

The Potential “Core” of Vitamin D Receptor and Vitamin D Hypothesis: Synthesis of Common Basis of Some Autoimmune Diseases and Associated Cancers via Autophagy

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Abstract

Nutrigenomics may tell us how various nutrients interact with the genome and potentially cause alteration of gene expressions. One nutrient of particular interest is vitamin D, deficiency of which may lead to diseases in various human organ and muscle systems. Decoding the genetics of complex diseases such as autoimmune diseases and/or cancers associated with the aging process is vital to understand the controversies the beneficial effects of vitamin D supplementation on these diseases. Based on comparative advantages of different model system and recent ChIP-seq/ChIP-chip studies, we previously proposed one novel insightful hypothesis: the genetic regulatory network of Vitamin D Receptor (VDR, homologue of DAF-12 in *Caenorhabditis elegans*) may act as a common basis in preventing some autoimmune diseases and associated cancers. Further, such diseases may burst up with polygenic genetic mutations and/or variations in that deficiency of vitamin D and lacking of UVB lead to the mal-functional DAF-12/VDR and lose its buffering potential as a capacitor. The aberrance of environmental factor-induced DAF-12/VDR may counter-intuitively lead to *in situ* dys-regulation of the expression of an array of its target genes and locally-induced autoimmunity because of the citrullination of *in situ* dys-regulated genes, which may be mediated by the VDR-orchestrated autophagy process. Being consistent with the “hygiene hypothesis” and the “danger signals” theory, some VDR/DAF-12 targets may be directly involved in these processes. Several testable predictions will be briefly discussed.

Introduction

Vitamin D actually acts as a hormone in that it can not only be produced by our body, but circulates in the bloodstream, and acts on target tissues (Figure 1). Increased intake of vitamin D supplement has positive prevention of various cancers as well as the prevention of multiple chronic diseases, including cardiovascular disease, ADs [e.g. multiple sclerosis, type 1 diabetes mellitus, Rheumatoid Arthritis(RA)], and so on [1,2]. Moreover, vitamin D supplements can influence the blood-sugar levels of obese children and teens and may help them stave off the disease [3]. At another hand, obesity may cause vitamin D deficiency [4,5]. Further, an increased risk for complex diseases such as Autoimmune Diseases (ADs) and/or cancer is associated with the aging but their causes remains largely unclear. The huge demand on breakthroughs for such research is there, but enthusiasm for exploring vitamin D in autoimmune diseases and/or cancers may be somewhat dampened due to the unexpected insignificant beneficial effects with vitamin D supplementation in some clinical trials and some mounting discussion of common “misconceptions” about vitamin D [6,7]. However, according to “Occam’s razor”, we prefer a simple theory to a complex one: i.e. the genetic regulatory network of Vitamin D Receptor (VDR) may play a central role in preventing some ADs and associated cancers, and to help understand such controversies [1]. Further, we predict, an explicit molecular mechanism of the VDR in response to the environment will need classify different polygenic “at-risk” gene-sets (Zhang Y [1]). Besides, as a capacitor, similar to DAF-21/HSP90 and its homologue in *C. elegans* DAF-12, VDR may buffer disease-causing genetic mutations and/or variations.

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

We all need always respond to challenges of genetic variations and environmental insults. Particularly, genes near these DAF-12/VDR binding sites organise an extensive network of pathways for autophagy, interconnected microRNAs, longevity and cellular reprogramming and carcinogenesis [8]. Thus the balance between stability and the potential for change could be in part realized by means of the VDR receptor’s involvement in developmental robustness, probably similar to DAF-12

[8]. The vitamin D deficiency, and/or a lack of UVB could “enhance” the penetrance of some disease-causing variants; namely, mal-functional VDR genetically ‘sensitizes’ the pathways and destabilizes normal phenotypes to diseased status alongside fine adjustments of multiple signal transducers and/or simultaneously disturbing several developmental pathways as DAF-12/VDR [9] so that mal-functional VDR may indeed lower the threshold for disease exposure.

GRN of VDR as Common Basis for some ADs and Associated Cancers

Importantly, one Genome-Wide Association Study (GWAS) tells us that one allelic VDR variant may link to clinical autoimmune antibodies including anti-p150(TRIM33/TIF-1 γ)/p140(TRIM24/TIF-1 α) [10], whose natural auto-antigens may have a link with protein products encoded by *TIF-1 γ / α* , whose homologues *flt-1* and *nhl-2* are direct targets of DAF-12/VDR [1,9]. DAF-12/VDR target genes from our ChIP-chip screening showed dozens of overlaps with validated homologues identified in human VDR studies and significantly enriched near genes that are pathologically associated with ADs and cancer [9] (Figure 1), such as human *RPC-1/C.elegans rpc-1* [11], *FBN1/fbl-1* [12], *SPAG16/WDR5.1*, *BLK1/src-1* [13], which are involved in

