review

Gene expression regulation by retinoic acid

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Abstract **Over the last quarter century, more than 532 genes have been put forward as regulatory targets of retinoic acid. In some cases this control is direct, driven by a liganded heterodimer of retinoid receptors bound to a DNA response element; in others, it is indirect, reflecting the actions of intermediate transcription factors, non-classical associations of receptors with other proteins, or even more distant mechanisms. Given the broad range of scientific questions continually under investigation, researchers do not always have occasion to classify target genes along these lines. However, our understanding of the genetic role of retinoids will be enhanced if such a distinction can be made for each regulated gene. We have therefore evaluated published data from 1,191 papers covering 532 genes and have classified these genes into four categories according to the degree to which an hypothesis of direct versus indirect control is supported overall. We found 27 genes that are unquestionably direct targets of the classical pathway in permissive cellular contexts (Category 3 genes), plus 105 genes that appear to be candidates, pending the results of specific additional experiments (Category 2). Data on another 267 targets are not evocative of direct or indirect regulation either way, although control by retinoic acid through some mechanism is clear (Category 1). Most of the remaining 133 targets seem to be regulated indirectly, usually through a transcriptional intermediary, in the contexts studied so far (Category 0).** —Balmer, J. E., and R. Blomhoff. **Gene expression regulation by retinoic acid. *J. Lipid Res.* 2002.** 43: **1773–1808.**

Supplementary key words gene regulation • transcription • retinoic acid receptors • tretinoin • RAR • RXR

Background

Beginning in at least the late 1960s, there was tremendous interest in whether the differentiating and tumor suppressing activities of retinoids reflected a genetic mechanism, on analogy to the steroid hormones, or an epigenetic one. It had been known for some time that retinoids could influence mRNA levels in certain cells, but also that they could increase activity on membrane-bound ribosomes. Any number of different mechanisms were possible, and quite a few were proposed. In a particularly prescient statement of 1976, Sani and Hill (1) wrote, "The action of retinoic acid in reversing preneoplastic and neoplastic lesions may be due to a hormone-like effect involving induction and/or suppression of gene activity." However, no conclusive experimental evidence had yet been adduced. As far as we know, it was Blalock and Gifford (2) who first provided such evidence when they showed, in 1977, that interferon synthesis can be suppressed at a transcriptional level by a protein induced by all-*trans* retinoic acid (RA). To make their case they used transcription blockers, protein synthesis inhibitors, and a kinetic argument.

It is now known that RA can influence gene expression and protein production in many ways, but in terms of molecular mechanisms, a single, predominant, classical pathway has emerged: all-*trans* retinoic acid plus a dimer composed of a retinoic acid receptor and a retinoid X receptor (an RAR.RXR dimer) and a more or less regular DNA response element. In this paper, genes that respond through this pathway are called "direct" targets of the classical RA pathway; those that respond to RA through other molecular mechanisms, but do respond, are called "indirect" targets. Since Blalock and Gifford's paper nearly a quarter century ago, more than 532 genes have been put forward as regulatory targets of RA; and while the distinction between direct and indirect regulation is now well entrenched, it is not necessarily germane to every study. Nevertheless, a great deal of suggestive data has been generated and it can be used to construct a tentative classification of RA's targets along these lines.

Constructing a classification table

There is a simple but powerful motivation for constructing such a classification: progress in understanding RA's role at a genomic or proteomic level will require determining which regulatory events are handled through which cellular circuits. This paper is an attempt to begin that process in a systematic way. In what follows, we have evaluated the experimental evidence presented in more than 1,191 published articles and have prepared a preliminary categorization of RA's targets according to the de-

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gree to which *current* research supports an hypothesis of direct versus indirect control. More specifically, we have constructed a table (see Gene Table at the end of this article) that briefly summarizes the experimental evidence available for each target gene and "rates" the degree to which the combined evidence supports or opposes the notion of direct regulation in at least one cellular context. Where the evidence is very strong, constituting proof or something close to it, we call the gene a Category 3 gene. Where the combined evidence suggests or demonstrates indirect regulation (in the contexts studied, and no other investigations show or suggest direct regulation elsewhere), we have called the gene a Category 0 gene. Categories 1 and 2 are positioned between these two, with the evidence for direct regulation somewhat stronger for Category 2 genes. All four categories are more rigorously characterized below.

It should be stressed that the numeric designations used for the categories are nothing more than tags. With a very few exceptions (which always clearly marked), the Category 0 genes are regulatory targets of RA every bit as much as Category 3 genes. They are simply regulated in different ways. Category 1 and Category 2 genes are also targets, although current research does not allow us to conclude quite so much about the mechanisms employed in these cases. Emphatically, the classification does not mean to impugn the work reported in the any of papers considered. The distinction between direct and indirect regulation is not necessarily relevant to many valid research goals, and a great deal of valuable work has been done in clinical, developmental, and basic science without addressing these questions even obliquely.

Of necessity, the Gene Table is long and complex. However, the genome projects, various proteomic studies, and the preliminary gene ontologies produced over the last few years have made it clear that work on some very interesting biological questions will require dealing with vast amounts of data. Gene expression regulation by RA encompasses a number of such questions and a compilation like the Gene Table would seem to be an economical way to approach some of them.

The classical RA pathway

Four basic concepts are central to any description of the classical RA pathway: ligand involvement, receptor dimerization, DNA binding, and the resulting transcriptional modulation of the gene (occasionally, one of the genes) whose regulatory element has been bound. It sometimes happens that the gene under investigation is *not* the gene whose regulatory unit has been bound, but that RA has regulated an intermediary which in turn regulates the gene of interest. In these cases, the intermediary factor (usually another transcription factor) may be a direct target, while the gene under study is an indirect target. Other types of indirect regulation include RA's ability to influence mRNA stability, to activate nuclear receptor dimers other than an RAR.RXR, and so forth.

It might seem arbitrary, uninformative, or unnecessarily stringent to restrict "direct" regulation to the classical RA pathway and to consign all other regulatory modalities to the catch-all category, "indirect" regulation. However, each alternative regulatory pathway represents a distinct type of genetic event. Perhaps each deserves its own Gene Table. We chose the classical RA pathway as a branch point in the present work, *i*) because of its preeminent historical position, *ii*) because the distinction between direct and indirect regulation through this pathway is well established and frequently studied, and *iii*) because many suggestive and highly relevant studies are available, even though questions of molecular mechanism are not necessarily raised in them.

The Gene Table is intended to cover every gene now known to be regulated by retinoic acid. The last attempt at delineating a complete set of such genes was published by Chytil and Raiz-ul-Haq in 1990 (3). They listed more than 125 proteins that we now take to be monogenic, plus a number of other proteins of less clear provenance. Gudas et al. took a slightly different starting point 4 years later, and wrote detailed descriptions of most RA targets known at the time. They categorized them primarily along functional or homology lines (4).

Literature reviews

Retinoid science is an immense field. Two recent reviews, both of which are comprehensive within their scopes but neither of which attempts a complete list of RA-regulated genes, are by Nagpal and Chandraratna (5) and a cross-lab group led by De Luca (6). Two more specialized reviews, on receptor-specific ligands (7) and on discoveries made through receptor knockouts (8), expand on topics that turn up frequently in the Gene Table, but are treated only generically. Beyond these, virtually every area of regulatory, clinical, and developmental application has its own reviews. To mention just a few, see (9) for retinoid metabolism, (10) for retinoids and cancer, (11) or (12) for two topics in developmental work, and (13) for dermatological issues. An updated collection of methods papers has recently been published. It contains valuable information on traditional as well as innovative experimental techniques involving the retinoids, their receptors, and associated molecules. See (14) and the papers following it. A detailed characterization of what is currently known about the molecular and even atomic mechanisms that permit direct RA-activated transcriptional regulation is presented in (15). Although these events are beyond the scope of the present paper, they underpin many of the routes of gene regulation covered here.

The retinoid receptors are members of a much larger group of transcription factors, the so-called nuclear receptors. An encyclopedic overview of this large and important class of proteins is Gronemeyer and Laudet's 1995 monograph (16). It remains invaluable even though its publication preceded some of the more recent work on co-regulators, intermediary factors, and the chromatin connection. For an update in those areas, see Rosenfeld and Glass (17). Chawla et al. (18) recently reviewed the connection between the nuclear receptors and lipid physiology, and both RARs and RXRs play roles in this. Finally, two collec-

tions of particularly noteworthy reviews appeared in the mid-1990s: one covering various aspects of the nuclear receptors and the other, various aspects of the retinoids. See (19) and (20), respectively, and the articles that accompany them.

METHODS

Selecting genes for inclusion in this analysis

The Gene Table does not cover every gene ever investigated in conjunction with retinoic acid, although we hope it includes every known target. Because RA has the power to initiate fundamental phenotypic changes in many cells, it is sometimes used only as an agent to set up an experiment: differentiated versus non-differentiated cells, for example. Genes investigated only in such settings were excluded. Overall, our basic filter for including or excluding genes was whether or not an explicit claim of regulation by retinoic acid had been advanced. We did not require that the regulation be attributed to the classical RA pathway. In some cases, direct regulation was investigated or implied; in others it was indirect regulation; and in some, the mode of regulation was not addressed, either explicitly or implicitly.

Although we made every effort to identify and follow up on "novel" genes identified in differential display-type experiments, we have not included any genes so totally uncharacterized that they have not yet even been named. See (21) for some examples. Nor have we included fragments so far identified only as ESTs. See (22) and (23) for examples of these.

