Current Synthetic and Systems Biology

ISSN: 2332-0737

Zhang, Curr Synthetic Sys Biol 2013, 2:1
DOI: 10.4172/2332-0737.1000e102

Editorial Open Access

Synthetic and *Systems Biology*: Toward Achieving Impossible Missions and Deciphering Human Complex Disease Genetics

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Many pioneering works have inspired researchers to stay up-to-date on synthetic and system biology. Several cases that were originally thought to be exceptionally difficult, if not impossible, have been carried out successfully, such as Craig Venter's creation of the world's first synthetic life form. At a system level, nucleic reprogramming succeeded in frog half a century ago (reviewed in [1]); but doubts about whether or not this was impossible lingered until 40 years later, when a cocktail of four transcriptional factors systematically reprogrammed the somatic cells to stem cells [1-3]. Other cases include that telomerase reactivation may lead to the reversal of tissue degeneration in aged telomerase-deficient mice [4] and muscle-derived stem/progenitor cell dysfunction acts as a healthspan and lifespan limiting factor for murine progeria reversal [5]

Here, we focus on the latest impossible or exceptionally difficult missions, plus those of the future, i.e. decoding the complex diseases genetics and their possible modified nutritional, tour and other benign environmental treatments, which most of us could easily have and best exercise. Some complex diseases currently considered "difficult – to be addressed" are largely diseases of aging. For instance, starting for relatively simple neurodegenerative disorders like Parkinson's disease (PD) , today, no drugs exist to address the underlying pathology; for autoimmune diseases (ADs), no one is even sure what causes such outcomes; and for cancer, though billions of dollars have been invested and millions of articles published, there is still a long way to go to deal with them both theoretically and therapeutically to satisfy researchers and sufficiently match the expectations of patients. Successful creation of disease models and screening of targets are expected to be identified for such diseases and thus help slow or even prevent disease progression.

Latest Achieved Impossible Mission

Genetically engineered yeast cells with forced expression of alpha-synuclein has recently been is established as a robust model for the toxicity of this protein, which underlies PD but is lacking in yeast in nature [6,7]. Similarly, a *Caenorhabditis elegans* worm model has been successfully created for PD [2].

Though efficient, a target-based screening approach for some aging-related diseases has a serious limitation that it essentially takes place in a test tube, which is far from a real tissue, organ or organism, and hardly reveals or replicates the process of aging and development (i.e. the three physical dimensions and the time dimension are incomplete in those studies) so that some scrutinized drugs may behave differently when they are moved from the *in vitro* environment into a living organism. However, some " proteins believed to be "undruggable were promisingly targeted [7] and "impossible" disease modelling (e.g. for PD) has been achieved along with a living organism system-level platform [6,7].

However, if most human complex diseases are the consequence of the ensemble effects of polygenic variation at many loci, then both their functional relationships and their identities are keys to understanding the disease physiology. Systems Biology has the ability to analyse such widespread genetic variation and elucidate ultimately the cause- effects of disease mechanisms. This may spur new thinking if the current chasm between correlations of genome loci and causality is stemming in part from a limiting theoretical framework currently -derived from Mendelian genetics [8]. Of certain, experimental evidence is required from cells, tissues, or the rare patient, to clarify the role of a specific gene in a disease via a synthesis of multiple biological disciplines with emphasis here on the role of genetic variations identified in genome wide associated studies (GWAS) that are likely intrinsic to the biological process and solid confirmation of tractable experimental models.

Accomplishing Mission Impossible: the example of protection from ADs and associated cancers via the genetic regulatory network of the vitamin D receptor (VDR) and vitamin D

Importantly, VDR mediate the majority of cellular responses to vitamin D and environment insults that have potential in synthetic biology. The responsiveness of VDR to ligands and stimuli make them ideal sensory receptor modules of synthetic gene networks.

