

Genetic Basis of DAF-12/Vitamin D Receptor (VDR) in Autoimmune Immunity, Autoimmune Diseases and Associated Cancers

Yue Zhang*

Research Center, University of Montreal Hospital (CHUM), Notre-Dame Hospital, Montreal, Quebec H2L 4M1, Canada

Along with ageing, there is an increased risk for autoimmune diseases and/or cancers and no one is sure what causes such outcome. The vitamin D supplementation in the management of patients with rheumatic diseases and its controversy [1]. Indeed, the beneficial effects of vitamin D on Autoimmune Diseases (ADs) and cancers remain uncertain [1,2]. However, for the presence/absence of Vitamin D Receptor (VDR) within muscle [1], VDR might be transiently stable, similar to nuclear hormone receptor DAF-12, most closely-related to vertebrate VDR in nematode *Caenorhabditis elegans* [3-5]; thus some findings may be inconsistent even exacerbated with different genetic backgrounds. DAF-12 has its involvement in ageing and longevity [6-8]. Currently, the Rheumatoid Arthritis (RA) therapy is with a failure of anti-TNF therapy alone, but a better inhibition of human Th17-mediated synovial inflammation has been obtained alongside 1,25(OH)₂D₃—an active vitamin D metabolite [5]. Interestingly, human Matrix Metalloproteinase 3 (MMP3) gets involved in this processing and its homologue *H36L18.1* as direct target candidate of DAF-12/VDR [3]. The highly-conserved targets (e.g. MMP3) of DAF-12/VDR [3] may be extrapolated to have synergic functions with its other evolutionarily-“fresh” targets (e.g. IL-6) [9,10]. Unless we truly understand such processes, some controversies may remain and precise therapies could hardly be developed to correct harmful cell behaviours in cancer or autoimmune diseases (ADs) [2,11]. Strikingly, one Genome-Wide Association Study (GWAS) suggests that one allelic VDR variant may link to clinical autoimmune antibodies including anti-p150(TRIM33/TIF-1γ)/p140(TRIM24/TIF-1α) [9], whose natural auto-antigens may be related to protein products encoded by *TIF-1γ/α*, their homologues *flt-1* and *nhl-2* as direct targets of DAF-12/VDR [3]. Our CHIP-chip screening for DAF-12/VDR target genes [3] actually revealed many overlaps with validated homologues identified in human VDR studies and significantly enriched near genes that are pathologically associated with ADs and cancer [12]. Further, genes near these DAF-12 binding sites include an extensive network of autophagy-related genes, interconnected microRNAs, longevity factors, genes homologous to cellular reprogramming and carcinogenesis in mammals [3,13], etc. (Figure 1, and Zhang Y, A&R, *in preparation*). Autophagic dysfunction may promote the development of ADs such as lupus [14]. Surprisingly, DAF-12/VDR binding is frequent in genomic regions of genes whose homologues in human encode products closely-related to auto-antigens targeted by autoimmune antibodies [15]; which may cause diseases such as myositis, RA (Figure 1, and Zhang Y, A&R, *comments in preparation*). Genetically and/or physically, most of these targets intertwine in functional clusters/networks. Moreover, DAF-12/VDR acts as a capacitor to buffer internal/external challenges via multiple regulatory systems [3]. As a functional equivalent, human VDR may buffer detrimental effects of mutations of its targets, i.e. compensate to such mutations and ensure normal health. Environmental fluctuations, such as vitamin D deficiency and/ or a lack of UVB, likely enhance weaker phenotypes of mutations from VDR targets in patients, such synergic effects eventually lead to ADs and/or cancer. Data are waiting for completely clarifying these issues, but we predict, dys-expression of a subset of human VDR targets may cause cell-attractors shift, break down robustness of health, thus lead to ADs and carcinogenesis [13,16] (Figure 1). Other VDR targets function in response to danger signals, including *hmgbl/hmg-1.2*, *grp78/hsp-3*, *hsp90/daf-2* [3]. Finally, VDR

malfunction may result in over-expressions of reprogramming factors such as *c-myc* [17], *lin-28* [3], and reprogram cells to cancerous stem-like [13,16] and/or immunogenic [18].

