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Vitamin D Receptor and Cancer

Vitamin D Receptor Structure

Vitamin D target tissues contain a specific vitamin D nuclear receptor (VDR). VDRs are present in more than 30 cell types particularly those responsible for calcium homeostasis, immune function, endocrine, hematopoiesis and tumors. VDR is a 51kDa steroid, thyroid protein hormone. VDR shows more than 95% homology between species. The VDR contains an N-terminal DNA-binding domain (DBD). This acts as a cysteine-rich recognition domain on a sulfhydryl protein. In the C-terminal there is present a ligand-binding domain (LBD). In response to increased parathyroid hormone (PTH) and calcitriol synthesis of the VDR receptor increases (Bak, 2006).

VDR Gene Polymorphisms

Numerous common polymorphisms are located in the VDR gene. Namely FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236). The polymorphisms BsmI, ApaI and TaqI are strongly linked with each other as when one polymorphism is presentit can predict the occurrence of the others. In fact they almost always occur with each other. This is known as linkage disequilibrium.

In the DNA sequence FokI is the "start codon." Its function is to signal the position of the protein chain formation in DNA sequence the protein chain. ATG is the DNA sequence for a start codon encoding the amino acid methionine. The VDR gene is composed of two possible start codons which are positioned very close to one another at the initial gene position. At the right, the SNP rs2228570 (T/C) results in methionine (M, Met) substitution. Therefore it becomes encoded by the three-letter codon ATG, for a threonine (T, Thr) amino acid, encoded by ACG at position 1 of the protein (Met1Thr). Therefore this eliminates the first start codon, to result in the use of the second start codon producing a VDR protein. As a result the 'T' allele creates a longer VDR protein which is composed of 427 amino acids than the 'C' allele which creates a shorter VDR protein composed of 424 amino acids. Even though these VDR proteins are of different lengths, both are functional VDR proteins.

On the other hand the BsmI, ApaI and TaqI polymorphisms and other polymorphisms present on the VDR gene, are so close to each other that they are almost always inherited with each other by chance alone. The 'G' allele of BsmI (b), 'G' allele of ApaI (a) and 'T' allele of TaqI (T) are generally detected together forming baT. The alleles 'A' BsmI, 'T' ApaI and 'C' TaqI association forms Bat (Takeshige, 2015). This is summarized in Table 1.

Reference SNP ID	Rs2228570	Rs1544410	Rs7975232	Rs731236
Traditional Name	*FokI*	*BsmI*	*ApaI*	*TaqI*
Allele	T C(G,A)	G A	G T	T C
Traditional Name Variant	f F	B B	A A	T t
Amino Acid	Met Thr	Non-coding	Non-coding	Lie Lie

Table 1. VDR Polymorphisms

Antioxidant effects of Vitamin D and Cancer

Antioxidant Effects

When liganded, VDR can inhibit expression of factors which generate reactive oxygen species (ROS) and factors which remove ROS intracellularly preventing tissue damage. It can upregulate the expression of NADPH oxidase through genomic action or stimulate the synthesis of reactive nitrogenspecies through the influx of Ca2+ into the cells- this is non-genomic promotion. These actions can not only increase cancer cells' sensitivity to drugs but may also promote vascular calcification and fat deposition in adipocytes i.e. major ROS production species Yet more studies are required regarding vitamin D as an antioxidant (Ke et al., 2016).

Colorectal cancer

1,25-(OH)2-D3 can reduce the growth of rapidly dividing colon tumor cells and reverse colonocytes from a malignant to a normal phenotype. These properties are due to VDR activation which inhibits signaling through β-catenin (a mediator of the Wnt pathway). This stimulates apoptosis. On the other hand VDR can also bind to bile acid and lithocholic acid i.e. a potent enteric carcinogen. VDR expression appears to decline during the progression of colon cancer and this has been associated with the upregulation of cancer transcriptional repressors which bind to VDR-promotors shifting catabolism from calcifediol to calcitriol. These suppress the inflammation process. (Takeshige, 2015).

