D-Hormone and the Immune System

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ABSTRACT. D-hormone [1,25$(OH)_2$ D_3] is an important immune system regulator that has been shown to inhibit development of autoimmune diseases including experimental inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes. Paradoxically, other immune mediated diseases (experimental asthma) and immunity to infectious organisms were not found to be affected by D-hormone treatment. The effectiveness of D-hormone treatment of autoimmune diseases is due to inhibition of the development and function of Th1 cells and the induction of other Th cells including Th2 cells. We report results of microarray analysis of colons from D-hormone treated mice with experimental IBD. Two hundred thirty-nine genes were inhibited and 298 genes were upregulated in the colon by D-hormone treatment of mice with IBD. Of interest was the D-hormone mediated inhibition of 3 tumor necrosis factor-α (TNF-α, lipopolysaccharide-induced TNF-α factor, and TNF receptor) related genes in the colon. It is likely that the effectiveness of D-hormone treatment of experimental autoimmunity is due in part to the inhibition of the TNF family of genes. D-hormone is a selective regulator of the immune system, and the outcome of D-hormone treatment depends on the nature (infectious disease, asthma, autoimmune disease, etc.) of the immune response. (J Rheumatol 2005;32 Suppl 76:11-20)

Key Indexing Terms:
VITAMIN D RECEPTORS
IMMUNE SYSTEM
TUMOR NECROSIS FACTOR
CALCITRIOL
ANIMAL DISEASE MODELS

The discovery of the vitamin D receptor (VDR) in the cells of the immune system and the fact that activated dendritic cells produce the vitamin D hormone[1] suggested that vitamin D could have immunoregulatory properties. VDR, a member of the nuclear hormone receptor superfamily, was identified in mononuclear cells, dendritic cells, antigen-presenting cells, and activated T lymphocytes.

A physiological role for vitamin D in the immune system is suggested by the presence of the VDR in primary lymphoid organs. The primary lymphoid organs (bone marrow and thymus) are the centers where the immune system develops and differentiates[2,3]. However, VDR knockout (KO) mice have normal thymuses, normal myelopoiesis of the bone marrow, and no overt abnormalities in other immune system compartments[4]. Recently it has been shown that when activated, the VDR knockout mouse has overactive and inflammatory T cells; moreover, in animals susceptible to inflammatory bowel disease (IBD), this results in a fulminating form of IBD[5]. The function of VDR in the primary lymphoid tissues is not known, but arguably there is a role of the D-hormone in regulating the processes occurring there.

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VITAMIN D AND AUTOIMMUNITY

Autoimmune diseases are diseases where the immune system's ability to discriminate between self- and non-self tissue fails. People with diseases like multiple sclerosis (MS), arthritis, and IBD have T cells that target self and drive the immune system to induce inflammation in the peripheral tissues. The causes of the inappropriate immune attacks are not known; however, it is clear that both genetic and environmental factors contribute to the etiology of these diseases.

T cells have been shown to be central for the pathology of autoimmune disease. Specifically, type 1 helper (Th1) cells, which secrete interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) have been shown to transfer autoimmune disease in mice. Treatments that can directly or indirectly block Th1 cell function are effective for suppressing autoimmunity. Type 2 helper cells (Th2) secrete interleukin 4 (IL-4), which inhibits the differentiation of Th1 cells. Other regulatory T cells produce transforming growth factor-β1 (TGF-β1) or IL-10, which also inhibit Th1 effector cell function.

Vitamin D status has been linked to autoimmune diseases in humans. Recently a large population study (Nurses Health Study I and II) showed that women in the highest quintile of vitamin D intake had a 40% reduced rate of developing MS[6]. Similarly, vitamin D intake was inversely associated with rheumatoid arthritis in the Women's Iowa Health Study, which contained data from 29,368 women[7]. Experimentally it has been shown that vitamin D deficiency exacerbates both IBD and MS in animals[8,9]. Further, D-hormone has been shown to suppress experimental MS and IBD in mice[8,9]. Interestingly, D-hormone has been shown to effectively inhibit autoimmunity even when animals were vitamin D sufficient.

Table 1. In vivo effects of D-hormone in mice with targeted gene deletions.

Genotype	Effects of D-hormone	Experimental Models Tested	References
Wildtype	Suppressed	MS, lupus, IBD, arthritis, type-1 diabetes	5,8,9,16,17
IL-4 KO	Reduced	MS	11
VDR KO	No effect	MS	12
IL-2 KO	No effect	IBD	13
IL-10 KO	Suppressed	IBD	9

IN VIVO TARGETS OF D-HORMONE

In vivo targets of the D-hormone in experimental MS include a number of inflammatory cytokines (Table 1). D-hormone treatment of mice with experimental MS resulted in inhibition of lymphocyte accumulation in the lymph nodes[10]. Mice treated with the D-hormone had fewer cells secreting TNF-α and IFN-γ[10]. In addition, D-hormone treatment increased the level of IL-4 and TGF-1 produced in the animals[10]. The ability to produce IL-4 is important for the function of D-hormone, since D-hormone treatment was ineffective for suppressing experimental MS in mice that were deficient in IL-4 (IL-4 KO, Table 1)[11]. As expected, D-hormone was ineffective at inhibiting experimental MS in VDR KO animals[12]. Vitamin D deficiency accelerated the development of IBD in IL-10 KO mice, and colitis symptoms in IL-10 KO mice were suppressed by D-hormone treatment (Table 1)[9]. Conversely, the colitis that develops in IL-2 KO mice was unaffected by vitamin D status[13]. In addition, colitis in IL-2 KO mice was not suppressed by D-hormone treatment (Table 1)[13]. The net result of D-hormone treatment in experimental autoimmunity includes decreased symptoms, which parallel the reduced production of Th1 associated cytokines and TNF-α, and a concomitant increase in cytokines that correspond to the resolution of inflammation and decreased severity of autoimmunity. IL-4 and IL-2 production have been shown to be crucial for the effectiveness of D-hormone in experimental autoimmunity. Overall, the action of D-hormone *in vivo* functions to suppress autoimmunity by inhibiting Th1 cell associated responses and increasing Th2 and other regulatory T cell processes.