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. Together, miRNA and miRISC regulate the levels and translation of many heterochronic genes. Finally, DAF-12/VDR regulates its own expression and is also a target for miRNA. The system of different programs could intertwine well and merges as one perfect unit at beginning [3]. Here genetic regulatory network is partially built on physical association between DAF_12/VDR and its target genes; further detailed confirmation for some gene expressions is still needed. NCBI Aceview has been used for the identification of gene homologues online.

b. After developmental cell divisions complete and damage dilution reduces, a majority of transcriptional programs (gene expression profiles) continues, but the aging and tissue regeneration programs start. The ADs and cancer-initiation paradigm shift might emerge while the robustness of health breaks down. The system communications of different programs go awry during the procession. Finally, this process could be reprogrammable [3,13] and thanking Mr. David Salisbury (Vanderbilt University) for elements for the illustration.

References

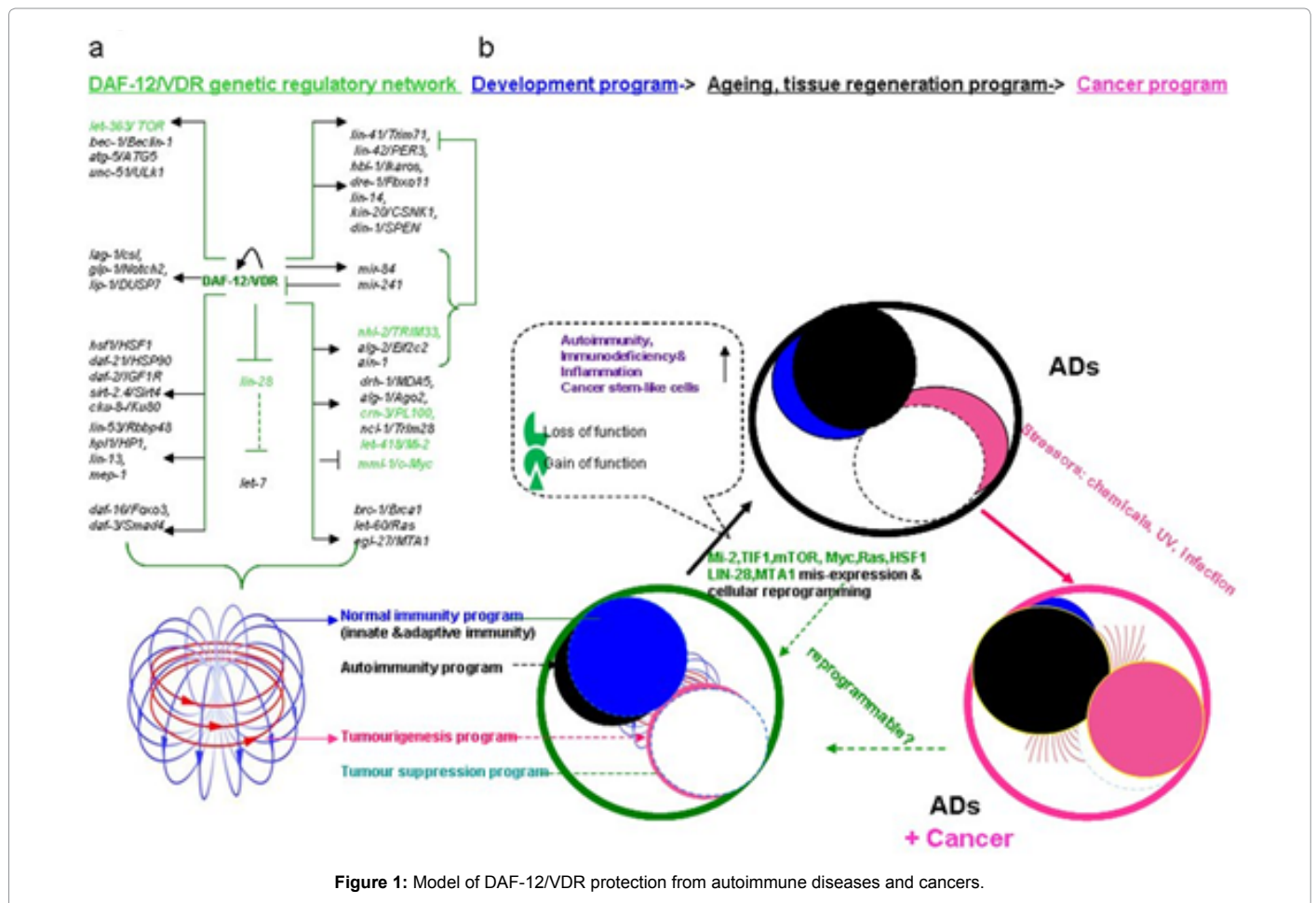
1. Abrahamsen B, Harvey NC (2013) The role of vitamin D supplementation in patients with rheumatic diseases. *Nat rev Rheumatol* 9: 411-422.
2. Nicholas J (2011) Vitamin D and cancer: uncertainty persists; research continues. *J Natl Cancer Inst* 103: 851-852.
3. Hochbaum D, Zhang Y, Stuckenholtz C, Labhart P, Alexiadis V, et al. (2011) DAF-12 regulates a connected network of genes to ensure robust developmental decisions. *PLoS Genet* 7: e1002179.
4. Zhang Y (2013) Gaps! Transgenesis, model organisms, and human diseases. *Clon Transgen* 2: e103.
5. van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Cornelissen F, et al. (2012) TNF blockade requires 1,25(OH)₂D₃ to control human Th17-mediated synovial inflammation. *Ann Rheum Dis* 71: 606-612.