An analysis of this sort would ideally be limited to work done in "normal" cells or individuals; the activities of RA and its receptors in aberrant cell types would then be handled separately as exceptions. We have tried to do this up to a point. Work on cells that have suffered catastrophic DNA events that are likely to have affected RA's activity, certain viral integrations, extraordinary recombinations, engineering experiments, and the like, have been excluded except to make occasional special points. In particular, work on acute promyelocytic leukemia (APL) cells, which generally express oncogenic RARα fusions, have been largely excluded on this ground. Nevertheless, a great deal of research has been done on RA's activities in APL cells and we refer the reader to (24) for a review. Of course, many common cell lines contain genomic anomalies that are *not* likely to have affected RA's activity overall: HepG2 and Caco-2 lines, for example. For the purposes of this work, such cell lines are considered normal.

As a rule, we did not consider experiments in which RA was used in conjunction with another treatment, although we tried to take note of any controls using RA alone. The exception to this is where some form of external "activation" seems to be required for *any* expression of the target gene, for example, the interleukins. It should be stressed that by excluding combo-treatments we automatically ruled out many studies using RA plus cAMP (or RA plus cAMP and theophylline) rather than RA alone. We did, however, consider these experiments if they confirmed points suggested elsewhere by RA alone. This is an admitted limitation of the present work, but the complexity of regulatory interactions in these cases is still overwhelming.

Constructing a database of papers and genes

Using various free text and MeSH (Medical Subject Headings) strategies at the United States National Library of Medicine's PubMed gateway, we created a database of more than 4,000 papers relevant to the regulation of gene expression by retinoic acid. We identified the gene or genes considered in each paper, and, based on abstracts, selected what appeared to be the most relevant studies for each gene. Using this set of abstracts and the associated MEDLINE coding, we determined which species had been investigated, located the gene's official name at LocusLink (25), and performed supplementary searches based on official nomenclature, curated aliases, and any novel names or aliases applied to orthologs. This process was iterated as necessary, and eventually led to a list of relevant papers for each gene. These entries were then re-evaluated at the abstract level and the most promising papers (for our purposes) were gathered and consulted for data, discussions, and further citations. New candidate genes went through the same process as they turned up. By the end of the project, nearly 8,000 papers (not including reviews) had been considered to one degree or another.

For each gene, we then studied the scientific evidence presented in the selected papers and evaluated the degree to which a direct regulatory pathway had been demonstrated, suggested, or brought into question. This information was distilled into several short standardized phrases and incorporated into the Gene Table, along with species information, any alternative names and symbols used in the selected studies, and references to the most essential papers.

Concordance of working and official gene names

Most genes have several names. By "official nomenclature" we mean names and symbols approved by (or pending before) the Human Genome Organization Nomenclature Committee, the Mouse Genome Informatics Nomenclature Committee, the International Rat Genetic Nomenclature Committee, or the Zebrafish Nomenclature Committee. We have followed official nomenclature whenever possible. This can be confusing when the official name of a gene is either uninformative, uncommon, or simply designed for a purpose that is not one's own. For example, most readers probably would not recognize *Nr2f1* as the name of the gene that encodes COUP-1. However, while understandable from a historical perspective, the proliferation of trivial names (for both genes and proteins) has been scientifically unhelpful and using official names solves the problem. The lists of alternatives and aliases kept by the nomenclature committees and at LocusLink should quickly resolve any questions.

It is not always easy to determine which gene has been studied in a given paper, or which papers deal with the same gene; and this is not limited to older papers. It can be particularly problematic when several species, or several apparently unrelated scientific questions, have been studied in different papers. In a number of cases, we had to align published primer sequences with groups of homologs, follow LinkOuts to cited sequences at the National Center for Biotechnology Information's Entrez system, or even BLAST nucleotides strings taken from journal figures.

As a rule, the Gene Table uses the gene symbol from the species discussed in the earliest paper cited; when no approved, pending, or interim name was available for the gene in that species, we generally chose the mouse version. The nomenclature committees try to keep symbols and leading phrases invariant over vertebrate species (except for orthographic differences) so this is little more than a matter of choice. In order to save space, only symbols, not full names, are used in the first column of the table.

Trivial names from cited papers

The second column of the Gene Table, "Name in refs," lists only the gene or protein designations used in the papers cited. It does not include other aliases, no matter how common they may be in the literature. **Table 1** provides a concordance between these working names (or abbreviations) and the symbols used in

TABLE 1. Concordance of trivial names and symbols

Common Name	Gene Table
14.5-D lectin	Lgals1
25-hydroxyvitamin D3-24-hydroxylase	CYP24
34 kDa lectin	Lgals3
92 kDa gelatinase	MMP9
A4	Clta
ACS	FACL2
Activin A	INHBA
Acyl-coA synthase	FACL2
ADD1	Srebf1
ADH3	ADH1C
Aggrecanase	ADAMTS4
α 1-microglobulin	Ambp
α-SM	Acta2
Aminopeptidase-B	RNPEP
AML2	RUNX3
ANF	Nppa
ANP	Nppa
Antithrombin III	SERPINC1
AP-2	TFAP2A
AP-2.2	Tcfap2c
Ap-B	RNPEP
Apolipoprotein(a)	LPA
ARP-1	Nr2f2
Arrestin	SAG
ATX	ENPP2
β 1-AR	Adrb1
β-amyloid precursor protein	App
Bone sialoprotein (BSP)	IBSP
Bone sialoprotein I	Spp1
Brn-3.2	Pou4f2
c-abl	Abl1
Calcineurin A	PPP3CA
Calcineurin B	PPP3CB
CBFA3	RUNX3
CD10	MME
CD11a	ITGAL
CD11b	ITGAM
CD15	Fut4
CD157	BST1
CD18	ITGB2
CD23	FCER2
CD31	PECAM1
CD43	SPN
CD50	ICAM3
CD51	Itgav
CD71	TFRC
CD82	KAI1
CD95	PTPN13
CD95	TNFRSF6
CD95 ligand	Tnfsf6
c-fms	CSF1R
Cg B	Chgb
CGRP	Cal1
Cholesterol sulfotransferase	SULT2B1
CIP1	Cdkn1a
CL-20	EMP1
clusterin	Trpm2
c-myb	MYB
c-myc	MYC
Collagenase	MMP1
Connexin31	Gjb3
Connexin43	Gja1
Contact	Gdf5
Cornifin	SPRR1B
COUP-TF II	Nr2f2
COUP-TF1	Nr2f1
COX-1	Ptgs1
COX-2	PTGS2
CRBPI	Rbp1
CRBPII	Rbp2
CT	Cal1
Cu/Zn superoxide dismutase	Sod1
Cx43	Gja1
Cyclin D3	CCND3
Cyclin E	Ccne1
Cyclooxygenase-1	Ptgs1
D3	Dio3
D9	Stra13
DEAD box protein	DDX1
DEAD box protein p72	DDX17
D-III	Dio3
Dopamine D2 receptor	Drd2
DOR	OPRD1
Drg1	NDRG1
Dystroglycan α, β	DAG1
E3	Laptm5
EAT	MCL1
E-cadherin	CDH1
E-MAP-115	Mtap7
EndoA	KRT8
EndoB	KRT18
Endolyn	Cd164
eNOS	NOS3
Epithelin	Grn
ERA-1	Hoxa1
Erk2	Mapk1
ET-1	EDN1
F1	Ngp
F3	Cntn1
FAK	PTK2
Fas	TNFRSF6
FasL	Tnfsf6
FATP	SLC27A1
FBPase isozyme	Fbp2
FGF-BP	HBP17
Focal adhesian kinase	PTK2
Fra-1	Fosl1
Fru-1, 6-P2ase	Fbp1
Galectin-7	LGALS7
GCNF	Nr6a1
Gelatinase A	MMP2
Gene 33	MIG-6
GLUT 2	Slc2a2
GLUT 3	Slc2a3
gp91-phox	CYBB
gp96	TRA1
GR	NR3C1
GST 5.7	Gsta4
H218	Gpcr13
HAKR e	AKR1C3
HB-EGF	DTR
HER4	ERBB4
HERG	KCNH2
HGFL	MST1
HIOMT	ASMT
hlx-1	dbx1a
HNF-1 α	Tcf1
HNF-1 β	Tcf2
HNF-3 β	Foxa2
HNF-3 α	Foxa1
Hox-1.6	Hoxa1
HOX3D	HOXC5
Hox-2.b	Hoxb4
Hox-4.2	Hoxd4
hRDH-TBE	RDHL
HSP86	Hsp86-1
HSP90	Hsp86-1
HSPCA	Hsp86-1
HSPG	SDC2
Htf9-a/RanBP1	Ranbp1
IAP	ALPI
ICE	CASP1

continued

TABLE 1—*Continued*

Common Name	Gene Table
Ikaros	Znfn1a1
IL-1b stimulating gene	BIRC3
Importin α	Kpna2
INK4B	CDKN2B
iNOS	Nos2
J6 serpin	Serpinh1
K2e	KRT2A
K6	KRT6A
k-casein	Csnk
K-FGF	FGF4
KOR	Oprk1
Krox-24	Egr1
L-14	Lgals1
L-34	Lgals3
Lamins A/C	Lmna
Lefty	Ebaf
Lewis x	Fut4
LFA-3	CD58
Liver/bone/kidney AP	Akp2
l-myc	MYCL1
LNGFR	Ngfr
LOX-1	Olr1
LPL	Lpl
l-selectin	SELL
MAC-1	ITGAM
Major histocompatibility class I (H2K, -D, -L, -Q, etc.)	H2
MASH1	Ascl1
Mash-2	Ascl2
MCAD	ACADM
MCP-1	SCYA2
M-CSF	CSF1
mda-6	Cdkn1a
MDR1	ABCB1
mdr3	ABCB1
Meis2	Mrg1
MK	Mdk
MLN/CAB1	MLN64
MnSOD	SOD2
MOR	OPRM1
Mox1	Meox1
mph1	Edr1
mrp2	ABCC2
MRP-8	S100A8
Msx-1	Msx2
mWnt-8	Wnt8d
MZF-1	ZNF42
Na, K-ATPase	Atp1a3
$Na^+/H+$ antiporter	SLC9A1
N-cadherin	CDH2
Ndr1	NDRG1
NEP	MME
NGFI-B	NR4A1
NHE-2	Slc9a2
NIS	SLC5A5
NKX3.2	Bapx1
nm23-H1	NME1
NMDAR1	GRIN1
NN8-4AG	Rrg1
nNOS	NOS1
NOR-1	NR4A3
NSP-A	RTN1
NSP-C	RTN3
ntcp	SLC10A1
Nur77	NR4A1
Nurr1	NR4A2
ob	Lep
Oct3	Pou5f1
Oct3/4	Pou5f1
OP	Spp1
Osteocalcin	BGLAP
Osteonectin	Sparc

