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

Yue Zhang1,2*

1Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC H2L 4M1, Canada
2Osteoarthritis, Obesity and Metabolism Unit, University Health Network, Toronto Western Hospital, Toronto, ON M5T 2S8, Canada

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 decoding the genetics of 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

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-1γ/p140(TRIM24/TIF-1α) [10], whose natural auto-antigens may have a link with protein products encoded by TIF-1γ/a, 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/fibl-1 [12], SPAG16/WDR5.1, BLK1/src-1 [13], which are involved in

*Corresponding author: Yue Zhang, CRCHUM, Notre-Dame Hospital, 1560 Sherbrooke Street East, Pavilion DeSeve, Room Y2625, Montreal, Quebec, Canada, Tel: 1-514-890-8000, Fax: 1-514-412-7583, E-mail: zhanglee2006@gmail.com

Received December 12, 2013; Accepted December 13, 2013; Published December 15, 2013


Copyright: © 2013 Zhang Y. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
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 cathelin. 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,
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 could be largely mediated by VDR-controlled 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 could be largely mediated by VDR-controlled autophagy process and consequently end with autoimmunity.
autoantibody repertoire in periodontitis: a role in the induction of autoimmunity

21. Ireland JM, Unanue ER (2011) Autophagy in antigen-presenting cells results
in presentation of citrullinated peptides to CD4 T cells. J Exp Med 208: 2625-
2632.

arthritis is associated with antibodies that activate PAD4 by increasing calcium

thymic epithelium shapes the T-cell repertoire and is essential for tolerance.
Nature 455: 396-400.

Impact DM Editing and Susceptibility to Type-1 Diabetes. Front Immunol 4:
262.

Natural IgG autoantibodies are abundant and ubiquitous in human sera, and
their number is influenced by age, gender, and disease. PLoS One 8: e60726.

involvement in autoimmune rheumatic disease risk and prognosis. Ann Rheum
Dis 72: 473-475.


Immune-mediated pore-forming pathways induce cellular hypercitrullination
and generate citrullinated autoantigens in rheumatoid arthritis. Science
translational medicine 5:209.