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Emerging Vitamin D Receptor-Centered Patterns of Genetic Overlap across Some Autoimmune Diseases and Associated Cancers

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Genetic Regulatory Network (GRN) of Vitamin D Receptor-Centered Hypothesis

An increased risk for complex diseases such as Autoimmune Diseases (ADs) and/or cancer is associated with the aging process but we are not sure what causes such outcomes. With comparative advantages of different model system and recent Genome-Wide Association Studies (GWAS), and ChIP-seq/ChIP-chip studies, we distilled out one attention-deserved Vitamin D receptor –centered hypothesis: the genetic regulatory network of vitamin D receptor (VDR, homologue of DAF-12 in *Caenorhabditiselegans*) may play a central role as a common basis preventing some autoimmune diseases and associated cancers [1-3]. Further, we predict, similar to DAF-21 /HSP90VDR may buffer disease-causing genetic mutations and/or variations the diseases phenotype may come up with polygenic genetic mutations and/or variations along with deficiency of vitamin D and lacking of UVB and mal-functional DAF-12/VDR with lose of its buffering ability as a capacitor [1,3,4]. Decoding the genetics of these complex diseases associated with the aging process is helpful to understand the controversies the beneficial effects of vitamin D supplementation on them [5]. We highlighted that environmental factor-induced mal-functional DAF-12/VDR may be postulated to cause in situ dys-regulation of expression of an array of its target genes (in press, whose citrullination of such in situ dys-regulated genes might be tightly mediated by VDR-orchestrated processes and consequently ends with autoimmunity. If it were the case, those "loci" identified by GWAS collectively have a significance of gene function [1,6].

GRN of VDR (and DAF-12) may Act as a Capacitor

We human beings survive well the challenges of genetic variations and environmental factors via the robustness of complex genetic regulatory networks in our bodies, possibly including one of VDR as a capacitor and probably similar to DAF-12 in *C.elegans* [7]. Decreases in the VDR pathway resulting from of vitamin D deficiency and/or a lack of UVB could enhance some disease-causing morphological variants. Moreover, GRN of DAF-12/VDR intertwines microRNA regulations, autophagy, longevity and cellular reprogramming, and forward or feedback loops [4]. When VDR function is in studys-regulated due to genetic defects or by vitamin D unavailability, it may remodel many different processes alongside adjustments of multiple signal transducers and thereby simultaneously disturbing several developmental pathways as DAF-12/VDR if out of its buffering capability, the ADs and associated cancers may come to the patients [1,8].

GRN of VDR may be Consider as Common Basis for ADs and Associated Cancers?

Although further testing is awaiting for, one GWAS reveals that one allelic VDR variant may link to clinical autoimmune antibodies including anti-p150 (TRIM33/ TIF-1γ)/p140(TRIM24/TIF-1α) whose natural self-antigens may correlate with protein products encoded by *TIF-1γ/α*, whose homologues *flt-1* and *nhl-2* are direct targets of DAF-12/VDR [8,9]. DAF-12/VDR target genes from our ChIP-chip screening showed many overlaps with validated homologues identified in human VDR studies and significantly enriched near genes that are pathologically associated with ADs and cancer [8]. But it is necessary to experimentally test these overlaps in human VDR.

One **of our recent experiences is as follow**

Once new key regulators for ADs were published online first, we predicted, they would act as putative target candidates of DAF-12/VDR; amazingly, the majority if not all turned out to be the case. For instance, key regulator FBN1 responsible for fibrosis and autoimmunity in mouse models of scleroderma is found as the homolog of *fbl-1* in *C. elegans*, the putative target of DAF-12/VDR [10]. Another GWAS identified genetic variants for joint damage progression in autoantibody-positive rheumatoid arthritis (RA) and three key genes (sperm-associated antigen 16 (*SPAG16*), and Matrix Metallopeptidase1 and 3 (*MMP1 and MMP3*) [11]. They are among human homologue candidates of DAF-12/vitamin D receptor (VDR) target genes [2,7,8,12]. However, Miller et al. reporting on GWAS of Dermatomyositis (DM), found a genetic overlap with other ADs, as the first genetic predispositions towards ADs shared with DM [13]. The latest case is *rpc-1* responsible for both the scleroderma and cancer [14]. Moreover, other patterns of genetic overlap across ADs have emerged [13,15]. Likely, a malfunction of VDR could affect the pathogenesis of RA and associated cancers expanding to many other ADs, Paraneoplastic Neurological Diseases(PND) and DM (Table 1) [1,13,14,16,17-24]. In addition, VDR ChIP-seq in primary CD4+ cells relates serum 25-hydroxyvitamin D levels to autoimmune disease [25]. In closing, the patho-physiology of ADs (at least subgroup) may share their common underlying mechanisms of genetic regulatory network of VDR.

