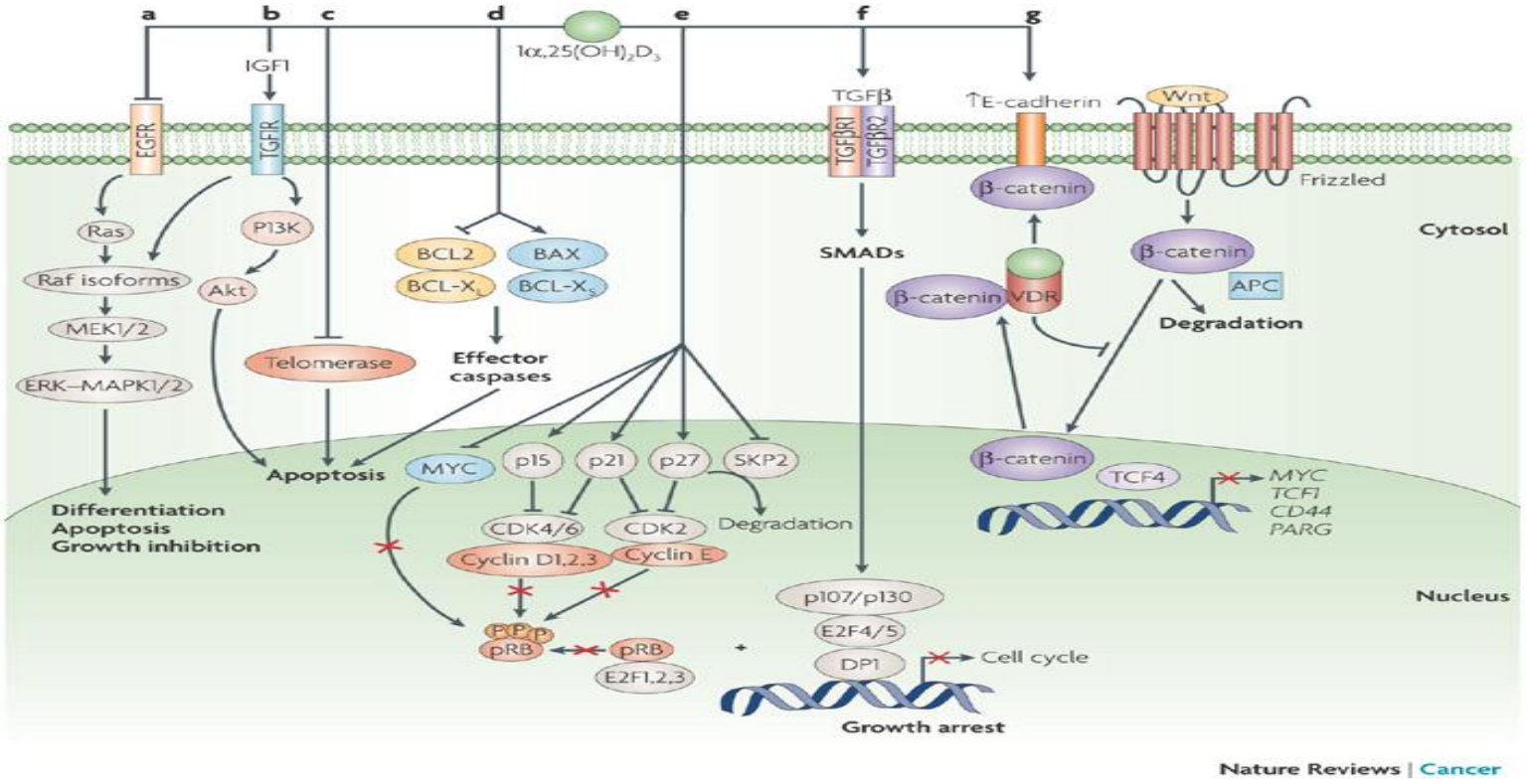
VDR binding and Human traits



Common traits showing enrichment of VDR binding identified by ChIP-sequencing after calcitriol stimulation.

Ramagopalan S. et al. Genome Res. 2010

Cross-talk with other growth factors or cytokines regulating cell survival



Deeb K et al 2007

Vitamin D3 is may modulate differentiation, growth and apoptosis cellular signals through cross-talk with other growth factors and cytokines like EGFR, IGF-I, TGFβ and Wnt. Vitamin D3 can modulating MAPK- ERK siginalling and PI3 Kinase- Akt signalling thus affecting cell survival.

Vitamin D signalling, cardiovascular disease and the metabolic syndrome

- Emerging evidence from animal models of disease and human studies.
- Vitamin D may be implicated in pathophysiology of diabetes and cardiovascular disease through modulating MAPK, PI3K and Smad signalling.

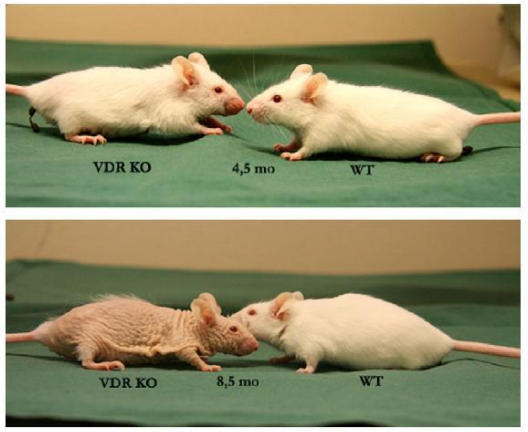


Fig. 2. Phenotype of VDR knockout mouse (KO) compared to wildtype littermate (WT; NMRI background strain) at the age of 4.5 (top) and 8.5 (bottom) months.