NOVEL D-HORMONE TARGETS IN THE COLON OF MICE WITH EXPERIMENTAL IBD

When D-hormone targets were probed in experimental IBD, results were consistent with previous findings: Untreated vitamin D deficient IL-10 KO mice developed more severe IBD, as shown by larger small intestine/body weight ratios (9.0 ± 0.6%) compared to the D-hormone treated IL-10 KO mice (6.5 ± 0.7%). Based on the high expression of TNF-α in the colons of IL-10 KO mice (data not shown), microarray analysis was done using colon tissue. Microarray analysis was performed exactly as described[14] and repeated once using total RNA from different mice (Tables 2 and 3). The inclusion criteria for genes reported were (1) the gene was up- or downregulated 2-fold or more in one of the experiments, (2) the gene was up- or downregulated by 1.3-fold or more in the second experiment in the same direction as the first, and (3) the microarray spot for the gene had a combined median fluorescent intensity (median green fluorescence median background + median red fluorescence median background) of more than 100 on both array replicates. Two hundred thirty-nine downregulated (Table 2) and 298 upregulated (Table 3) potential targets of the D-hormone were identified using these criteria.

Table 4 shows the results for 6 genes. The expression of VDR is known to be positively regulated by the D-hormone. As expected, D-hormone treatment of the IL-10 KO mouse increased the expression of VDR mRNA in the colons of D-hormone treated mice. Interestingly, calmodulin and calcium binding protein A6 (calcyclin) are expressed in colonic tissue, and it seems reasonable that vitamin D would increase expression of these calcium regulators. Three genes (TNF-α, lipopolysaccharide-induced TNF-α factor, and TNF receptor) involved in the regulation of TNF-α were inhibited by D-hormone in the colons of IL-10 KO mice. The inhibition of these TNF-α related genes by D-hormone correlated with decreased severity of colitis in D-hormone treated IL-10 KO mice. Elevated TNF-α secretion has been shown to play a role in Crohn's disease, and treatments that inhibit TNF-α secretion have been shown to be effective for treating IBD in humans.

D-HORMONE SELECTIVELY REGULATES IMMUNE FUNCTION

Clearly, D-hormone is a potent suppressor of autoimmune diseases. Based on the ability of the D-hormone to suppress autoimmunity and to prolong allograft survival, scientists have labeled it "immunosuppressive". However, the effect of the D-hormone on immune function has not been shown to be broadly immunosuppressive. D-hormone treatment was tested for an effect on the ability of a host to fight an infection with *Candida albicans* or Herpes simplex virus[15]. Mice were treated with the D-hormone at levels previously shown to be effective at prolonging allograft transplants[15]. As controls, mice were

Table 2. Genes downregulated by D-hormone in whole colon tissue of IL-10 knockout mice. *The ratio is the inverse of the average of the median intensities of red fluorescence over green fluorescence. Negative ratios represent the factor by which genes were inhibited by D-hormone treatment. All values are the means of 2 independent experiments.