Immunologists were awarded the 2011 Nobel Prize in Pathology and Medicine, but autoimmunity remains largely unclear, if not mysterious. For one century, controversy and uncertainty has persisted on the beneficial effects of vitamin D supplementation against ADs and/or cancers [9-13]. Morever, we predict, without a thorough understanding of the underlying mechanisms, it is insufficient to solely rely on a semi-"shotgun" strategy for clinical trials. The gaps will make this topic backward without aging and development data. Based on genome-wide target genes screened with different model organisms at different stages, the genetic regulatory network (GRN) revealed that heterochronic gene DAF-12/VDR acts as a potential common basis preventing some ADs and associated cancers, and may help resolve such controversies [14] as follows: the explicit molecular mechanism of the VDR in response to the environment will first need go along with different polygeneic gene sets. As a capacitator, DAF-12/VDR may buffer genetic mutations and/or variations. Environmental factor-induced malfunctional DAF-12/VDR may lead to local dys-regulation of the expression of an array of its target genes [14] (Table 1 I,II), followed by their citrullination, mediated by its orchestrated autophagy

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Received November 09, 2013; **Accepted** November 12, 2013; **Published** November 15, 2013

Citation: Zhang Y (2013) *Synthetic* and *Systems Biology*: Toward Achieving Impossible Missions and Deciphering Human Complex Disease Genetics. Curr Synthetic Sys Biol 2: e102. doi: 10.4172/2332-0737.1000e102

I. Confirmation of DAF-12/VDRtarget genes in previous publications.	
Human *STAM/C. elegans gene name: C34G6.7, VDR/daf-12,TNFAIP3/Y50C1A.1, FCRL3/ttn-1, FOXP3/fkh-7, RASGRP3/rgef-1, Cyp24a/cyp-44a1, CYP-0a1/cyp-13b1, PRKCQ/T13H5.8, CD93/F56H11.1,NFkB/lit-1, HDAC6/F41H10.6, CCNC/cic-1, JMJD3/D008.1, JMJD2, HDAC/hda-2, PTPN0 /Y41D4A.5, IGFBP5/C54E4.2, CD6/ C06B8.7 and CBP1/p300.*	
II. Key autoimmune disease-related pathways and DAF-12/VDR target gene.	
Pathway	**Representative DAF-12/VDR target genes**
Autophagy	*TOR/let-363, Beclin1/bec-1, ATG5/Atg5, ULK1/unc-51*
Interconnected heterochronic and microRNA genes	*LIN28/lin-28, PER3/lin-42, TRIM71/lin-41, Eif2C2/alg-2, Ago2/alg-1, TIFγ/TRIM33/nhl-2, Ikaros/ hbl-1, CSNK1E/Kin-20, lin-14, ain-1 and ain-2.*
Notch pathway (and Alzheimer's disease)	*CSL /lag-1, NOTCH2/glp-1, lst-2,DUSP7/ lip-1, apl-1, CCT5/cct-5 and SPEN/din-1.*
RNA interference	*MDA (CADM140)/drh-1, eri-5, and rde-4.*
SynMuv B/DREAM pathway	*Rbbp48/lin-53, HP1/hpl1, Mi-2β/let-418 and mep-1, lin-13.*
Sex determination complex	GLI1*/tra-1* and *sdc-1.*
Cellular reprogramming and carcinogenesis	*Rbbp48/lin-53, MDA(CADM140)/drh-1, c-Myc/mml-1, LIN28/lin-28, MDR-1/pgp-9, PGK1/ pgk-1, AKT1/akt-1, AKT2/akt-2, RAS/let-60, PDK1/pdk-1,CDK4/cdk-4, CDK5/cdk-5, TNFAIP3/ Y50C1A.1, TOR/let-363, Beclin1/bec-1, SMAD4/ daf-3, BRCA1/brc-1 , MTA1/egl-27 and DDX6/ cgh-1.*
Aging/longevity	*Mi-2β/let-418, HSF1/hsf-1, FoxO/daf-16, VDR/daf-12, TOR/let-363, Beclin1/bec-1, SIRT4/Sir-2.4, IGF1R/daf-2, INS/ins-7, Ku80/cku-80 and KRIT1/kri-1, MTA1/egl-27.*