continued

TABLE 1—*Continued*

Common Name	Gene Table
Osteopontin	Spp1
OT	OXT
p15	CDKN2B
p190 GAP-associated protein	Arhgap5
p21	Cdkn1a
p34(CDC2)	CDC2
P450RAI	Cyp26
p47-phox	NCF1
p53	Trp53
p67-phox	NCF2
p68 kinase	PRKR
p75NTR	Ngfr
PACAP	ADCYAP1
PACAP1 (Type I) receptor	ADCYAP1R1
PACAP2 (Type II) receptor	VIPR1
PAFR	PTAFR
PAI-1	SERPINE1
PAI-2	SERPINB2
P-cadherin	CDH3
PCD5	Pcp2
PCDHX	PCDH11
PCDHY	PCDH22
PEPCK	Pck1
PGHS1	Ptgs1
PGHS2	PTGS2
pgp1	ABCB1
PK	Pk3
PKC	Pkca
PKC β 1	PRKCB1
Placental lactogen	CSH1
Plasminogen activator inhibitor 1	SERPINE1
Plasminogen activator inhibitor 2	SERPINB2
pRbAp46	Rbbp7
proinsulin	INS
promyelocytic defensin-1	DEFA1
ProT α	PTMA
Psoriasin	S100A7
PTHrP	Pthlh
RA28	FXYD3
Rae-28	Edr1
Rae-30	Fbp2
Rb	RB1
RBP	RBP4
RC3	NRGN
RDH	Rsdr1
Retinal fascin	FSCN2
Rex-1	Zfp42
Rh1	Rho
RIG1	RARRES3
RIHB	Mdk
RIP140	NRIP1
RIS-1	S100A7
RMUC176	Muc3
Rod-specific opsin	Rho
RTP	NDRG1
RTR	Nr6a1
S14	Thrsp
Sar1a	Sara
SCCE	KLK7
SCF	Kitl
Sgp-2	Trpm2
SLAP	SLA
SPA	Sftpa1
SP-B	SFTPB
SP-C	SFTPC
Spr1	SPRR1B
SSAT	Sat
SSEA-1	Fut4
SSeCS	Akap12
ST3	MMP11
Stem cell factor	Kitl

continued

TABLE 1—*Continued*

Common Name	Gene Table
Stra1	Efnb1
Stra10	Mrg1
Stra11	Wnt8d
Stra3	Ebaf
Stra7	Gbx2
Stromelysin	MMP3
Stromelysin-3	MMP11
Survivin	BIRC5
TBRII	Tgfbr1
TF	F3
TF CA150	TAF2S
TfR	TFRC
TGase K	Tgm1
TIG1	RARRES1
TIG2	RARRES2
TIG3	RARRES3
TIS10	PTGS2
Tissue factor	F3
TM	THBD
TNAP	Akp2
TopoII	TOP2A
t-PA	PLAT
TR2-11	Nr2c1
TR4	NR2C2
TrkA	Ntrk1
Trkb	Ntrk2
TrkC	NTRK3
TRP-2	DCT
Ulip	DPYSL3
u-PA	PLAU
VAChT	Slc18a3
Vesicular acetylcholine transporter	Slc18a3
Vitronectin receptor	Itgav
WAF1	Cdkn1a
Xlim-1	Lhx1
Y1R	NPY1R
zif268	Egr1

Concordance of common names and the official symbols used in the Gene Table for cases where there are significant differences between them.

the Gene Table, but only for cases where the two are very different. Throughout, we have suppressed the distinction between genes and the proteins they encode.

The species designations column

The third column of the Gene Table lists the "species" studied in the papers cited. Although we made no systematic attempt to classify animals below the genus level, most of the designations are accurate. The following abbreviations are used: Bt, *Bos taurus* (cattle); Cf, *Canis familiaris* (dogs); Cj, *Coturnix japonica* (quails); Cp, *Cavia porcellus* (guinea pigs); Dm, *Drosophila melanogaster* (fruit flies); Dr, *Danio rerio* (zebrafish); Gc, *Geodia cydonium* (Geodia sponges); Gg, *Gallus gallus* (chickens); Hs, *Homo sapiens* (people); Ma, *Mesocricetus auratus* (hamsters); Mf, *Macaca fascicularis* (macaques); Mm, *Mus musculus* (mice); Oc, *Oryctolagus cuniculus* (rabbits); Rn, *Rattus norvegicus* (rats); Ss, *Sus scrofa* (pigs); Tr, *Takifugu rubripes*; (puffer fish); Xl, *Xenopus laevis* (frogs).

The regulatory directions column

For each gene, we have noted the predominant regulatory direction attributed to RA, up or down. This can be problematic in situations where, intuitively, RA can effect opposite actions in different cellular contexts: up during differentiation, for example, and down during growth inhibition. Again, we concentrated on what was most frequently reported. Genes are marked 'vrs' (various) when there is no obvious predominant direction. For all such genes, it should be clear from our comments whether the category rating is based on a single regulatory direction or on the data taken as a whole. For example, there are several clear demonstrations that the rapid down-regulation of *Myc* is indirect in the cell types in which this has been investigated. This seems likely to apply whenever *Myc* is down-regulated. Its rapid up-regulation in other contexts, however, has not convincingly been shown to be indirect anywhere. *Myc*'s Category 2 rating therefore refers to its rapid up-regulation following a moderate dose of RA in certain situations. The comments column should make this clear. Everything in the table is based on currently available data, of course, and as additional contexts are studied, more cell types, different developmental stages, unusual environmental situations, and so forth, the picture will only get more complex.

Stock phrases used in the summary column

Every phrase in the Gene Table and every category rating should be read with the implicit qualification, "in the cell types or at the developmental stages studied." Even the paradigm of classical RA regulation, RARβ, is not under RA control at all times or in all cell types. To keep the table as concise as possible, and to make comparisons easier, we used the following stock phrases when applicable: *1*) "No good d/t data" means we found no experiments using dose and time conditions within our limits for suggestive data. The phrase does not impugn the work referred to but was chosen for its brevity. In particular, minute-by-minute observations using physiological doses of ligand are only rarely relevant in clinical research or developmental work. In fact, pharmacological doses may be the only effective therapies in certain clinical situations and teratological doses have been indispensable in some truly seminal developmental studies. In ordinary circumstances, however, it is generally assumed that direct transcriptional modulation is rapid and that it can be initiated with a physiologically moderate dose of ligand. Ideally, unless there is a transport problem, one would like to see experiments using nanomolar concentrations of RA and making observations within minutes. However, the number of experiments conforming to these standards is very small, so we set 1 μM × 6 h as the upper limit for "suggestive" data. This was a necessary compromise given the range of scientific questions addressed in the papers consulted. *2*) "Specific ligands" refers to either receptor-selective ligands or ligands that do not have the full complement of biological effects associated with all-*trans* retinoic acid (for example, ligands that help sort out AP-1 events). *3*) The phrase "functional binding site" implies that a whole range of thoughtfully-designed tests has been performed, and that a more or less recognizable response element has been identified. The phrase is distinguished from such other notations as "functional motifs" (for which no dimer binding or native transcriptional verification has been made), "binding sites" (from which heterologous promoters can be driven), "motifs" (which are supported by sequence analysis only), and so forth. The phrase "no motif found" says that a promoter or other presumed control region was inspected in at least one of the papers cited, but that no candidate motif was found. *4*) "Other NRs" indicates that other nuclear receptors are known to be involved in the gene's regulation in some cells. The importance of noting this stems from the cross-talk that can occur between nuclear receptors, and from the similarity of nuclear receptor binding sites (which can be confounding when extreme dose conditions are used). *5*) "During differentiation" (or a similar phrase) indicates that the gene has only been studied during differentiation, growth control, proliferation control, cell cycle arrest, apoptosis, wound healing, hypertrophy, or any of the other wholesale cellular or phenotypic changes RA can effect. We did not always include such an annotation. *6*) " . . . not

for RA . . . " or " . . . not for RA alone . . . " means that the referenced experiments, or parts of them, have been done with ligands other than all-*trans* RA, usually 9-*cis* or a synthetic, or with RA plus an additional factor. *7*) "d/t borderline" signals that while at least some data fall within our dose/time limits, they are right on the borderline. This is meant to draw attention to the compromise inherent in the limits imposed for "suggestive" data. *8*) "Probably indirect" is more specific than it sounds. It indicates that a transcriptional intermediary, as opposed to another indirect mechanism, is most likely involved: RA regulates X and X regulates Y. The particular intermediary is noted in some cases.

The citations column

We have attempted to evaluate RA's role in the control of 532 genes and could not possibly cite every relevant paper. Each paper we do cite makes a point directly connected to the Gene Table: a first assertion of RA control, a regulatory direction, a time or dose curve, a binding site, a species, or something else. In addition, we have cited a (very) few papers of particular historical importance even though the research described may have preceded the experimental techniques or genetic models that underpin today's RA work. To save space, we have used PubMed Unique Identifiers (PMIDs) rather than traditional citations.