GenBank Accession No.	Name	Ratio*	Combined Median Intensities
X02339	CD3 antigen delta polypeptide	-1.65	318
D16313	Krt1-15	-1.66	891
X97817	Sema5a	-1.66	753
AJ243590	Drg2	-1.7	1074
AF030896	I kappa B epsilon	-1.74	384
M68489	Thymidine kinase 1	-1.76	736
D87902	ADP-ribosylation factor 5	-1.76	10399
AF069953	Gng3	-1.77	632
AF164119	Binder of Rho GTPase 3	-1.77	3346
M33151	Histocompatibility 2 L region	-1.78	26765
AF171100	LPS-induced TNF-alpha factor (LITAF)	-1.8	4392
L24118	TNF alpha-induced protein 2	-1.82	734
AF109918	Tomm40	-1.82	815
AF218249	Atp6n1	-1.84	997
AF133093	Host cell factor C1	-1.85	1476
NM_011824	Cysteine knot 1, BMP antagonist 1	-1.85	1126
L02844	CD22 antigen	-1.88	1366
M91000	Somatostatin receptor 3	-1.88	750
U20372	Calcium channel beta 3 subunit	-1.89	2965
NM_010601	K+ voltage-gated channel subfamily H, 3	-1.9	307
M93275	Adipose differentiation related protein	-1.9	666
U76306	Solute carrier family 6, member 2	-1.92	1100
AF159090	MHC psoriasis candidate gene	-1.92	811
AF139221	Immunoglobulin kappa chain variable 28	-1.93	843
M81445	Gap junction membrane protein beta 2	-1.94	480
AF097512	Peroxisomal biogenesis factor 14	-1.95	875
U08354	Melanocortin 5 receptor	-1.95	1076
U47543	Ngfi-A binding protein 2	-1.97	514
NM_010739	Lymphocyte antigen 64	-1.98	17424
U46923	G protein-coupled receptor 19	-1.98	701
U58888	SH3 domain protein 3	-2.01	259
L29468	Cofilin 2 muscle	-2.02	750
D86725	Mini chromosome maintenance deficient 2	-2.06	490
U51014	Peptidase 4	-2.06	738
AF039663	Prominin	-2.08	571
M55412	Guanine nucleotide binding protein alpha q	-2.08	379
AJ222969	Periaxin	-2.08	854
U89906	Alpha-methylacyl-CoA racemase	-2.08	263
M60778	Integrin alpha L	-2.1	950
AF126427	Mab-21-like 2	-2.11	721
D14883	Kai1	-2.11	2997
NM_013863	Bcl2-associated athanogene 3	-2.11	530
AF162768	EST AF007010	-2.12	18153
U43186	Map3k2	-2.13	257
X59300	GABA-A receptor subunit gamma 3	-2.13	570
L36962	Metaxin	-2.14	612
L15447	nuclear ribonucleoprotein polypeptide A	-2.16	1982
U97079	U5 small nuclear ribonucleoprotein 116 k	-2.16	1216
X65493	Intercellular adhesion molecule 2	-2.16	263
X57796	TNF receptor superfamily, 1A	-2.16	1829
AB026805	Synaptotagmin 8	-2.17	225
AF108214	Eukaryotic translation initiation factor 3, S4	-2.17	433
D28599	Chondroitin sulfate proteoglycan 2	-2.19	698
AF087680	Valyl-tRNA synthetase 2	-2.2	2346
U42384	Fibroblast growth factor inducible 15	-2.21	379
NM_011390	Solute carrier family 12 member 7	-2.22	2043
M38337	Milk fat globule-EGF factor 8 protein	-2.23	1952
M23109	Coagulation factor IX	-2.23	681
U43844	Cyclin D3	-2.27	1382
U89489	LIM domain binding 2	-2.27	332
AB000713	Claudin 4	-2.29	460
NM_019692	GTP-binding protein Roc2	-2.32	2589
J03928	Phosphofructokinase, liver, B-type	-2.33	2013
AF192558	Mitochondrial carrier homolog 1	-2.34	275
AB019003	CFTR/MRP, member 5a	-2.34	431
NM_011176	Suppression of tumorigenicity 14	-2.36	2183
U73198	GDI gammma	-2.38	1471
Z22923	Procollagen type IX alpha 2	-2.38	465
AF126798	Fatty acid desaturase 2	-2.39	548
X02611	Tumor necrosis factor alpha	-2.4	362
AF297082	Guanylate cyclase 1, soluble alpha 3	-2.43	298
AB041568	Hypothetical protein MNCb-1213	-2.43	2911
AB016424	RNA binding motif protein 3	-2.47	415
AF026481	Eukaryotic translation initiation factor	-2.47	628
U20780	Ubiquitinating enzyme E2	-2.49	477
AF216306	Down syndrome critical region gene c	-2.5	249
AJ230108	Annexin A5	-2.51	342
U96963	Diaphanous homolog 1	-2.52	705
Y07915	Ets variant gene 6 (TEL oncogene)	-2.54	563
J02809	Growth associated protein 43	-2.54	2081
Y13832	Maternally expressed gene 3	-2.56	371
Y15443	Tumor-suppressing transferable fragment 3	-2.58	230
X75832	Glycine receptor alpha 1 subunit	-2.59	443
AF111715	Acyl-malonyl condensing enzyme	-2.6	380
D87898	ADP-ribosylation factor 1	-2.6	360
U85786	Sodium channel voltage-gated type I beta	-2.62	417
M27073	Protein phosphatase 1 catalytic subunit	-2.63	496
AF026123	Synaptojanin 2	-2.63	248
NM_019560	Syntaxin 1 b-like	-2.64	506
U95607	Hsp40 homolog subfamily B member 3	-2.65	532
NM_013569	K+ voltage-gated channel subfamily H, 2	-2.65	434
AF134238	Placental protein 6	-2.65	277