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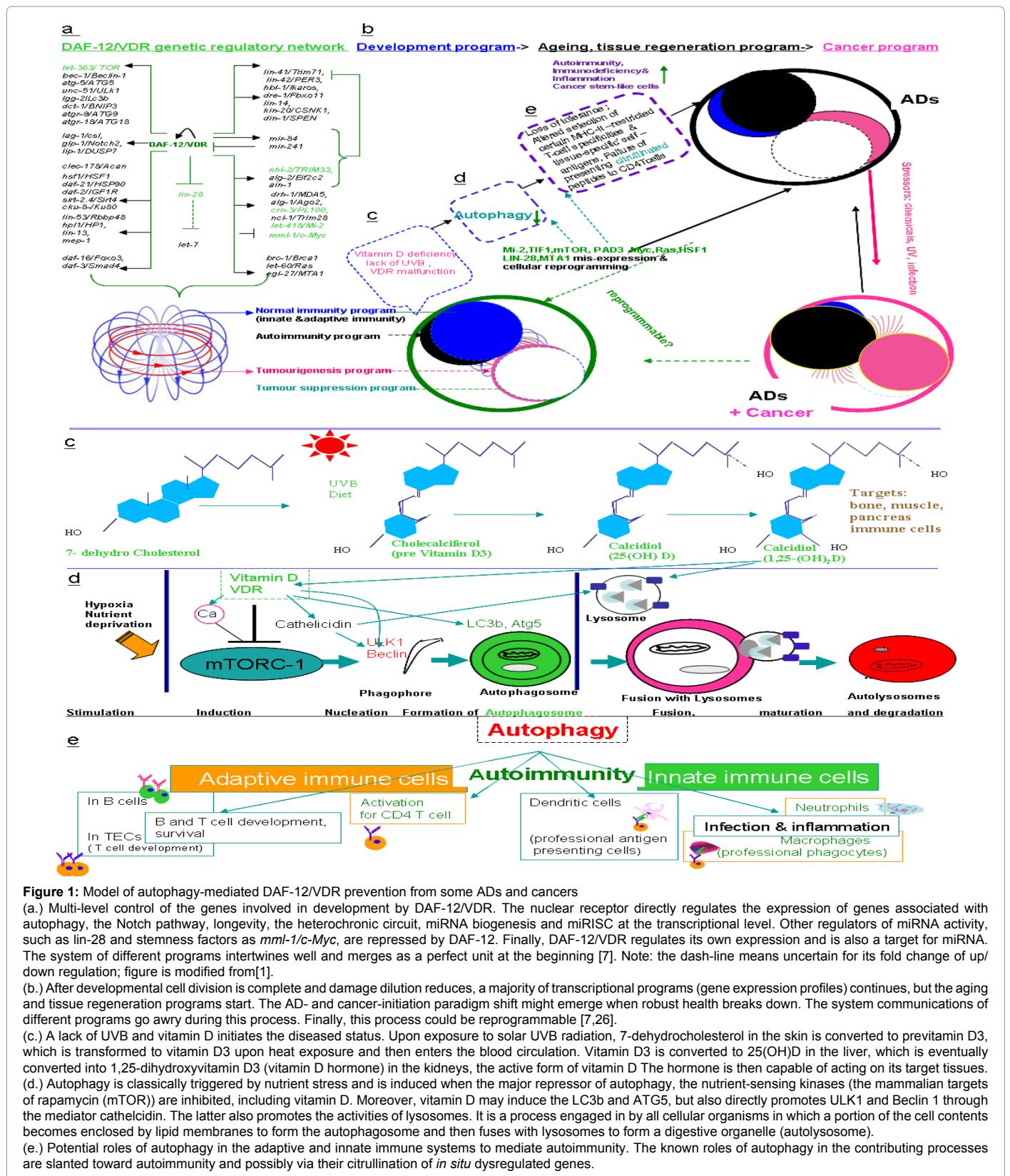


Figure 1: Model of autophagy-mediated DAF-12/VDR prevention from some ADs and cancers

(a.) Multi-level control of the genes involved in development by DAF-12/VDR. The nuclear receptor directly regulates the expression of genes associated with autophagy, the Notch pathway, longevity, the heterochronic circuit, miRNA biogenesis and miRISC at the transcriptional level. Other regulators of miRNA activity, such as lin-28 and stemness factors as *mml-1/c-Myc*, are repressed by DAF-12. Finally, DAF-12/VDR regulates its own expression and is also a target for miRNA. The system of different programs intertwines well and merges as a perfect unit at the beginning [7]. Note: the dash-line means uncertain for its fold change of up/down regulation; figure is modified from [1].

(b.) After developmental cell division is complete and damage dilution reduces, a majority of transcriptional programs (gene expression profiles) continues, but the aging and tissue regeneration programs start. The AD- and cancer-initiation paradigm shift might emerge when robust health breaks down. The system communications of different programs go awry during this process. Finally, this process could be reprogrammable [7,26].

(c.) A lack of UVB and vitamin D initiates the diseased status. Upon exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to previtamin D₃, which is transformed to vitamin D₃ upon heat exposure and then enters the blood circulation. Vitamin D₃ is converted to 25(OH)D in the liver, which is eventually converted into 1,25-dihydroxyvitamin D₃ (vitamin D hormone) in the kidneys, the active form of vitamin D. The hormone is then capable of acting on its target tissues.