III. Autoimmune diseases, DAF-12/VDR target genes and well-known auto-antibodies of clinical importance.		
Type of diseases	**Representative DAF-12/VDRtarget genes**	**Representative auto-antibodies (α- = anti-)**
Diabetes mellitus	*HSP90/daf-21, MDA/CADM140/drh-1*	α-HSP90 andα-MDA/CADM140.
Systemic lupus erythematosus	*Ago2/alg-1; Eno1/enol-1, c-Myc/mml-1, La/ SSB and /C44E4.4CALR /crt-1, TCP-1/cct-1, NOD2/F28C1.3*	α-Su/Ago2, α-c-Myc, α-La/SSB, α-TCP-1 and α-NOD2 .
Polymyositis and dermatomyositis	*SSB/C44E4.4, U1-RNP/SNRNP70/rnp-7, c-Myc/mml-1, Mi-2β/let-418, TIFβ/TRIM28/ ncl-1, TIFα/TRIM24/flt-1, TIFγ/TRIM33/nhl-2, PM/Scl-100/crn-3, Zo/frs-1, PL-12/AARS/ ars-1, Ku80/cku-80, MDA (CADM140)/drh-1, SSA/TRIM0/cnb-1, Su/Ago2/alg-1, SM/lsm/ Y47G12B.14 , PLCL1/pll-1, BLK/src-1*	α-Lo/SSB, α-U1-RNP/SNRNP70, α-c-Myc, α- Mi-2β, α-TIFβ/KAP1/TRIM28, α-TIFα/ TRIM24/p140, α-TIFγ/TRIM33/p150, α-PM/Scl-100, α-Zo, α-PL-12/AARS, α-Ku80, α-MDA (CADM140), α- Ro-/SSA/TRIM0, α-Su/Ago2, α-SM.
Scleroderma	*PM/Scl-100/crn-3, TIFβ/TRIM28/ncl-1, Scl-70/ TOP-1, FBN1/Fbl-1, U1-RNP/SNRNP70 /rnp-7, p27/Y39A1A.3*	α-PM/Scl-100, α-TIFβ/TRIM28,α-PM/*Scl-70*, α-U1-RNP/SNRNP70.
Crohn's disease	*NOD2/F28C1.3*	α-NOD2.
Sjögren's syndrome	*Ro-SSA/cnb-1, p27/Y39A1A.3, CALR /crt-1,*	α-Ro-SSA.

Note: the original full list for the DAF-12 target genes online available in supplementary materials [17] and turn to NCBI Aceview for their human homologues or *vice versa*

Table1: Representative DAF-12 and VDR shared conserved target genes and classic auto-antibodies -related target genes.

process, and consequently end with autoimmunity (Table 1 III). In fact, there are abundant and ubiquitous natural IgG auto-antibodies in human sera, and their quantity is influenced by age, gender and disease [15]. In nature, the reversal of a diseased status with vitamin D supplementation is more difficult and/or complex than the breakdown of robust health. Lastly, after long-term selection for some populations, some diseases might be even independent of the malfunction of DAF-12/VDR. But would these findings apply in human cells? To answer that question, other research will be needed.

However, Miller FW et al. [16], reporting on genome-wide association study (GWAS) of dermatomyositis (DM), revealed a genetic overlap with other ADs, the first identification of genetic predispositions towards ADs shared with DM. Moreover, the patterns of genetic overlap across ADs have emerged [11,16] . Further, our recent ChIP-chip screening for DAF-12/VDR target genes [17,18], along with NCBI Aceview, may reveal many translatable targets overlapping with validated homologues identified in human VDR studies that are significantly enriched near genes that are pathologically associated with ADs [2,19], including phospholipase C-like 1 (**PLCL1**), B lymphoid tyrosine kinase (**BLK**), i.e. *pll-1* and *src-1* respectively. Further, one new study reported that integrin-modulating therapy prevents fibrosis and autoimmunity in mouse models of scleroderma. The key regulator FBN1 for scleroderma is the homologue of *fbl-1* in *Caenorhabditis elegans* [20]. Another GWAS identified a genetic variant for joint damage progression in autoantibody-positive rheumatoid arthritis (RA) [21]. Interestingly, sperm-associated antigen 16 (*SPAG16*), matrix metallopeptidase 1 and 3 (*MMP1* and *MMP3*) are VDR [17,22-24] target genes too, i.e. *wdr-5.1* (*C14B1.4)* and *H36L18.1* respectively (but there is a single congruent *C. elegans* homologue for human *MMP1* and *MMP3*) . This is the first time for a VDR target gene variant that has the significance of being a "beneficial" locus, i.e. uniquely, SPAG16 influences MMP-3 activity and protects against joint destruction in autoantibody-positive RA. Further, it is known that *Wdr-5.1* is a component of the conserved H3K4 trimethylation (H3K4me3) complex and negatively regulates lifespan in *C. elegans* [24]; interestingly, WDR-5.1 activity also antagonizes SynMuv transcriptional repressors, which antagonize worm RAS signalling [25]. Vitamin D3 regulates matrix metallopeptidase (MMP-