X91144	Selectin platelet (p-selectin) ligand	-2.66	849
Y00769	Integrin beta 1 (fibronectin receptor be	-2.68	747
M13446	Tubulin alpha 2	-2.68	583
U18366	Cardiotrophin 1	-2.77	1264
NM_013754	Insulin-like 6	-2.82	5131
U76832	Syntaxin 4A (placental)	-2.83	420
AF082348	Bone morphogenetic protein 15	-2.84	477
AB028860	Hsp40 homolog subfamily B member 12	-2.85	493
X68837	Secretogranin II	-2.87	338
AF047542	Cytochrome P450 2c37	-2.89	494
U45665	Cut-like 2	-2.89	241
M86390	Moesin	-2.92	511
AB040710	Carbohydrate sulfotransferase 7	-2.92	708
U90123	Hematologica/neurological expressed seq 1	-2.93	325
AB041556	RIKEN cDNA 1110020M21 gene	-2.97	448
AB030183	RIKEN cDNA 2010004O20 gene	-2.98	1204
AF016190	Gap junction channel protein alpha 9	-3	360
AF055666	Kinesin light chain 2	-3.03	393
NM_010701	Leukocyte cell derived chemotaxin 1	-3.03	227
AF127245	Selected mouse cDNA on the X	-3.04	1732
U00445	Glucose-6-phosphatase catalytic	-3.04	395
AF004927	Opioid receptor sigma 1	-3.06	1661
AB018421	Cytochrome P450 4a10	-3.07	752
AF216832	Gap junction channel protein alpha 4	-3.12	374
AB032605	Piwi like homolog 1 (Drosophila)-like	-3.13	420
D10911	A disintegrin and metalloprotease domain	-3.13	5659
AF093671	Peroxisomal biogenesis factor 11b	-3.17	571
AF140683	F-box and WD-40 domain protein 2	-3.18	837
X70887	FK506 binding protein 4 (59 kDa)	-3.18	772
NM_011339	Inducible cytokine subfamily B, member 15	-3.21	611
AB006329	SRY-box containing gene 13	-3.23	498
AJ252157	Forkhead box O1	-3.24	327
X14897	FBJ osteosarcoma oncogene B	-3.24	593
U88566	Secreted frizzled-related protein 1	-3.26	511
X97227	CD53 antigen	-3.3	603
U95736	Friedreich ataxia	-3.31	1194
U26176	Somatostatin receptor 4	-3.31	466
M86751	Immunoglobulin kappa chain variable 28	-3.32	449
L20899	RAS nucleotide-releasing factor 1	-3.34	595
AF184900	Complement component 6	-3.34	300
AF227149	Candidate taste receptor T2R19 gene	-3.38	664
M31654	Growth hormone releasing hormone	-3.41	564
Y13344	Adenosine A2a receptor	-3.42	963
Y14334	Arachidonate 12-lipoxygenase 12R type	-3.43	255
D70848	Zinc finger protein of the cerebellum 2	-3.44	313
X60831	Transcription factor UBF	-3.44	736
AF003691	Keratin-associated protein 14	-3.48	933
AB019374	Mitogen activated protein kinase kinase	-3.51	242
J03880	UDP-Gal:betaGlcNAc beta 14	-3.51	326
AF202893	Kinesin family member 21B	-3.51	246
AJ003128	Huntingtin-associated protein 1	-3.54	606
X66473	Matrix metalloproteinase 13	-3.55	388
AF176098	Polymerase (DNA directed) mu	-3.59	626
AF092921	Cysteine rich protein	-3.61	351
NM_013620	Olfactory receptor 68	-3.61	342
U92793	Alpha glucosidase 2 alpha neutral subunit	-3.63	521
AB022600	Membrane cofactor protein	-3.63	312
AF027865	Butyrophilin-like 2	-3.64	858
NM_009428	Transient receptor protein 5	-3.66	750
NM_011976	Ig, TM and short cytoplasmic domain	-3.66	738
AJ223206	Scrapie responsive gene 1	-3.68	428
X79003	Integrin alpha 5 (fibronectin receptor a	-3.68	558
AJ243502	Fatty acid-Coenzyme A ligase long chain	-3.76	422
X87671	SH3-domain binding protein 1	-3.78	936
AE000665	Mus musculus TCR beta locus	-3.87	1333
X16511	Homeo box C6	-3.92	221
AF069954	G protein gamma 3 linked gene	-3.95	1020
L32836	S-adenosylhomocysteine hydrolase	-3.95	246
X67685	Ubiquitin-like 1	-3.95	1522
AF047726	Cytochrome P450 2c39	-3.97	761
AB041581	RIKEN cDNA 2600017P10 gene	-4.04	319
Z14249	Mitogen activated protein kinase 3	-4.06	253
AF121081	Solute carrier family 37	-4.06	1261
U86090	Kinesin family member 5B	-4.06	317
X52101	Polypyrimidine tract binding protein	-4.07	327
X69722	Insulin receptor substrate 1	-4.08	526
M16356	Major urinary protein 2	-4.13	283
U37500	RNA polymerase II 1	-4.13	693
M83380	(v-rel) oncogene related B	-4.15	347
NM_020494	DEAD/H box polypeptide 13	-4.16	408
AF176523	F-box and leucine-rich repeat protein 8	-4.18	405
X14759	Homeo box msh-like 1	-4.2	1090
Y15110	Glial cell line derived neurotrophic factor	-4.21	1091
AF195056	VPS10 domain receptor protein SORCS	-4.25	180
U02554	Serum amyloid A 4	-4.34	761
Mouse	Mouse mRNA for TI-227	-4.34	757
X63615	Calcium/calmodulin-dependent protein kinase	-4.46	610
L27990	Sjogren syndrome antigen A1	-4.53	715
AF035399	Neurotrophic tyrosine kinase receptor	-4.6	2057
M83344	Pregnancy specific glycoprotein 17	-4.67	2502
X72862	Adrenergic receptor beta 3	-4.71	410
AF181984	Ca2+/calmodulin-dependent kinase Pnck	-4.73	443
X65635	Melanocortin 1 receptor	-4.76	391
AF057526	Rhesus blood group-associated A glycoprotein	-4.8	759

D89902	Keratin-associated protein 6-2	-4.95	254
M75721	Serine protease inhibitor 1-1	-4.95	1262
AF011422	Vomeronasal organ family 2 receptor 12	-4.97	252
AF218253	ATPase H+ transporting lysosomal I	-5.08	688
AF096867	Synapsin II	-5.09	1316
AF078905	Hemoglobin X alpha-like embryonic chain	-5.11	776
AB010149	Adenylate cyclase activating polypeptide	-5.12	746
D84376	Phosphatidic acid phosphatase 2a	-5.12	331
L29006	Solute carrier family 7 member 2	-5.13	656
X82687	RIKEN cDNA 1810027O01 gene	-5.21	482
NM_013909	F-box and leucine-rich repeat protein 6	-5.28	339
X58250	H2.0-like homeo box gene	-5.32	439
AJ131357	Chemokine (C-C) receptor 10	-5.35	355
X00479	Cytochrome P450 1a2	-5.54	835
AF033201	Cleavage and polyadenylation specific factor 4	-5.55	1107
AL078630	GABA B receptor 1	-5.68	549
AJ011107	Mus musculus mRNA for 3'UTR of Clc1 gene	-5.9	1046
AJ236881	SHP2 interacting transmembrane adaptor	-5.98	469
AF083876	Epithelial membrane protein 2	-6	314
AF045663	RAD9 homolog (S. pombe)	-6.16	589
X94998	Fibromodulin	-6.25	387
AB024427	Ring finger protein 11	-6.31	884
AF082526	Mitogen activated protein binding protein	-6.46	729
L04538	Amyloid beta (A4) precursor-like protein	-6.59	764
AF104410	Vascular endothelial zinc finger 1	-6.8	357
AJ007396	Sal-like 2	-7.08	1291
AB003502	G1 to phase transition 1	-7.35	480
U19755	Thyroid transcription factor 1	-7.59	1698
AF050182	Period homolog 3	-7.63	213
NM_013616	Olfactory receptor 64	-7.66	826
L03529	Coagulation factor II (thrombin) receptor	-7.78	331
AJ010109	Adenylate kinase 1	-7.84	416
U29156	Epidermal growth factor receptor pathway	-8.07	391
D89787	Endothelial PAS domain protein 1	-8.27	226
U28405	Chemokine (C-C) receptor 1-like 1	-8.4	766
U73902	Emerin	-8.58	736
D45903	Syntaxin binding protein 1	-8.82	487
AB041616	Hypothetical protein MNCb-3350	-9.47	268
AB001737	Immunoglobulin kappa chain variable 28	-9.56	389
M75717	Serine protease inhibitor 1-5	-9.92	843
AF026216	Mitogen activated protein kinase kinase	-9.95	3198
AF047725	Cytochrome P450 2c38	-11.49	377
U81453	Myosin VIIa	-11.64	452
U80891	DNA segment KIST 4	-12.66	233
L10075	Immunoglobulin mu binding protein 2	-12.75	818
Z48781	Ephrin B1	-15.11	1897
AJ243572	Cyclic nucleotide gated channel beta 3	-16.09	444
AF073881	Mus musculus myotubularin homologous prot.	-16.12	489
AF132483	Cyclin-dependent kinase 6	-17.24	420
M32452	Carbonic anhydrase 1	-19.8	2070
M62541	Membrane-spanning 4-domains subfamily A	-21.74	643
X56842	Wingless-related MMTV integration site 3	-33.9	265
U38261	Superoxide dismutase 3 extracellular	-35.34	966