(d.) Autophagy is classically triggered by nutrient stress and is induced when the major repressor of autophagy, the nutrient-sensing kinases (the mammalian targets of rapamycin (mTOR)) are inhibited, including vitamin D. Moreover, vitamin D may induce the LC3b and ATG5, but also directly promotes ULK1 and Beclin 1 through the mediator cathelicidin. The latter also promotes the activities of lysosomes. It is a process engaged in by all cellular organisms in which a portion of the cell contents becomes enclosed by lipid membranes to form the autophagosome and then fuses with lysosomes to form a digestive organelle (autolysosome).

(e.) Potential roles of autophagy in the adaptive and innate immune systems to mediate autoimmunity. The known roles of autophagy in the contributing processes are slanted toward autoimmunity and possibly via their citrullination of *in situ* dysregulated genes.

the pathogenesis of one or more types of ADs. It seems that the pathophysiology of ADs may share their common underlying mechanisms of genetic regulatory network of VDR.

Autophagy, VDR and Loss of Tolerance

Autophagy is an essential, homeostatic process for cell survival,

differentiation, development and, in some cells, cell death. It is engaged in by all cellular organisms in which a portion of the cell contents becomes enclosed by membranes to form the autophagosome and then fuses with lysosomes to form a digestive organelle (autolysosome). Vitamin D3 induces autophagy in human monocytes/macrophages [14]. Autophagy induction by vitamin D inhibits both *Mycobacterium tuberculosis* and human immunodeficiency virus type 1 [15,16]. Moreover, studies of cross-talks between autophagy and autoimmunity have emerged [17,18]. Furthermore, the antibody response in periodontitis is predominantly directed to the unmodified/uncitrullinated peptides of the RA auto-antigens examined in [19]. Autophagy in antigen-presenting cells, a potential process under the control of the VDR/DAF-12 genetic regulatory network [9], causes presentation of citrullinated peptides to CD4 T-cells [20].

The loss of tolerance could lead to the autoimmune response extensively evolving into the response of presymptomatic Rheumatic Arthritis (RA) [19]. The PAD3 enzyme, the homologue as one target of DAF-12 target, similar to its elevated expression upon initial inflammatory stimuli, may cause (aberrant) citrullination of target molecules and subsequently lead to pathological effects [21]. Therefore, human VDR may expectedly prevent a loss of tolerance in the auto-antibodies' response in RA. As mentioned in (Zhang Y [1]), DAF-12/VDR could control an array of target genes, some of which have their own redundant functions. Similar to DAF-12's synergy with its target genes in the mutations phenotype, though a weak or no symptom of mutations/variants occurs with particular VDR target genes that have a predisposed genetic tendency to develop a disease in patients, under the right conditions, an environmental factor, e.g. a deficient vitamin D level or a lack of UVB, together with host factors, might trigger the loss of tolerance in the autoimmune response [19]. One possibility is that normal autophagy in the thymic epithelium needs to shape the T-cell's repertoire and is essential for tolerance in that it focuses the MHC-II-peptide repertoire of the Thymic Epithelial Cells (TECs) on their intracellular milieu, with many 'tissue-specific' self-antigens [22]. In the thymus, the autoimmune regulator (*Aire* and *let-418*, a *daf-12/VDR* target, is its homologue in *C. elegans*) regulates the ectopic expression of "tissue-restricted" antigens in medullary TECs [23]. Because the human sera have natural IgG autoimmune antibodies [24], the mal-functional VDR could modify the levels of a subset of auto-antibodies, at least those sourced from some of its targets, and consequently break down tolerance locally and leads to autoimmune disease Ads [24-26]. Of certain, other pathways could also contribute to citrullination here [21,27,28]. In closing, 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, and then leads to locally-induced autoimmunity, whose citrullination of *in situ* dys-regulated genes could be largely mediated by a VDR-orchestrated autophagy process and consequently end with autoimmunity.

Conclusions and Perspectives

VDR and their targets are involved in the pathogenesis of one or more types of ADs, so promisingly to be targeted for prevention and/or treatment of RA, DM, other ADs and associated cancers. The citrullination of *in situ* dys-regulated genes may be mediated by its orchestrated dys-regulated autophagy process, and consequently raise the possibility of autoimmunity. Further testable predictions include: 1). to confirm newly identified DAF-12 ChIP-chip targets as VDR ChIP-seq targets in human contexts. 2). to establish some human VDR targets as DAF-12 targets in other developmental stages if missing in our newly identified DAF-12 ChIP-chip targets. 3). to check out if any *in*

situ citrullination of dys-regulated genes are due to VDR-orchestrated autophagy process in Rheumatic Arthritis (RA). 4). to examine if VDR truly acts as a capacitor to buffer some genetic mutations in ADs. 5). to test if highly-conserved targets (e.g. *MMP3*) of DAF-12/VDR may have synergic functions with its other evolutionarily- "fresh" targets (e.g. *IL-6*) [1]. Probably, by means of targeting autophagy as a basis for the health-promoting effects, therapeutic supplementation with a definitive range of systematically -optimized dosages of vitamin D would show its maximal beneficial effects within a combined treatment of such diseases.

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