PMIDs are the unique record numbers assigned to journal articles at the National Library of Medicine. They can be used in PubMed, National Library of Medicine Gateway, and other National Institutes of Health databases to retrieve citations, abstracts, cross-links to GenBank sequences or other sequence-based information, external links to full-text articles where available, and so forth. Unmodified identifiers are valid queries, type or paste the number(s) into the Search Box, at all appropriate National Library of Medicine front ends, but in complex queries or in other databases the tag "[PMID]" may be required.

The category ratings column

The ratings reflect overall assessments. Experimental evidence varies from gene to gene and there is no algorithm that can assign a category automatically. Investigators use different techniques and have different scientific questions in mind; the quality of figures varies, and the threshold of "proof" varies from lab to lab. For each gene then, the rating expresses our overall reading of the evidentiary situation based on all the work considered. Again, not all of the studies were designed to investigate mechanisms, so we are imposing extrinsic considerations in some cases.

Category 0. There is no particular reason to believe that this gene is directly regulated through the classical RA pathway.

Case 1. Indirect regulation has been demonstrated in a context that seems likely to apply generally and no other data suggest that direct regulation is likely in other contexts. Indirect regulation can include the existence of RA-regulated transcriptional intermediaries, non-transcriptional or post-transcriptional effects, and so forth.

Case 2. Hexamer motifs have been found in a location that might represent a regulatory unit, but no other evidence of RA involvement has been offered in any paper we know of.

Case 3. An historical correction has been made and the gene is no longer thought to be under RA control.

Category 1. There is solid evidence that the gene is controlled by RA and no indirect mechanism has been demonstrated experimentally. At the same time, the available data do not justify a prediction, or even suggest which way a prediction should go: direct or indirect regulation.

Case 1. Induction or suppression has been shown, but the dose and/or time conditions exceed our limits for "suggestive" data.

Case 2. Physiological, clinical, or dietary information (or evidence from transgenics, knock-ins, or knockouts) strongly implicates RA, but there is no particular reason to posit direct regulation through the classical RA pathway.

Case 3. mRNA studies are lacking but protein studies or other evidence suggests that further work should be done.

Category 2. The gene is a strong candidate for direct regulation, but specific data are lacking.

Case 1. Transcriptional effects have been demonstrated under suggestive dose and time conditions but *i*) no binding site connection has been made, or *ii*) the involvement of an RAR.RXR dimer is not clear.

Case 2. There is highly promising binding site information plus basic inductive or suppressive data.

Category 3. A persuasive case has been made, or can be made based on currently available data, that the gene is directly regulated by RA in at least one genetically "normal" cell type.

Requirement 1. Transcription-based induction or suppression (within the limits of 1 μM or less × 6 h or less) has been confirmed in some reasonably general context.

Requirement 2. Evidence of RAR.RXR involvement has been produced or strongly implied.

Requirement 3. A functional binding site, preferably conserved, has been found and tested in a broad panel of experiments.

RESULTS AND DISCUSSION

The number of genes per category

We have evaluated published data pertaining to RA's regulation of 532 genes and have summarized the data in the Gene Table. Based on current research, 27 of these genes are unquestionably controlled through the classical RA pathway in some cellular context(s). Genes falling into this category were subjected to a high level of scrutiny in order to ensure, as far as possible, that they would never have to be removed, although indirect mechanisms may be used in other contexts as well. They are marked as Category 3 genes. Another 105 genes are in Category 2. They can be modulated at the transcriptional level in less than 6 h following an administration of 1 μM RA or less, but other indicators of direct regulation have not yet been explored. In most cases, the data still lacking relate to response elements or RAR.RXR involvement.

Category 0 encompasses two cases. First, there are 124 genes that seem to be regulated indirectly in the contexts studied. We are aware of no data or arguments suggesting that these genes might be directly regulated through the classical RA pathway in other cellular contexts. Nine other genes (*Adh1*, *BTK*, *FSCN2*, *Htf9c*, *IBSP*, *Itgb7*, *Lpl*, *Ranbp1*, and *Slc9a2*) were also put into Category 0. They are discussed in the literature, but there is no strong reason to believe that they are regulated by RA at the transcriptional level. In two cases, *Adh1* and *Lpl*, suspected or predicted mRNA changes were not confirmed, and while most of the others contain motifs resembling RA response elements, there is no evidence suggesting that these motifs, which can be highly ambiguous in the best of circumstances, represent biologically active retinoic acid response elements.

The remaining 267 genes, slightly more than half of

those we evaluated, fall into Category 1. They are regulated by RA in some way, but the data available at present do not allow us to predict direct versus indirect control. Most have not yet been studied except in long-term or high-dose contexts, and for many, the ultimate interest has been clinical, developmental, or diagnostic rather than mechanistic. Additional work will need to be done to push these genes into more informative categories.

In fact, future research may change the classification status of any gene in the table. The method used to select Category 3 genes was designed to be sufficiently rigorous that no gene would easily be struck from the group, but there is no reason why any one of them might not be regulated indirectly in other contexts as well. Beyond that, we expect future research to find that many of the Category 2 genes are direct targets, and that some of the Category 1 genes are as well. In fact, some of the Category 0 genes may turn out to be direct targets too, but in contexts that have not yet been studied.

Regulatory direction

In terms of regulatory direction, 311 genes are always or almost always up-regulated in the contexts studied, 109 are always or almost always down-regulated, and the rest are quite variable. Most investigators now believe that direct regulation through the classical RA pathway is always inductive, although there is no theoretical reason why this should be so (and it is not true of some other transcription factors). Nevertheless, all the Category 3 genes are up-regulated and only three of the Category 2 genes are usually down-regulated. One Category 3 gene, *Hoxb1*, is marked "various" because it can be directly up-regulated in some contexts, but down-regulated, probably indirectly, in others. Given that many transcriptional events seem to be regulated cyclically, a "various" regulatory direction should probably be much more common than the data imply; most likely this is due to a lack of measurements taken along a fine enough time continuum. **Table 2** summarizes category and direction data for the 532 genes. (The reader is reminded that gene expression *in the presence* of RA is the topic here. The repression of basal transcription by RAR.RXR in the *absence* of RA is an entirely different matter.)

The types of genes regulated

Not surprisingly, the set of genes currently known to be regulated directly through the classical RA pathway does not form a unified or predictable group, either in function or in sequence. (For the record, the human versions of these 27 genes are spread over 13 autosomal chromosomes.) However, two subsets deserve special mention: *i*) genes that are somehow related to the handling, metabolism, function, or presumed evolutionary history of the retinoids, and *ii*) genes containing homeobox domains. Using symbols from the Gene Table, the first group includes *RARA*, *RARB*, *RARG*, *Rbp1*, and *CRABP2*, together with several more tenuous members: *ADH1C* (which can metabolize retinol), *CRYAB* (which is loosely related to photoreception), and *Drd2* (which contains a rhodopsin family, 7 transmembrane receptor domain). The other subset, genes that contain homeobox domains, consists of *Hoxa1*, *HOXA4*, *Hoxb1*, *Hoxb4*, *Hoxd4*, *Cdx1*, and *Pit1*.

Although no regulatory or evolutionary theory formally justifies it so far, it is tempting to see a certain logic in several other genes directly regulated by RA: *HSD17B1* is involved in the function of other nuclear receptors; *H1F0* is activated at differentiation and points of development; one of *SFTPB*'s functions is developmental; *IL2RA* is involved in apoptosis; *Ucp1* is expressed only in brown adipose tissue (and is therefore connected to dietary lipids); *ETS1* ultimately derives from the E26 virus (and a number of viral control regions contain sequences that can respond to RA); *Foxa1* and *Egr1* are expressed early in differentiation. The other Category 3 genes are *CD38* (which was originally identified as a differentiation antigen), *Tgm2*, and *Pck1*.

We found 105 Category 2 genes that can be more or less rapidly up- or down-regulated at the transcriptional level in the presence of RA. Some of these genes are probably regulated directly. It would be surprising if there were a common thread among them, and there is not. They encode proteins of almost every imaginable type.

However, several domain architectures turn up a number of times among the Category 2 and 3 genes and should probably be mentioned. Taking the 132 genes in these two categories together, 11 contain homeobox domains (*Cdx1, GBX2, Hoxa1, HOXA4, Hoxb1, Hoxb4, Hoxd4, LHX1, Meis1, NCX,* and *Pit1*) and six encode zinc finger proteins (*NR2C2, NR4A3, RARA, RARB, RARG*, and *Egr1*). Of those six, five are nuclear receptors with both c4 zinc finger domains and nuclear receptor ligand-binding domains. Five of the genes in the two categories are from the lipocalin/cytosolic fatty-acid binding protein family (*APOD, Crabp1, CRABP2, Rbp1,* and *RBP4*); and five contain tyrosine kinase catalytic, or eukaryotic protein kinase,

TABLE 2. Category and direction summary

Category/Regulatory Direction	0	1	2	3	Total
Up	63	130	92	26	311
Down	40	66	3		109
Variable	21	71	10	1	103
NA	9				9
Total	133	267	105	27	532

Genes regulated by retinoic acid, predominant regulatory direction versus gene ratings (see text). NA, direction not determined in the literature or no mRNA regulation found.

domains (*CSF1R, EGFR, LYN, Tgfbr1,* and *Tgfbr2*). Three of the genes encode helix-loop-helix DNA-binding domain sequences (*MYC, MYCN,* and *Srebf1*); three encode short chain dehydrogenases (*HSD17B1, HSD17B2,* and *RDHL*); and three contain TGF-β propeptide domains (*Ebaf, Gdf5,* and *Tgfb3*).