Table 3. Genes upregulated by D-hormone in whole colon tissue of IL-10 knockout mice. *The ratio is the average of the median intensities of red fluorescence over green fluorescence. Positive ratios represent the factor by which genes were increased by D-hormone treatment. All values are the means of 2 independent experiments.

GenBank Accession No.	Name	Ratio*	Combined Median Intensities
L31398	Dynamin 2	1.65	758
AB026432	Damage specific DNA binding protein 1	1.67	505
AF019661	Proteasome subunit, alpha type 5	1.67	1946
AF189817	Mus musculus evectin-2	1.67	4512
D29987	4-hydroxyphenylpyruvic acid dioxygenase	1.68	1446
AF109905	Chloride intracellular channel 1, clone MGC:6371	1.68	2809
NM_009304	Synaptogyrin 2	1.69	1199
M74149	Creatine kinase brain	1.69	3404
M25149	Transplantation antigen P91A	1.69	753
AF153449	RIKEN cDNA 1810009F08 gene	1.7	640
AF072370	Unc-51 like kinase 1	1.71	885
AF043285	Ribosomal protein S7	1.72	17448
Z31557	Chaperonin subunit 6a (zeta)	1.73	2699
U07159	Acetyl-Coenzyme A dehydrogenase	1.73	5404
X74856	Ribosomal protein L28	1.73	56327
J05277	Hexokinase 1	1.73	19786
AF10912	Efemp2	1.75	456
AF077002	Ywhah	1.76	514
M85078	Csf2ra	1.77	8942
U84903	Ribosomal protein L23-like	1.77	2786
D10715	Drg1	1.77	559
AF093064	Syntaxin 8	1.78	913
AF110520	RIKEN cDNA 2400007M02 gene	1.78	6224
D28117	Ppm1a	1.78	1242
Y10386	Serping1	1.78	4918
Y17159	Lymphocyte antigen 57	1.78	2812
X16834	Lectin galactose binding soluble 3	1.79	15847
AF119955	Programmed cell death 6 interacting protein	1.79	656
AF152838	Frap1	1.8	730
AF139179	P38ip-pending	1.82	801
X61434	Pkacb	1.82	960
AF132449	Smoothelin	1.82	1675
D31898	Ptprr	1.82	454
U96810	Suppressor of Ty 4 homolog 2	1.82	629
AF084548	Vasodilator-stimulated phosphoprotein	1.83	1715
X14194	Nidogen 1	1.83	707
U38981	RIKEN cDNA 0610009H04 gene	1.83	206
Y11682	Ribosomal protein mitochondrial S12	1.84	762
AF013490	Ptpn9	1.84	378
AF030559	Atp5b	1.84	3261
X73359	Amino-terminal enhancer of split	1.85	12513
L25885	Galgt1	1.85	1789
AB025405	Signal peptidase complex (18kD)	1.86	535
M29462	Malate dehydrogenase soluble	1.86	2017
D50464	Stromal cell derived factor receptor 2	1.87	530
AF062655	Ser/Arg-related nuclear matrix protein	1.88	563
U96116	Hadh2	1.88	1019
U37720	Cell division cycle 42 homolog	1.89	1752
L07577	Heat shock protein 25 kDa	1.89	1713
AB016044	Geranylgeranyl diphosphate synthase 1	1.9	210
AF089751	P2rx4	1.9	660
AF255774	Solute carrier family 4 member 2	1.9	563
AF038546	Cathepsin S	1.91	5124
AJ010045	Guanine nucleotide regulatory protein	1.92	2028
Y07693	Nuclear factor I/C	1.92	653
D87903	ADP-ribosylation factor 6	1.92	971
U58512	Rho-associated coiled-coil forming kinase 1	1.93	1025
U05809	Transketolase	1.93	2882
AF176910	Cullin 1	1.93	1164
AF033565	CDC-like kinase 3	1.93	699
AF071313	Cops3	1.95	1538
AJ242874	Troponin I skeletal slow 1	1.95	1994
AF030001	Tenascin X	1.96	239
U53514	Guanylate kinase 1	1.97	301
AF143374	Dermatopontin	1.97	317
AF181116	RIKEN cDNA 0610006G08 gene	1.99	708
U73820	UDP-N-acetyl-alpha-D-galactosamine:polyp.	2	334
D50367	Kinesin-associated protein 3	2.01	312
AF111172	Ceroid-lipofuscinosis neuronal 2	2.01	5045
V00829	Kallikrein 1	2.01	504
AF224724	Hepatocyte growth factor activator	2.02	834
AB024984	Actin related protein 2/3 complex subunit	2.02	2723
U35142	Retinoblastoma binding protein 7	2.02	538
U34883	3'-phosphoadenosine 5'-phosphosulfate s.	2.03	981
NM_016973	Sialytransferase 7	2.03	1262
X74438	Protein tyrosine phosphatase receptor	2.03	301
AF149291	Transgelin 2	2.04	2371
AF019662	Proteasome (prosome macropain) subunit a	2.04	1843
AF078840	5'(3')-deoxyribonucleotidase	2.05	482
AF263365	RAB3D member RAS oncogene family	2.05	2805
Y12577	ADP-ribosylation-like 4	2.06	1823
D78188	Granule cell differentiation protein	2.06	772
AF153827	N-sulfoglucosamine sulfohydrolase	2.07	1607
L28177	Growth arrest and DNA-damage-inducible 4	2.07	1726
AF033017	Potassium channel subfamily K member 1	2.08	3802
AB020202	Adenylate kinase 2	2.08	1012
X62940	Transforming growth factor beta 1 induc.	2.09	520
X78874	Chloride channel 3	2.09	427
D88769	Latexin	2.09	562
X15963	Cytochrome c oxidase subunit Va	2.1	1266
NM_010885	NADH dehydrogenase (ubiquinone) 1 alpha	2.1	3418
NM_010310	Guanine nucleotide binding protein alpha	2.1	3787