3) in cultured human cells [26]. A malfunction in VDR could thus affect the pathogenesis of RA and possibly associated cancers [2,14]. Particularly, RA therapy now remains a challenge with the failure of anti-TNF therapy alone [27], but better inhibition of human Th17-mediated synovial inflammation has been shown with 1,25(OH)2D3 – an active vitamin D metabolite [28]. Importantly, MMP3 contributes to this process [17,28,29]. The highly-conserved targets of DAF-12/VDR (e.g. *MMP3/MMP1*) [17] have synergic functions with its other evolutionarily "novel" targets (*e.g. Interleukin-6*) [29,30]. Strikingly, one GWAS previously reported that one allelic VDR variant may link to clinical autoimmune antibodies including the anti-p150 (TIF-1γ)/p140 (TIF-1α) [30] and *TIF-1γ/α* genes' *C. elegans* homologues, *flt-1* and *nhl-2*, are also direct targets of DAF-12/VDR (Table 1, III) [17]. In addition, the human homologues of other DAF-12/VDR targets genes such as *let-418 /Mi-2β* (best homologous to human AIRE) are associated with DM (Table 1 ,III) [17,31]. Since DAF-12/VDR may buffer internal or external challenges in *C. elegans [17]*, its functional counterpart human VDR may possibly prevent the breakdown of robust normal human health [16,32]. This is similar to DAF-12's synergy with its target genes in the mutation phenotype. Although a weak (or no) mutation phenotype appears with particular VDR target genes but there is still a genetic tendency to develop a disease in patients under the right conditions, an outside invader like a virus or environmental factor, e.g. vitamin D deficiency or a lack of UVB, might trigger ADs. Interestingly, Liu F et al. [33] showed that DAF-12/VDR plays a critical role in the innate immune response. In mammalian systems, VDR may have a more complex adaptive immune response than its conserved innate immune response [28,34]. A combination of factors including a genetic regulatory network and those from VDR and its target genes is probably at work for ADs.

However, further detailed investigation will need focus on other adult stages and embryonic stages for DAF-12/VDR will give a comprehensive view on genetic regulatory networks. Since human patients are outbreed and experimentally–intractable; cell culture and organelle has its innate limitations, but one of two developmental stages can easily cover the equivalent time span such as twenty years for some trials and be subject to genetic manipulation. Particularly, the *C. elegans* community had built a genome-wide RNA interference library to knock down any gene. We can systematically look at genetic interactions, and streamline -like in a factory for disruption of genes in pathways or in redundancy can be set up [35,36]. If using the mouse model, we may profit one-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering to disrupt multiple loci [37]. Lastly, because VDR are important pharmacological targets of such human diseases, genes encoding their protein/peptide ligands can also be incorporated as target genes of the response output elements of synthetic gene networks. Unlike some abovementioned mission, this is thus one possible mission for VDR to construct therapeutic synthetic gene networks. Besides, if this may be proven, excellent chance to elucidate that particularly their loci are also identifying as disease-causing target genes as well, consequently, they are not a list of unbiased candidates insufficient for implicating specific gene(s) in a disease, but promote the role of its target genes as being "causal," rather than just "associated," in a disease process, and VDR may be fit for latest modified Koch's postulates for complex human diseases and traits [8].

How about equipping the worm with an adaptive immune system? Right now, this is one seemingly impossible mission. If, indeed, it could work, then it will shed light not only AD prevention /cure but also on cancer immunotherapy. The next step will simply be using model organism genetics to identify a compound and its mechanism of action against the fundamental pathology of these diseases, a process which may benefit from the power of multiple organisms (particularly including living organism systems) [6,7]. We may eventually accomplish some new impossible missions in the future.

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