State of the science

Intuitively, the number of Category 3 genes found in this work is surprisingly small, given the conservation of three RAR genes plus a triad of RXRs and multiple isoforms of all. The largest cohesive group of Category 2 or 3 genes consists of those somehow connected to the retinoids or nuclear receptors, the "infrastructure" of the regulatory system itself. And while evolution may not be particularly parsimonious, one suspects that the machinery of the classical RA pathway with all its complexities and autoregulatory loops has been conserved, not to regulate *itself*, but because it is uniquely useful in controlling, directly or indirectly, a particular range of genetic events in various cells and at different times of life. This suggests that the group of Category 3 genes will grow as new data become available on genes already in the table, and as new targets are discovered. There is circumstantial evidence for this, too. Since at least the mid-1980s, subtraction or differential-display experiments using RA have been turning up "novel" genes and there is no sign that this is slowing down. Many of these genes have not been investigated beyond the original paper mentioning them, and most are probably cases of indirect regulation. Nevertheless, this adds an exciting dimension to the RA field and points to quite a few experiments waiting to be done.

In works that deal with a large number of genes, it has become customary to summarize functions, family memberships, and other quiddities, "ontologies" as they are now called in a puzzling use of the word. This is done as a first step in finding underlying biological regularities, and we have done it for that reason in this paper. However, its significance should not be overplayed. Duplications of whole genes, coding plus regulatory and non-coding regions, do not endure evolutionary time unchanged, and it is by now perfectly clear that non-coding regions are far more labile than coding regions. While some progress has been made in identifying regulatory elements analytically, see (26) or (27), for example, intervening sequences seem to be highly variable. Indeed, the evolutionary comings and goings of regulatory signals remain almost completely mysterious, and RA response elements, which are almost always found in traditional promoters or extended, multi-function enhancers, are short, degenerate, ambiguous signals ripe for evolutionary experimentation. One would therefore expect only coincidental functional or formal resemblances among the complete set of genes controlled by RA. What this tells us is that many interesting and surprising results remain to be found: genes whose regulation by retinoic acid is not a priori predictable.

Over the last quarter century, a substantial body of knowledge has been built up concerning gene expression regulation by RA. That work has contributed significantly to our understanding of context-regulated transcription, vertebrate development, and a host of important clinical issues. From the particular perspective of this paper, much of the work we consulted was tantalizingly close to helping answer the direct-versus-indirect question even though it was not originally designed to address that question at all. In other cases, elucidating a molecular pathway was a primary research goal and a clear answer was determined; and in a few cases, intriguing scientific issues have turned up when regulatory mechanisms do not seem to be as clear-cut as originally expected, as with *LAMB1* (28–32). Of course, many RA studies seek clinical or nutritional information, and the poignant need for such studies is beyond question; yet in the larger scheme, knowing which regulatory events are direct and which are indirect can perhaps lead to superior pharmacological and nutritional protocols as well as to progress in basic science.

ENDNOTE

For many of the genes considered in this paper, there are entire labs with years of expertise and a broader interest than the gene's potential regulation by RA. People from these labs may see connections or alternatives that were not obvious to us. Similarly, the number of papers potentially relevant to a work of this sort is huge, and we were repeatedly reminded that neither titles nor abstracts need hint at all the results reported. Finally, while MeSH indexing and MEDLINE coding are invaluable tools and basic to virtually every biomedical research project now carried out, they are just as fallible as bench work. For all of these reasons, it would be surprising if we had not missed important ideas or papers.

We think of this paper as a working document and hope that our errors and oversights will generously be pointed out by our colleagues so that the table can be updated, improved, and maintained, by us or by another group, as an evolving assessment of RA's genetic workings.

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Gene Table

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
ADH1C	ADH3	Hs	Up	Induction; functional binding site; negative TRE nearby.	0001996113; 0001321136; 0008388158	3
CD38	CD38	Hs, Mm	Up	Induction; differentiation controls; specific ligands; functional binding sites; evidence from transgenics.	7690555; 0008394323; 0007511050; 0009160665; 0009624127; 10969805	3
Cdx1	Cdx1	Mm, Hs[a]	Up	Induction; conserved functional binding site.	7649373; 10938132	3
CEBPE	C/EBP epsilon	Hs	Up	Rapid induction during differentiation; functional binding site; specific ligands.	9376579; 9177240; 0010330422	3
CRABP2	CRABP-II	Hs, Mm	Up	Induction; conserved functional binding sites.	0001654334; 1309505; 0001313808; 0001327537; 0001334086; 0008071361; 0009856825	3
Cryab	αB-crystallin/small HSP	Mm	Up	Induction; functional binding site.	0009651402	3
Drd2	dopamine D2 receptor	Hs, Mm, Rn	Up	Induction; functional binding site; evidence from transgenics.	7990648; 0009405615; 0009721718; 9452386	3
Egr1	Egr-1, zif268, Krox-24	Mm, Rn	Up	Induction; functional binding site (characterized as a single half-site).	1936556; 1793734; 1708092; 0007877619; 8176254	3
ETS1	Ets1, ets-1	Hs, Mm	Up	Rapid induction during differentiation; functional binding motifs (single hexamer and DR5).	3060792; 7689222; 0010773887; 11327309	3
Foxa1	HNF-3α	Mm	Up	Rapid induction during differentiation; no protein synthesis required; functional binding site.	8029022; 7649373; 9260895; 0010388516	3
H1F0	H1° histone, H1 degree	Mm, Hs	Up	Early induction during differentiation; functional binding site (DR8); other NRs.	2846273; 1988682; 0008078070; 0007576177; 0008559662	3
Hoxa1	ERA-1, Hox-1.6, Hoxa-1	Mm, Dr	Up	Induction; conserved functional binding site; whole animal evidence (including transgenics).	0003422432; 0002906112; 0001360810; 0007743939; 0008631251; 0008999919; 0009053316	3
HOXA4	hoxa-4	Hs, Mm	Up	Induction; upstream functional binding site and downstream RA-responsive enhancer; whole animal evidence including transgenics; site conservation.	0008759021; 0009570764; 9272954; 0010679930	3
Hoxb1	Hoxb-1	Mm, Gg, Tr, Hs	vrs[b]	Induction; functional binding sites (5′ and several 3′); whole animal evidence including transgenics; site conservation.	0007914354; 0007916164; 0007831296; 0007831297; 0008999919; 0009463349; 0009671595; 0009869297	3
Hoxb4	Hox-2.6, Hoxb-4	Mm, Tr, Gg	Up	Induction; conserved functional binding site; evidence from transgenics.	0007878040; 9272954; 0009697850	3

continued

Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Hoxd4	Hox-4.2, Hoxd-4	Mm, Hs	Up	Induction; functional binding sites (5′ and several 3′); whole animal evidence including transgenics; site conservation; some discussion that at least some effects may be indirect.	2898782; 0008093325; 0007908827; 0008674428; 0009360992; 0009347914; 10940626	3
HSD17B1	17HSD type 1[c]	Hs	Up	Induction; specific ligands; functional binding site.	0008013376; 0008614400; 9048588	3
IL2RA	IL-2R α	Hs	Up	Induction; an upstream region at least partly responsible has been identified; additional paracrine effect from RA induction of IL2 has been discussed.	7678784; 0008157276; 9130512	3
Pck1	PEPCK	Rn, Hs, Mm	Up	Induction; functional binding sites; whole animal evidence; other NRs.	2176887; 0001848696; 0001656224; 0007831301; 0008626419; 0009078282; 9202079	3
Pit1[d]	Pit-1	Mm, Rn, Ma, Hs	Up	Induction; conserved functional binding site (also acts as VDRE); Pit1 binding required for activity; clinical evidence.	0008504933; 0007588287; 0009027335; 0010077004	3
RARA	RAR-α2	Hs, Mm, Tr	Up	Isoform 2 induction; conserved functional binding site.	2825025; 2825036; 0001658797; 0010452951	3
RARB	RARβ	Hs, Mm, Rn, Gg	Up	Induction (isoforms 2, 4); conserved functional binding site; isoforms 1, 3 appear not be RA regulated.	2833708; 2836738; 0002542014; 0002153268; 0002177841; 0002164682; 0001663808; 0008384988; 0008011555; 7649373; 11073974	3
RARG	RAR γ	Hs, Mm, Rn	Up	Isoform 2 induction; conserved functional binding site.	0001320193; 0008394693; 0009142499	3
Rbp1	CRBPI	Mm, Rn	Up	Induction; conserved functional binding site.	2546063; 0001648481; 0001339275	3
SFTPB	SP-B	Hs, Rn, Mm	Up	Induction; region responsible for RA effect binds receptors; indirect effect likely as well; functional motifs; evidence from dominant negative.	0008404646; 0008944731; 0009575874; 0009700083; 0010070102; 0010617585	3
Tgm2	TGase 2	Mm, Hs, Rn	Up	Induction; controls for differentiation; specific ligands; unusual functional binding site of three hexamers: hex(n7)hex(n5)hex; requirement for both RA and 9-cis, at least in some systems.	6149218; 2859286; 2900242; 2565341; 1705423; 9516142; 0008626785; 9516142	3
Ucp1	ucp, upc-1	Rn, Mm	Up	Induction; conserved[e] functional binding sites; specific ligands; whole animal studies; other NRs/factors.	0007929091; 0007890689; 0008754778; 0008940169; 9659286; 10921912; 0010600643	3