D29016	Farnesyl diphosphate farnesyl transferase	2.11	1050
Z31555	Chaperonin subunit 5 (epsilon)	2.12	643
AF129888	Suppressor of initiator codon mutations	2.12	459
AB025099	Kruppel-like factor 5	2.13	3033
M84145	Fumarylacetoacetate hydrolase	2.14	754
U10406	Capping protein beta 1	2.15	4343
AF018952	Aquaporin 8	2.15	1340
M93422	Adenylate cyclase 6	2.17	629
M63961	Guanylate nucleotide binding protein 1	2.17	360
Z54179	Gene trap locus 3	2.18	295
NM_011185	Proteasome (prosome macropain) subunit b	2.18	1443
M32010	H2-K region expressed gene 4	2.19	2738
AF015790	Phospholipid scramblase 2	2.19	4015
U62295	Cytochrome P450 2j6	2.2	1352
L32973	Thymidylate kinase family, LPS-inducible	2.21	363
U37438	Crp-ductin	2.23	1392
AJ243964	Dickkopf homolog 3	2.23	478
U04710	Insulin-like growth factor 2 receptor	2.24	983
D31969	Vitamin D receptor	2.24	584
U59283	ATP synthase H+ transporting mitochon.	2.24	21637
X60671	Villin 2	2.25	509
X80899	Silica-induced gene 81	2.25	1195
AF119675	RAB25 member RAS oncogene family	2.25	5345
AJ002730	Ubiquitously transcribed tetratricopeptide	2.27	1064
NM_009750	Brain expressed X-linked 3	2.28	1396
U29402	Ribosomal protein large P1	2.29	50772
NM_011831	Insulin-like 5	2.31	3918
X97755	Phenylalkylamine Ca2+ antagonist	2.31	2162
Z31553	Chaperonin subunit 2 (beta)	2.32	759
U97170	Protein kinase inhibitor gamma	2.33	410
AF133093	RIKEN cDNA 2310039H09 gene	2.37	430
M18186	Heat shock protein 84 kDa 1	2.38	3020
AF076192	Protein phosphatase 2a catalytic subunit	2.38	3337
AB031386	RIKEN cDNA 1810009M01 gene	2.38	2513
AF134858	Espin	2.39	486
U30840	Voltage-dependent anion channel 1	2.4	432
AF151637	Postsynaptic protein Cript	2.41	1345
U73445	Dihydrolipoamide dehydrogenase	2.41	1157
AF096285	Serine/threonine kinase receptor associa	2.42	963
AF064748	Plasma membrane associated protein S3-12	2.43	392
AB041557	Similar to RAP1 protein	2.44	22958
D13759	Mitogen activated protein kinase kinase	2.45	954
NM_011875	Proteasome (prosome macropain) 26S	2.47	1024
Y12229	Utrophin	2.47	541
AF144101	Succinate-CoA ligase GDP-forming alpha	2.48	2778
U77083	Alanyl (membrane) aminopeptidase	2.48	352
AF240469	Nicastrin	2.5	616
L21671	Epidermal growth factor receptor pathway	2.5	2377
AF240630	IQ motif containing GTPase activating pr.	2.5	5744
U31966	Carbonyl reductase 1	2.5	1081
U16740	Capping protein alpha 1	2.5	554
M93310	Metallothionein 3	2.51	591
X60961	Cadherin 1	2.53	7810
AF217484	Interferon-stimulated protein (20 kDa)	2.54	1431
AB032825	Transcription elongation factor A (SII)	2.55	1000
U40575	Single-minded 1	2.58	16734
U35312	Nuclear receptor co-repressor 1	2.6	733
U36588	Transgelin	2.6	62175
M25365	H1 histone family member 2	2.6	1858
AF249870	P53 apoptosis effector related to Pmp22	2.6	741
D89572	Syndecan 4	2.62	2654
X61432	Calmodulin	2.62	8271
Y07708	NADH dehydrogenase (ubiquinone) 1 alpha	2.62	3845
U78085	Ribosomal protein S5	2.62	15811
AF090686	Transcobalamin 2	2.64	481
AF116268	Guanine nucleotide binding protein alpha	2.65	6012
AF047600	SMC-like 1	2.65	567
NM_010751	Max dimerization protein	2.67	542
AC002397	Dentatorubral pallidoluysian atrophy	2.67	300
AF009513	Plasma glutamate carboxypeptidase	2.67	271
L02918	Procollagen type V alpha 2	2.69	626
AB022100	Cadherin 13	2.69	223
AF234625	Pre-B-cell colony-enhancing factor	2.72	417
U30839	Voltage-dependent anion channel 3	2.73	7509
AF156958	NTF2-related export protein 1	2.73	300
D78647	Tyrosine 3-monooxygenase	2.73	1701
U15571	Amyloid beta (A4) precursor-like protein	2.74	1107
U13393	Proteasome (prosome macropain) subunit b	2.75	478
AJ400878	Predicted gene ICRFP703B1614Q5.6	2.76	597
L01062	ATP synthase H+ transporting mitochon.	2.77	712
X73959	Tenascin X	2.78	450
NM_009897	Creatine kinase mitochondrial 1	2.78	1948
AF004591	ATX1 (antioxidant protein 1) homolog 1	2.79	4422
AF030343	Enoyl coenzyme A hydratase 1 peroxisomal	2.8	1408
M64298	ATPase H+ transporting lysosomal	2.81	1370
M22432	Eukaryotic translation elongation factor	2.81	15080
AF129086	STIP1 homology and U-Box containing prot.	2.82	592
X95403	RAB2 member RAS oncogene family	2.85	3083
X52940	Cytochrome c oxidase subunit VIIc	2.86	16378
D00926	Transcription elongation factor A (SII)	2.86	651
X59990	Catenin alpha 1	2.86	1301
AF035527	Ets homologous factor	2.87	526
Y11929	Coxsackievirus and adenovirus receptor	2.9	3968
AF098508	Dynactin 3	2.9	744