Perspectives

Before a definitive rejection or acceptance of the hypothesis can be made, further studies are warranted including first confirmation of VDR in mammalian systems. If being accepted, much attention will need pay to preventive effects of vitamin D, particularly if some processes under the control of VDR are irreversible like "one-way" traffic. However, without a thorough understanding of the mechanisms

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Aceview mapping of homologues of the DAF-12/VDRtarget genes to key genes described in recent AD or associated cancer-related publications		
Gene (Human homologue of the VDR target/*C.*eleganshomologue of the DAF-12 target)	**Type of diseases**	**References**
ZGPAT/C33H5.17	UC,CD	[21]
CCR7 /R106.2	T1D	[21]
PLCL/pll-1	CD,DM	[13,21]
RPL19PB/rpl19	MS	[21]
TNFAIP3/Y59C1A.1	RA, SLE, UC, SSc	[21]
Pxk/ wnk-1	SLE	[21]
IKZF1/PRDM16/egl-43,the closest DAF-12/VDR binding loci 15 kb distant from the *R53.5, R53.6, R53.7a, R53.8* regions.	CD	[21]
BLK/src-1	SLE,RA,DM	[13, 21]
RBPj/lag-1	T1D, RA	[21]
GOT1/T01C8.5	CD, UC	[21]
Jak2/csnk-1/Y106G6E.6	CD, UC	[21]
IFIH1/drh-1	Multiple	[21]
Jak2/ csnk-1	CD, UC	[23]
NKX2.3/ceh-24.	CD,UC	[23]
SMAD3/daf-3.		[23]
PRDM1/blmp-1, the closest DAF-12/VDR binding locus in ChIP-chip online target list <10 kb distant from the Y106G6H.1 region.	CD,UC	[23]
HNF4a/nhr-64.	UC	[23]
LAMB1/lam-1/W03F8.5.	UC	[23]
xpa-1 /K07G5.2, the closest DAF-12/VDR binding locus in the ChIP-chip online target list to the K07G5.1 and K07G5.6 regions.	PND	[17]
Smarcal1/C16A3.1, the closest DAF-12/VDR binding locus in the ChIP-chip online target list to the C16A3.6, C16A3.7a, C16A3.8and C16A3.11 regions.	PND	[17]
ELF1/elf-1.	PND	[17]
DBR1/C55B7.8 the closest DAF-12/VDR binding locus in the ChIP-chip online target list 5 kb distant from the C55B7.3 region.	PND	[17]
TIFα/TRIM24/flt-1	DM, cancer	[18,27]
TIFβ/TRIM28/ncl-1	DM, cancer	[18]
TIFγ/TRIM33/nhl-2	DM, cancer	[18]
AIRE/Mi-2β/let-418	DM, cancer	[22,24]
Foxp3/fkh-7	DM, cancer	[22,24]
ADAM33/adm-2	Asthma	[22]
GPRA/gnrr-1/F5D7.3	Asthma	[22]
RPC-1/rpc-1	SSC, cancer	[14]
Topoisomerase I /top1	SSC	[14]
Note 1: T1D: Type 1 Diabetes; SLE: Systemic lupus erythematosus; DM: dermatomyositis; SSc: Systemic scleroderma; CD: Crohn's disease; CeLD: Celiac disease; MS: multiple sclerosis; RA: Rheumatoid arthritis; PND: Paraneoplastic neurological disorder; UC: Ulcerative colitis. **Note 2:** the original full list for the DAF-12/VDR target genes online target is available in the supplementary materials [8]. See NCBI Aceview for their human homologues or vice versa.		

Table 1: Representative DAF-12 and VDR -shared/conserved target genes and the type of associated AD and cancers.

of ADs and associated cancers, it seems to be too early to claim that the majority of Americans and Canadians are receiving adequate amounts of both calcium and vitamin D, though it is necessary to warn of the toxicity of vitamin D with bigger doses for some populations [26,27]. Studies should also classify the different degrees of "at-risk" genotype (Zhang Y, *in press*) in that the vitamin D deficiency likely remains under recognised, undetermined and untreated. As we human beings are out-breeding, the models may be extremely useful in eventually contributing to an understanding of the effects of vitamin D and its receptors at complex diseases such as ADs and associated cancers at both cellular and organism levels [6,16].

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