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
ABCC2	mrp2	Hs, Rn[f]	Up	Natural induction not shown (Rn promoter plus exogenous RARa.RXRa in Hs cells); dose not clear; binding site functional in hybrid system.	0010722729	2
ACADM	MCAD	Hs	Up	Reporter induction; functional binding site; other NRs; considerable discussion of physiological relevance.	0001328196; 0008314750; 8754802; 0009271417	2
Adrb1	β 1-AR	Rn, Mm	Up	Induction during differentiation (although rapid in some systems); functional binding site (also DR5 TRE); appears indirect at least in some systems.	9025717; 0009441829; 0009448745	2
Akp2	TNAP, liver/bone/kidney AP	Mm, Rn, Hs	Up	Induction; motif; an additional (and perhaps more important) indirect enhancement of steady state mRNA levels may occur during precursor mRNA processing.	1849403; 1939166; 0008071372; 0008817450; 0010530919; 0010691970	2
APOA1	apo A-I	Hs, Mf, Rn	Up[g]	No good d/t data; several functional binding sites; possibly RXR.RXR; other NRs; specific ligands; at least one study found opposite in vivo and in vitro effects.	0001646397; 8399088; 0007918317; 0007658149; 0008626539; 0008604295; 0009392425; 0010194513	2
APOA2	apo A-II	Hs, Rn	Up	No good d/t data; specific ligands; functional binding site; possibly RXR.RXR; RXR transfection may activate without addition of ligand; other NRs; no RA effect in some systems.	0007918317; 0008668150	2
APOC3	apolipoprotein C-III	Hs	Up	No good d/t data; several functional binding sites; other NRs; specific ligands; possibly RXR.RXR.	0009691099; 0009893992	2
APOD	apoD	Hs	Up	Induction; independent of protein synthesis; specific ligands.	7929425; 8943263	2
ASMT	HIOMT	Hs	Up	Induction.	8752109	2
AT-RA 6[h]	AT-RA 6	Hs	Up	Induction.	0009415824	2
BIRC3	IL-1b stimulating gene	Hs	Up	Induction.	11146166	2
CDKN2B	p15, INK4B	Hs	Up	Induction with borderline d/t conditions; no significant change reported (but data not shown) in one short-term mRNA study.	10479451; 10812241	2
CETP	CETP	Hs	Up	No good d/t data; reporter induction (measured at 48 h); region responsible for RA effect identified and binding verified.	0010329401	2
Cfh	complement factor H	Mm	Up	Induction possible but not clearly shown[i]; functional binding site.	0001700780; 1828229	2
CHAT	ChAT	Hs, Mm	Up	Induction, but d/t borderline; many studies have been in differentiating systems; potential motifs; specific ligands; other NRs; may be at least partly post-translational.	2924123; 2924124; 8057782; 7919195; 0007673184; 0007790895; 7745608	2
Crabp1	CRABP I	Mm, Rn	vrs	No good d/t data; appears to be part of a complex autoregulatory system; binding motif; may require protein synthesis; several indirect mechanisms have been proposed, as well as direct regulation.	2546063; 8382159; 0007528580; 7588278; 0008617785; 0008663043; 0009392513; 9142496; 9390004; 0010714763	2
Crygf	γ F-crystallin	Mm	Up	No good d/t data; a functional binding site is also functional for the TR and ROR systems.	0008436299; 0007877618; 0007650034	2

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
CSH1	placental lactogen	Hs, Rn	Up	No good d/t data; functional binding sites; other NRs.	8174790; 0007867602; 0007589779; 0007867602	2
Csnk	k-casein	Mm	Up	Induction.	7649373	2
CTSK[j]	cathepsin K/OC-2	Oc	Up	Induction.	0007639684	2
CYP24	24(OH)ase, 25-hydroxyvitamin D3-24-hydroxylase	Rn, Hs, Mm	Up	No good d/t data; functional binding sites (which are also VDREs); specific ligands; that RAR.VDR or RXR.VDR may explain RA induction has not been conclusively ruled out.	0007592579; 0009228086	2
Cyp26[k]	P450RAI, CYP26AI	Dr, Mm, Hs	Up	Induction (but long-term exposure may lead to repression); specific ligands.	0008939936; 0009228041; 0009250660; 0009740237; 0009442090; 0009716180; 0010583049; 11023996	2
DTR	HB-EGF	Hs, Mm	Up	Induction; evidence from transgenics.	9858142; 0010075925	2
Ebaf	Lefty, Stra3	Mm, Gg	Up	Induction; binding motif (Pal8); appears indirect, at least in some systems.	7649373; 0009496783; 0010331971; 0010500184	2
Edr1	Rae-28, mph1	Mm	Up	Early induction during differentiation.	0008070621; 0010653359	2
Efnb1	Stra1	Mm	Up	Induction.	7649373	2
EGFR	EGF receptor	Mm, Rn, Hs	vrs	Induction shown in some systems; d/t data for reduction (where it occurs) is not good; exogenous RAR plus nuclear proteins bind an identified upstream region; other NRs; there have been several proposals for indirect mechanisms.	6245371; 2540431; 2783693; 0002169350; 1748717; 0001515368; 0007859922	2
Epo	Epo	Rn, Mm, Hs	Up	No good d/t data; functional binding site; other NRs; evidence from receptor knockouts.	8050571; 11050012; 11297512	2
Fbp2	Rae-30, FBPase isozyme	Mm	Up	Early induction during differentiation.	0008070621; 8034042	2
FOLR1	folate receptor α	Hs, Mm	Up	Induction; no motif found.	7707421; 10216260	2
Gbx2[l]	Gbx-2, Stra7	Mm, Xl	Up	Induction, but at least partly indirect (Hoxa-1).	7649373; 8601031; 8652408; 10942599	2
Gdf5	Contact	Dr	Up	Induction (using dechorionated embryos soaked in RA-solution then extensively washed).	0009256353	2
Gh1	GH	Rn, Hs	Up	Induction; functional binding site; specific ligands; other NRs; indirect in some systems but possibly not all; other factors, such as Pit1, may be required for effective induction.	0002707148; 0008384845; 0007956917; 0008524311; 0008768885; 0009737723	2
Glut4	GLUT4	Rn	Up	Some data hard to interpret; induction likely; other NRs.	8119934; 7758830	2
Gnrh1	GnRH	Rn	Up	Induction; other NRs; (weak) functional binding site.	0009526050; 11245923; 11245924	2
GPX2	Gpx2	Hs	Up	Induction likely (but early data hard to read); motifs.	0010498757	2
GSTP1[m]	GSTP1-1, GSTP1*C	Hs	vrs	No good d/t data; repression appears indirect (AP-1 or tTG), however, induction may be direct; functional binding site.	8546677; 0009407047; 0009679546; 0010536361	2

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
H2	major histocompatibility class I (H2K, -D, -L, and -Q, etc.)	Mm, Hs, vrs[n]	Up	No good d/t data; functional binding sites, one of them highly conserved.	0003467324; 0001736309; 0008413217; 0008604312; 0008618036; 0009758167; 0009790391	2
HSD17B2	17 β-HSD type 2	Hs	Up	Induction; specific ligands.	11397877	2
Igf1	IGF-I	Rn	vrs	Rapid induction in some differentiating systems (followed by late decrease); down-regulation in probably indirect.	1572288; 0009258346	2
Igfbp6	IGFBP-6	Rn, Hs	vrs	Associated with growth or differentiation regulation; induction; motif and somewhat conserved functional binding site (DR15); at least partly indirect in some systems (protein synthesis and mRNA stability for induction, Hoxa-1 for reduction).	0007682065; 0008603611; 10942599; 11267670	2
Il1a	IL-1 α	Mm, Hs	Up	Induction of pre-mRNA; may require additional special factors for processing.	0008083217; 0007763262	2
IL1B	IL-1 β	Hs	Up	Induction of pre-mRNA likely; RA may also have an effect secondary to induction by other transcription activators.	0001646841; 0008489769; 0008360592; 0008083217; 0008702428; 0009783809	2
IL2RB	IL-2R β	Hs	Up	Induction; upstream control region not found.	7678784; 9268495	2
IRF1	IRF-1	Hs	Up	Induction (independent of GAS motif).	8704165; 9393879; 10319996	2
Itgb3	β 3 integrin	Gg	Up	No good d/t data; functional binding site overlaps a VDRE; other NRs.	0008891892; 0008702813	2
KRT5	K5	Hs	Dn	Suppression; an upstream cluster of hexamers that can bind RAR and suppress a CAT reporter has been found; AP-1 regulation; other NRs.	1711202; 0007505782; 7505756; 7519609; 0009326392	2
Lamb1-1	laminin B1	Mm, Hs	Up	Delayed induction in RA-differentiable cells; unusual putative RAR binding site that is somewhat conserved; induction requires protein synthesis; evidence from knockouts and lacZ transgenics; may be directly regulated but in an unusual way, perhaps.	6310600; 0002981185; 0002842348; 0002556699; 0001975589; 0001850696; 11335108	2
Lhx1[o]	Xlim-1	Xl	Up	Induction, but the persistence of an unintended RA effect after the 30 minute exposure and subsequent washes is discussed.	0007914163; 11112328	2
LYN	lyn	Hs	Up	Induction; some differentiation controls.	1987282; 7512079	2
MCL1	Mcl-1, EAT	Hs, Mm	Up	Induced early in differentiation but with some controls.	8790944; 8600156; 9655929; 10816607; 11339830	2
Mdk[p]	RIHB, MK	Gg, Mm, Hs	Up	Induction data not good; functional binding site conserved in Hs and Mm; some discussion that it may be indirect in chick.	0001993066; 0002018506; 8507561; 0007925417; 0007982887; 0007592548; 0009266025	2
Meis1	Meis1	Gg	Up	Induction (ectopic beads loaded with RA at an apparently physiological dose).	10952894	2
MGP	matrix Gla protein	Hs, Rn	vrs	No good d/t data; potential positive motifs; putative negative binding region.	2394711; 0001727694; 8214087; 0008319825; 0009122176	2