AB011473	Prefoldin 5	2.92	2386
AB030192	Atp5j2	2.93	21114
M91458	Sterol carrier protein 2	2.94	300
U43512	Dystroglycan 1	2.94	1762
L01640	Cyclin-dependent kinase 4	2.94	468
AF174535	Sulfide quinone reductase-like	2.95	427
AB010828	Craniofacial development protein 1	2.96	1269
AF031128	Peroxisomal membrane protein 3 35 kDa	2.96	311
Y14296	Kruppel-like factor 9	2.97	525
AJ249987	Taf2h	2.99	1736
J04953	Gelsolin	2.99	1277
AB030185	Edf1	3.01	1746
AF087695	Vertebrate homolog of C. elegans Lin-7	3.02	447
X03672	Melanoma X-actin	3.04	37296
M26689	Actin gamma 2 smooth muscle enteric	3.11	4345
AF236069	Ribosomal protein L29	3.12	1527
L49022	Calponin 1	3.18	6458
NM_009900	Chloride channel 2	3.2	739
L40632	Ankyrin 3 epithelial	3.21	1511
X64837	Ornithine aminotransferase	3.22	604
U37091	Carbonic anhydrase 4	3.24	1206
Y16256	Basigin	3.27	4600
U48363	Nascent polypeptide-associated complex a	3.28	869
AB031550	Phosphatidylcholine transfer protein	3.3	2782
AF038632	Mpv17 transgene kidney disease mutant	3.32	15700
AF006482	Entpd5	3.33	673
AF053367	PDZ and LIM domain 1	3.37	332
Z36270	TGFB inducible early growth response	3.39	434
M64403	Cyclin D1	3.41	365
D86609	RNA polymerase 1-3 (16 kDa subunit)	3.48	1424
AF004934	Serine/threonine kinase 25	3.48	2294
X15962	Ribosomal protein S12	3.49	12269
X13297	Actin alpha 2	3.49	18971
X66449	Calcium binding protein A6 (calcyclin)	3.52	68381
NM_011862	Protein kinase C and casein kinase	3.53	382
X61431	Diazepam binding inhibitor	3.53	585
M29464	Platelet derived growth factor alpha	3.53	2216
Y11505	Serine protease inhibitor Kazal type 4	3.58	3437
AF158022	Ribosomal protein L23	3.6	46177
M11686	Keratin complex 1 acidic gene 18	3.62	1262
L28116	Peroxisome proliferator activator receptor	3.66	1876
AF260271	Ribosomal protein L9	3.69	1305
U60001	Histidine triad nucleotide-binding protein	3.79	7562
M76763	Ribosomal protein S18	3.89	28957
D10464	RIKEN cDNA 0610007D04 gene	3.9	12243
AF093853	Peroxiredoxin 5 related sequence 3	3.92	8254
U93863	Ribosomal protein L21	3.94	3665

D29639	Hydroxylacyl-Coenzyme A dehydrogenase	3.94	4063
AF133093	Isocitrate dehydrogenase 3 (NAD+) gamma	3.96	623
L06047	Glutathione S-transferase alpha 4	4.04	868
AF029844	Eukaryotic translation elongation factor	4.08	8512
U65636	Proteasome (prosome macropain) subunit b	4.09	1701
AB031292	Proteolipid protein 2	4.15	1416
X66532	Lectin galactose binding soluble 1	4.18	3244
M62952	Ribosomal protein L19	4.18	6797
AF159368	Programmed cell death 10	4.28	3207
M62867	Y box protein 1	4.37	9757
AF117109	Kruppel-like factor 4 (gut)	4.42	1693
D90225	Pleiotrophin	4.44	1292
AF058956	Succinate-Coenzyme A ligase GDP-forming	4.47	617
NM_011607	Tenascin C	4.48	588
AF020185	Dynein cytoplasmic light chain 1	4.48	3181
X99921	S100 calcium-binding protein A13	4.48	1340
AF186115	Transmembrane protein 4	4.54	1119
Z47088	Transcription elongation factor B (SIII)	4.58	972
AF020039	Isocitrate dehydrogenase 1 (NADP+)	4.63	1509
AF033566	CDC like kinase 4	4.64	965
L04280	Ribosomal protein L12	4.65	18506
X55316	Nuclear transcription factor-Y beta	4.67	656
AB027237	Aldo-keto reductase family 1 member C12	4.69	702
M99054	Acid phosphatase 5 tartrate resistant	4.7	687
NM_007694	Chromogranin B	4.85	479
NM_010887	Ndufs4	4.86	1872
AF068921	Suppressor of clear C. elegans homolog	4.99	1232
X04724	Insulin II	5.26	1611
AF263743	Erbb2 interacting protein	5.32	2424
X87685	Sterol carrier protein 2 pseudogene 2	5.46	2359
Z46845	Glucagon	5.52	1273
M32240	Peripheral myelin protein 22 kDa	5.62	1312
U49112	Programmed cell death 6	5.65	977
M64278	Chromogranin A	5.68	1476
AB004789	Dolichol-phosphate mannosyltransferase 1	5.79	806
L08115	CD9 antigen	5.82	769
Y08702	Neuronal protein 15.6	5.83	573
L22550	Desmin	6.06	939
AF085809	Synapsin I	6.15	9714
AF216207	Ribosomal protein S19	6.24	5408
AB017156	Chloride channel calcium activated 3	6.33	3676
M13019	Thymidylate synthase	6.37	601
M11130	Serum amyloid A 2	6.44	30843
AF047727	Cytochrome P450 2c40	6.61	1107
X16319	Signal recognition particle 54 kDa	6.71	867
U67771	Ribosomal protein L8	6.72	3983
Y13071	26S proteasome-associated pad1 homolog	7.01	517