Gupta et al; (2011) enhance how serum 25-0H-D3 levels of more than 20 ng/mLor intakes of a minimum of 1000-2000IU/day show significant reduction in colorectal risk.

VDR single nucleotide polymorphism gene exists which has been associated with differences in colon cancer risk. Cdx-22 AA of FokI TT carriers showed twice the increased risk for colorectal cancer when compared with other genotypes. On the other hand those with Cdx-2-FokIA-T, FokI TaqIT-G, or Cdx-2-FokITaqIA-T-G haplotypes showed two to three fold increased colon cancer risk when compared with other haplotypes (Rai et al; 2017).

The most recent study which shows the relationship between vitamin D and cancer is the SUNSHINE Randomized Clinical Trial (RCT) performed by Ng, et al in 2019. This study has concluded that high vitamin D doses may help to hinder advanced colorectal cancer growth when combined with chemotherapy. In the RCT it was observed that disease progression in the participants of the high-dose group remained stationary for about 13 months in average, while those participants in the low-dose group remained stationary for around 11 months. Also it was observed that the participants before the SUNSHINE trial had low Vitamin D doses. Yet further research is required to identify the advantages of vitamin D in colorectal cancer.

Breast cancer

Breast cells express VDR. Liganded VDR functions in inhibiting growth, inducing apoptosis and stimulating expression factors which are involved in cell proliferation regulation. These function by blocking mitogenic signals which are estrogen-driven. Studies including those performed by Huss et al; (2019) and Al-Azhri et al; (2017) have found an inverse relationship between VDR expression and invasiveness of breast tumors. As in their research, even though more research is required, they have concluded that high VDR expression in invasive breast tumors is associated with favorable prognostic factors and low risk of breast cancer associated death. Therefore having high VDR expression is a positive prognostic factor. In fact Schwalfenberg, Genius & Hiltz (2009) have estimated that in Canada increasing 25-OH-D3 serum levels to 40–60 ng/mL yearly would prevent around 58,000 new cases of breast cancer each year while reduce breast cancer mortality by half.

Prostate cancer

Studies in human prostate cells have shown that calcitriol bind with VDR to bring about androgen signaling. This signaling brings about differentiation of stem cells to androgen-receptor positive epithelial cells while augmenting tumor-suppressing microRNAs. Hendrickson et al; (2011)

have found that circulating 25-hydroxyvitamin D interact with VDR decreasing proliferation and increasing apoptosis for some types of malignancies. Köstner et al; (2009) identified those carriers of the VDR Bsm1 B allele prostate cancer risk is less than those which do not carry the allele.

Skin cancer and polymorphisms

Vitamin D brings about keratinocyte proliferation by inhibition of β-catenin signaling and protection of UV-induced DNA damage. It does this by VDR which brings about upregulation of p53, inhibition of stress-activated kinases and nitric oxide suppression production. In the meta-analysis, Denzer Vogt and Reichrath (2011) studied the risk of melanoma exherted by VDR polymorphisms. The TaqI polymorphism (rs731236) is a restriction fragment length polymorphism (RFLP). In the meta-analysis it was conveyed that TaqI allele t was significantly less frequent among melanoma patients than among controls. Therefore one can deduce that t might confer protection to carriers against melanoma while T increases their risk. On the other hand, genotypes Tt + tt were less frequent among melanoma patients than among controls and were linked with significantly lower melanoma risk for Tt + tt vs. TT genotypes. BsmI polymorphism may alter gene expression by regulation of the stability of mRNA. The BsmI allele B was found to be less frequent among melanoma patients. Therefore one can deduce that B may confer protection for carriers against melanoma while b may put them at risk. The FokI f allele was identified to increase the risk of melanoma.

Conclusion

Throughout this article the role of VDR as an antioxidant and its role in cancer prevention was discussed. It was also seen how VDR polymorphisms confer protection or increase the risk for specific types of cancer. Even though this article enhanced on outbreaking discoveries in cancer prevention regarding VDR further studies are required.

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