*Corresponding author: Yue Zhang, PhD, CRCHUM, Notre-Dame Hospital, 1560 Sherbrooke Street East, Pavillon DeSève, Room Y2625, Montreal, Quebec, Canada H2L 4M1, Tel: 1-514-890-8000 ext 23875; Fax: 1-514-412-7583; E-mail: zhanglee2006@gmail.com

Received September 13, 2013; Accepted September 16, 2013; Published September 18, 2013

Citation: Zhang Y (2013) Genetic Basis of DAF-12/Vitamin D Receptor (VDR) in Autoimmune Immunity, Autoimmune Diseases and Associated Cancers. *Clon Transgen* 2: e105. doi:10.4172/2168-9849.1000e105

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.



- Held JM, White MP, Fisher AL, Gibson BW, Lithgow GJ, et al. (2006) DAF-12-dependent rescue of dauer formation in *Caenorhabditis elegans* by (25S)-cholestenoic acid. *Aging cell* 5: 283-291.
- Fisher AL, Lithgow GJ (2006) The nuclear hormone receptor DAF-12 has opposing effects on *Caenorhabditis elegans* lifespan and regulates genes repressed in multiple long-lived worms. *Aging Cell* 5: 127-138.
- Goudeau J, Bellemin S, Toselli-Mollereau E, Shamalnasab M, Chen Y, et al. (2011) Fatty acid desaturation links germ cell loss to longevity through NHR-80/HNF4 in *C. elegans*. *PLoS Biol* 9: e1000599.
- Kapoor SR, Chinoy H, Wedderburn LR, Oddis CV, McHugh NJ, et al. (2009) The Relationship Between the Vitamin D Receptor Gene and Anti-155/140 Antibodies in UK Caucasians with Idiopathic Inflammatory Myositis. *Arthritis Rheum* 60: 805.
- Noyola-Martinez N, Diaz L, Avila E, Halhali A, Larrea F, et al. (2013) Calcitriol downregulates TNF- α and IL-6 expression in cultured placental cells from preeclamptic women. *Cytokine* 61: 245-250.
- Alberts B (2010) Model organisms and human health. *Science* 330: 1724.
- Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, et al. (2010) A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. *Genome Res* 20: 1352-1360.
- Zhang Y, Moriguchi H (2011) Chromatin remodeling system, cancer stem-like attractors, and cellular reprogramming. *Cellular and molecular life sciences: CMLS* 68: 3557-3571.
- Choi AM, Ryter SW, Levine B (2013) Autophagy in human health and disease. *New Engl J Med* 368: 1845-1846.
- Ghirardello A, Bassi N, Palma L, Borella E, Domeneghetti M, et al. (2013) Autoantibodies in polymyositis and dermatomyositis. *Curr Rheumatol Rep* 15: 335.
- Bar-Yam Y, Harmon D, de Bivort B (2009) Systems biology. Attractors and democratic dynamics. *Science* 323: 1016-1017.
- Salehi-Tabar R, Nguyen-Yamamoto L, Tavera-Mendoza LE, Quailb T, Dimitrov V, et al. (2012) Vitamin D receptor as a master regulator of the c-MYC/MXD1 network. *Proc Natl Acad Sci USA* 109: 18827-18832.
- Zhao T, Zhang ZN, Rong Z, Xu Y (2011) Immunogenicity of induced pluripotent stem cells. *Nature* 474: 212-215.