M83749	Cyclin D2	7.33	709
M27347	RIKEN cDNA 1810009A17 gene	9.52	3985
AF119390	Sialyltransferase 10 (alpha-23-sialyltra	9.56	775
U57051	Homeo box B13	10.05	1127
AF044262	Anterior gradient 2	11.45	3645
X53929	Decorin	11.59	4144
D85391	Carboxypeptidase D	12.15	436
U50413	Phosphatidylinositol 3-kinase (p85 alpha)	13.11	560
X04574	Trypsin 2	13.75	355
AF076532	Kcne3	13.78	490
AB029487	Sulfotransferase family 1A, member 1	21.05	2460
X04573	Elastase 2	26.6	863
AF051102	Gamma-glutamyl hydrolase	48.81	476

Table 4. D-hormone targets 3 TNF-α related genes in the colon of mice with experimental IBD.

Gene	Experiment 1		Experiment 2	
	Intensity*	Ratio**	Intensity	Ratio
TNF-α	414	–2.1	309	–2.7
LPS-induced TNF-α factor#	4267	–1.7	4516	–1.9
TNF receptor	3494	–1.7	163	–3.1
VDR	745	2.6	422	1.9
Calmodulin	4663	1.7	11878	3.6
Calcium Binding Protein A6	97601	2.3	39160	4.7

* Combined median red and green intensities.
** The ratio is either the ratio of green fluorescence over red fluorescence (positive values) or the inverse (negative values). Positive ratios represent genes that are activated in the presence of D-hormone and negative ratios represent genes that are repressed in the presence of D-hormone.
# LPS-induced TNF-α factor was reanalyzed using quantitative real-time PCR.The expression of this gene was 4 to 461 times lower in colons of D-hormone treated IL-10 KO mice (n=4) compared to the D–control (n=4) colons. The microarray underestimated the efficacy of D-hormone to inhibit LPS-induced TNF-α.

either not treated or treated with the immunosuppressive drug cyclosporin A. The mice treated with cyclosporin A showed reduced survival following *C. albicans* and H. simplex infections[15]. Conversely, the D-hormone treated mice were not different from the untreated controls in their ability to survive either the *C. albicans* or the H. simplex infections[15]. D-hormone did not alter the ability of the host to mount an immune response to either *C. albicans* or H. simplex.

Asthma is a disease that is driven by Th2 cells responding to environmental antigens. Based on the ability of D-hormone to upregulate the Th2 cell response, we hypothesized that D-hormone might exacerbate experimental asthma. Two strains of mice were treated with D-hormone and then induced to develop experimental asthma. There was no effect of D-hormone on the inflammation and epithelial hyperplasia in the lungs of mice with asthma. Interestingly, VDR KO mice were also induced to develop asthma; however, asthma failed to develop in the lungs of these mice. The absence of inflammation in the lungs of VDR KO mice induced to develop experimental asthma suggests an important role for vitamin D signaling in the development of inflammation in the lungs. The D-hormone, however, had no effect on the severity of experimental asthma in mice. Together these data suggest that the D-hormone is a selective regulator of the immune system.

CONCLUSIONS

The *in vivo* effect of vitamin D status on immune function depends on the nature of the immune challenge. The most dramatic effects of D-hormone on the immune system seem to be in the control of Th1-driven autoimmunity. D-hormone had no effect on the ability of the host to fight infections with *C. albicans* and H. simplex. In addition, Th2-driven asthma was not affected by D-hor-

mone treatment. The vitamin D or VDR-deficient host has elevated Th1 cell responses and diminished Th2 associated responses. In the absence of the VDR, Th1-driven IBD is more severe and Th2-driven asthma does not develop. The evidence suggests a model where the effectiveness of D-hormone treatment of autoimmune diseases comes as a result of the inhibition of the development and function of Th1 cells and the induction of other CD4+ T cells including Th2 cells. The mechanisms underlying the paradoxical effects of D-hormone on autoimmune diseases and lack of effect on experimental asthma and infectious host resistance are still not known.

Glucocorticoids are broadly immunosuppressive drugs commonly used to treat a variety of diseases including autoimmune diseases. Autoimmune patients are at an elevated risk of developing osteoporosis as a result of the increased inflammation and glucocorticoid use. Studies have shown that D-hormone can increase bone mineral density and improve other bone markers in patients with IBD and MS. Clearly, there are direct effects of the D-hormone on bone health. It is also possible that the D-hormone mediates a reduction in inflammation that indirectly inhibits bone disease by halting further bone destruction. Little is known about the effect of vitamin D supplementation or D-hormone treatment on the severity of human autoimmune diseases. However, the potential benefits of D-hormone treatment for patients with autoimmune diseases include a reduction in glucocorticoid use, a reduction in the symptoms of their disease, and increased bone mineral density.

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