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
MIG-6[q]	gene 33	Rn	Up	Induction.	0008156927	2
MMP11	stromelysin-3, ST3	Hs, Mm	Up	No good time data for induction; conserved functional binding site; evidence from receptor knockouts; repression seen under extreme d/t conditions.	0007657606; 0009111003; 0009824353; 10993903	2
Mrg1	Meis2, Stra10	Mm, Gg	Up	Induction.	7649373; 9337137; 10952894	2
Mtap7	E-MAP-115	Mm	Up	Induction.	0010837026	2
MYC	c-myc	Hs	vrs	Rapid induction in some systems; rapid inhibition on others, but that appears to be indirect; some differentiation controls have been done.	2414665; 3691668; 0002459072; 2163931; 0008490200; 0008239509; 0008018561	2
MYCN	N-myc	Hs, Mm	Dn	Early and rapid suppression; differentiation associated; upstream region responsible has been identified.	3977910; 3855502; 2405249; 0001565467; 9570357	2
NCF1	p47-phox	Hs	Up	Induction; other NRs.	2398896; 7578267; 9145335	2
NCX	Ncx	Hs, Mm, Rn[r]	Up	Early induction during differentiation but with some controls; conserved motif necessary for RA effect.	0010446220	2
NES	nestin	Mm, Hs, Rn	Up	Differentiation associated; no good d/t data; conserved binding motif which other NRs also bind.	8522959; 0009104587; 9057134; 0010222142; 10876035	2
Ngfr	LNGFR, p75NTR	Rn, Hs	Up	Induction; a promoter region conferring the RA response has been identified; other NRs.	1964179; 0001446821; 1325442; 10816607; 10661835	2
Nr2c1	TR2-11	Mm	Up	No good d/t data; late reporter induction with exogenous RAR and RXR, or during differentiation with endogenous receptors; functional binding site (DR0).	0010393558; 10807954	2
NR2C2	TR4	Hs, Mm	Up	Induction.	0009593676; 0010201524	2
NR4A3	NOR-1	Hs	Up	Induction.	9070291	2
NRD1	NRD convertase	Hs	Dn	Induction; specific ligands; no motif found.	0009049835; 11042131	2
NRIP1	RIP140	Hs	Up	Induction; upstream region identified.	11467847	2
OXT	OT	Hs, Rn, Bt	Up[s]	Induction, but d/t data borderline; conserved functional motifs; other NRs.	0001657967; 0001311087; 0008383287; 0008195142; 0008674853	2
Pcp2	Pcp-2, PCD5	Mm	Up	Reporter induction; no good d/t data; functional binding site; other NRs.	0009224660	2
PIK3CG	PI3Kγ	Hs	Up	Induction.	0010392906	2
Pkca	PKC	Mm	Up	Induction is relatively rapid (or during differentiation), but appears to be at least partly indirect; functional binding site.	0002743337; 0001550338; 0010486248; 0010608897	2
PLAT	t-PA	Hs	Up	No good d/t data; functional DR5 binding site, but induction may depend on protein synthesis; requirement for Sp1.	0002542775; 0007706255; 0010452548	2
PTAFR	PAFR	Hs, Rn	Up	No good d/t data; functional binding site.	0008570633; 0009131130	2
RAI3	RAIG3	Hs	Up	Induction.	0009857033	2

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
RARRES3	TIG3, RIG1	Hs	Up	Induction, but d/t borderline; specific ligands; motifs noted in contig.	0009843971; 0010687848; 10955811	2
RBP4	RBP	Hs, Mm	Up	No good d/t data; two upstream regions of about 30 bp each, separated by another 30 bp region that apparently functions as an SP1 site, weakly bind various combinations of RARs and RXRs and drive a reporter, however, they contain no obvious classical binding sites.	0008077297; 0008810324; 11055551	2
RDHL	hRDH-TBE	Hs	Up	Induction.	11304534	2
RUNX3	AML2, CBFA3	Hs	Up	Early induction during differentiation but with some controls; specific ligands.	0010419474	2
S100A7	RIS-1, psoriasin	Hs	Up	Induction.	0007715611; 0008931868	2
SERPINB2	PAI-2, plasminogen activator inhibitor 2	Hs	Up	Induction; single hexamer motif noted but not tested.	2513217; 0008578452; 0010583214	2
Sftpa1	SPA	Rn	Up	Induction; motif.	0008944731	2
shh	Shh	Gg, Dr, Cj, Mm, Hs	vrs	Regulation rapid in some systems, but little good d/t data; evidence from dietary studies; specific ligands; functional binding site appears not to be conserved; the relationship between Shh and RA and several possible intermediate genes is not at all clear.	8269518; 7601313; 0008575626; 8625827; 8805369; 0009233805; 0009878825; 9753672; 0010331971; 0010500184	2
SLC10A1	ntcp	Hs, Rn[u]	Up	No good d/t data; functional binding site.	8662994; 0010722729	2
SLC5A5	NIS	Hs	Up	Induction, but d/t borderline; specific ligands.	9398654; 10890895	2
Spp1	osteopontin, bone sialoprotein I, OP	Mm, Gg, Oc, Rn	Up	Induction; additional RA effect at mRNA processing step; other NRs.	2175918; 8344389; 7746099; 0008702678; 9618139	2
Srebf1	ADD1	Mm	Up	Induction.	0009121491	2
Star	StAR	Mm, Rn	Up	Induction; an upstream region responsible for a 9-cis inductive effect was isolated but not tested with RA.	10221765	2
STAT1	STAT1	Hs, Mm	Up	No good d/t data; binding site (DR0) apparently functional, but with somewhat unusual characteristics; possibly indirect or reliant on RARb synthesis.	0008631848; 0009092506; 0010597280	2
Stra12	Stra12	Mm	Up	Induction.	7649373	2
Stra13	Stra13, D9	Mm	Up	Induction.	0008839844; 9284045	2
Stra2	Stra2	Mm	Up	Induction.	7649373	2
Stra4	Stra4	Mm	Up	Induction.	7649373	2
Stra6	Stra6	Mm	Up	Induction; evidence from receptor knockouts.	7649373; 0007644503	2
Stra8	Stra8	Mm	Up	Induction; evidence from receptor knockouts.	7649373; 9154799	2
Stra9	Stra9	Mm	Up	Induction.	7649373	2
STS	STS	Hs	Up	Induction probable but data hard to read; specific ligands; no motif found in published promoter sequence.	11284723	2
Tcfap2c	AP-2.2	Mm	Up	Early induction during differentiation.	0008660922	2
Tgfb3	TGF-β 3	Mm, Gg, Rn	vrs	Usually studied in association with differentiation or growth arrest; induction can be rapid; no motif found; other NRs.	1964159; 2146270; 1734039; 8385738; 0008557772; 9731743	2

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Tgfbr1	TBRII	Hs, Bt	Up	Induction.	7757990; 9699509	2
Tgfbr2	TGFb type II receptor	Bt	Up	Induction.	9699509	2
THBD	TM	Hs, Mm	Up	A so-called 'late response' gene; direct induction is possible, although other factors, particularly Sp1, seem to be involved; the response is enhanced by cAMP and blocked by cyclohexamide; specific ligands; RAR and RXR appear to be involved with a conserved DR4, but the involvement of ligand in this complex has been questioned.	1370608; 1312715; 0008389207; 0008207015; 7878635; 0008918245; 0010565546; 11036068	2
Ucp3	UCP3	Rn, Hs	vrs	No good d/t data; binding site functional in the presence of MyoD.	10694373; 11024001	2
Wnt8d	mWnt-8, Stra11	Mm	Up	Rapid induction.	7649373; 8887323	2
Aanat	AANAT	Cj	Dn	No good d/t data.	0010451022	1
ABCB1	MDR1, mdr3, pgp1	Hs, Mm, Ma	Up	Induction during differentiation; some differentiation controls; no good t/d data; conserved AP-1 site seems required.	2573830; 0001661134; 8101511; 0009667638	1
Abl1	c-abl	Mm	Up	No good d/t data; induced during differentiation.	2458954; 1371335	1
Acta1	α-skeletal actin	Mm	Dn	No good d/t data; other NRs.	8601621	1
Acta2	α-SM	Mm, Rn, Hs	vrs	During differentiation, growth control, wound healing, or other phenotype change; no good d/t data; specific ligands; probably indirect.	7728990; 10364073; 11230985; 11319755	1
ADAMTS5	Aggreganase-2	Bt, Hs, Rn	Up	See ADAMTS4.	7531436; 0007852317; 8603731; 10395742; 0010403768; 10936450	1
ADCYAP1	PACAP	Hs	Dn	No good d/t data.	0009285932	1
ADCYAP1R1	PACAP1 (Type I) Receptor	Hs	Dn	No good d/t data.	0009285932	1
Akap12[v]	SSeCS	Rn	Up	No good d/t data.	11181072	1
AKR1C3	HAKR e	Hs	Up	No good d/t data.	0009862446	1
Aldh1a1	ALDH1	Mm	vrs	No good d/t data; possible induction with low dose but suppression at higher dose; conserved (Hs, Mm, Rn) binding region but no clear motif; probably indirect (C/EBP β).	10995752	1
ALPI[w]	IAP	Hs	Dn	No good d/t data.	0010691970	1
Ambp	α 1-microglobulin	Rn	Up	No good d/t data.	0001371972	1
App	β-amyloid precursor protein	Rn, Hs, Mm	Up	No good d/t data; delayed induction; motifs in Intron 7 (including one in an Alu) but induction data usually relies on upstream regions only.	0007500834; 0008714200; 0009121703; 0009748493; 0010727079	1
AR	AR	Hs, Rn	vrs	No good d/t data; other NRs.	1428232; 8022710; 9182860; 10067845	1
Ascl1	MASH1	Mm, Hs	vrs	No good d/t data; differentiation associated.	1576967; 10080936; 11414696	1
Ascl2	Mash-2	Mm	Dn	No good d/t data; decreased during differentiation.	1576967	1
B3GNT5	β3Gn-T5	Hs	Up	No good d/t data; induction during differentiation but with some controls.	8621726	1
Bapx1	NKX3.2, BapX1	Mm, Gg	Up	No good d/t data.	0010469600	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
BCL2	Bcl-2	Hs	vrs	No good d/t data; most studies use differentiating systems, but some controls have been done; at least partly indirect; specific ligands.	8402688; 8572591; 8642855; 9192771; 10557066; 11181829	1
BIRC5	survivin	Hs	Dn	No good d/t data.	10698506; 11313272	1
Bmp2	Bmp2	Mm, Gg, Hs, Dr	vrs	Induction in some systems, but d/t borderline; no good d/t for suppression; generally studied during differentiation, development, or growth inhibition; specific ligands; yeast system; one upstream region conferring small RA effect has been isolated, but no functional binding motif has been found anywhere in the gene; several indirect mechanisms have been discussed, both in up-regulated and down-regulated cases.	1550961; 8385738; 8119128; 8788040; 0008739045; 9753672; 0009880512; 11054542; 10942599	1
Bmp4	Bmp-4	Mm, Hs	Dn	No good d/t data; at least partly indirect (Hoxa-1).	8788040; 10862743; 10942599	1
BST1	CD157	Hs	Up	No good d/t data; mRNA studies lacking.	11089918	1
CA2	CA II	Hs, Gg	Up	Induction during differentiation or with exogenous RARs; motif; other NRs (THRa, c-ErbA, VDR); down-regulated by long-term exposure to high RA concentration.	1700414; 0007916146; 7615086; 0010799323	1
Calb1[x]	Calbindin-D 28k	Rn, Hs, Gg	Up	Late induction; increased mRNA stability; other NRs.	0008076693; 0008584029; 9773502	1
CAMK2A	CaM kinase II, α-CaMKII	Hs, Rn	Up	No good d/t data; promoter region responsible identified.	0007913411; 8795626	1
Camk2d	delta CaM kinase II	Mm	Up	No good d/t data.	11146121; 11080189	1
Camkk1	CaMKKα	Mm	Up	Rapid induction during differentiation, but no good dose data; cell lines used have dominant negative RARa.	10560916	1
CASP1	ICE	Hs	Up	No good d/t data; late induction.	9276475	1
Casp3	caspase 3	Rn, Hs	Up	No good d/t data.	10733907; 11464863	1
Cbg	CBG	Rn	vrs	No good d/t data.	0007514032; 8645609	1
Ccne1	cyclin E	Mm	Up	No good d/t data; no significant change reported (but data not shown) in one short-term mRNA study; evidence from transgenics.	10479451; 11071877	1
Cd164[y]	endolyn, sialomucin	Rn	Up	No good d/t data.	11181072	1
CD44	CD44	Hs	vrs	No good d/t data; differentiation associated but some controls.	7576948; 9525482	1
CD58	LFA-3, CD58	Hs	vrs	Regulated during differentiation but some controls have been done; mRNA data lacking.	1706327; 1354203; 10959555	1
CD59	CD59	Hs	vrs	No good d/t data; differentiation associated.	7507222; 0009109513	1
CDC2	p34(CDC2)	Hs	Dn	No good d/t data; during differentiation but some controls; at least partly post-translational.	1751405; 9259311; 9233783; 0010447003	1
CDH1	E-cadherin	Hs	vrs	No good d/t data.	7984043; 8519658; 9590130	1
CDH2	N-cadherin	Mm, Gg	vrs	No good d/t data.	0008314004; 10590479; 11414696	1
CDH3	P-cadherin	Hs	Dn	No good d/t data.	7984043	1
Cdh6	cadherin-6	Mm	Up	No good d/t data; increased during differentiation; probably indirect (Hoxa-1) at least in some systems.	0009109513; 10942599	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Cdkn1a	mda-6, p21, WAF1, CIP1	Mm, Hs, Rn	vrs	No good d/t data; no significant change reported (but data not shown) in one short-term mRNA study; regulated during differentiation or growth arrest; differentiation controls; functional binding motif; knockout evidence; other NRs; probably at least partly indirect.	7936668; 0008702678; 0008940196; 8895764; 0009490650; 10479451; 0010645889; 11032820	1
CHGA	CHGA	Hs	Up	No good d/t data; promoter region conferring RA effect isolated.	0007576943	1
Chgb	Cg B	Mm	Up	No good d/t data; no motif found; probably indirect.	11014221	1
Clta	A4	Mm	Up	Rapid induction with high RA dose during differentiation in receptor-modified cells.	0008839844	1
CNTFR	CNTF receptor	Hs, Gg	Up	No good d/t data.	0008989665; 0009488162	1
Cntn1	F3	Mm	Up	No good d/t data; dispersed half-site motifs; probably indirect (possibly with Hox involvement).	0009332725	1
Col3a1[z]	α1(III) collagen	Gg	Up	No good d/t data.	3653521	1
Col4a2	collagen IV (α 2)	Mm	vrs	Slight early decrease followed by larger increase much later; this was an early work and the hybridizing clone was not sequenced; nor was a sequence for either Col4 chain available at the time; the clone was designated α 2 on the basis of estimated weight following in vitro translation; α 1 is discussed as well.	6310600	1
CR1	CR1	Hs	Up	No good d/t data.	10023853	1
Cryd1[aa]	delta 1-crystallin	Gg	Up	Induction of a cross-species transgene in the presence of exogenous RARb; no good time data.	9216065	1
CSF1	M-CSF, CSF-1	Hs	vrs	No good d/t data; may be at least partly post-transcriptional (when it is suppressed).	8217219; 9616179	1
CTSB	cathepsin B	Hs	Up	Induction during differentiation; no good d/t data.	0010534117	1
CYBB	gp91-phox	Hs	Up	No good d/t data; may require γ interferon.	7578267; 9447831	1
CYP1A1	cytochrome P4501A1	Hs, Rn	vrs	No good d/t data; DR4 binding site drives T3 and RA reporters.	0008024563; 0007697808; 0010462515	1
Cyp3a3	CYP3A	Rn	Up	No good d/t data.	0009154443	1
CYP4F2	CYP4F2	Hs	Up	No good d/t data; specific ligands; functional binding sites; other NRs; possibly RXR.RXR.	10860554; 11162441	1
Dab2	mDab2	Mm	Dn	No good d/t data.	10340473	1
DAG1	dystroglycan α, β	Hs	Dn	No good d/t data; decreased during differentiation.	0009109513	1
Dbx1	Dbx1	Mm	vrs	No good d/t data; specific ligands.	10399918	1
dbx1a	hlx-1	Dr	Dn	No good d/t data.	9019248	1
Dbx2	Dbx2	Mm	Up	No good d/t data; specific ligands.	10399918	1
DCT	dopachrome conversion factor, TRP-2	Mm, Hs	vrs	No good d/t data.	2107263; 11180971	1
DDX1[bb]	DEAD box protein	Hs	Dn	No good d/t data; decreased during differentiation.	0009109513	1
DDX17	DEAD box protein p72	Rn, Gg	Dn	Down-regulated during differentiation; no good d/t data.	0010718294	1
DIO1	type 1 iodothyronine deiodinase	Hs	Up	No good d/t data; TRE motif can mediate RA regulation.	8077363; 0009249039; 0009492050	1
Dio3[cc]	D-III, D3	Rn	Up	Slow induction; other NRs involved (including THRb).	7525478; 8770927; 10342885	1
DPYSL3	Ulip	Hs	Up	No good d/t data[dd]; increased during differentiation; the possibility of indirect action has been discussed.	0009115293	1
DSC2	desmocollin 2	Hs	Dn	No good d/t data; down-regulated during "apparent" inhibition of differentiation.	10421061	1
DSC3	desmocollin 3	Hs	Dn	No good d/t data; down-regulated during "apparent" inhibition of differentiation.	10421061	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
DSG3	desmoglein 3	Hs	Dn	No good d/t data; down-regulated during "apparent" inhibition of differentiation.	10421061	1
EMP1	CL-20	Hs	Dn	No good d/t data; inhibition during inhibition of squamous differentiation; specific ligands.	0007499420	1
ERBB2	c-erbB-2	Hs	Dn[ee]	No good d/t data; during growth inhibition or other phenotypic change.	9662255; 0009791009; 0010674883	1
ERBB3	c-erbB-3	Hs	Dn[ff]	No good d/t data.	0009791009; 0010674883	1
ERBB4	c-erbB-4, HER4	Hs	Dn	No good d/t data; studied during growth inhibition.	10383375	1
eve1	eve1	Dr	vrs	No good d/t data.	0009879709	1
Evx1	Evx-1	Mm	Dn	Decreased during differentiation; no good d/t data.	1971786	1
F3	TF, tissue factor, F3	Hs	Dn	Many studies involve differentiating systems[gg]; suppression rapid in some lines; other NRs; specific ligands; at least partly indirect (several mechanisms have been proposed).	7949172; 8632672; 9269772; 9585253; 10400422	1
FCER2	CD23	Hs	Up	No good d/t data; some differentiation controls.	7682243; 0008877104	1
FGF5	FGF-5	Mm	Up	Increased during differentiation; no good d/t data.	2318343; 10557354	1
Fgf9	FGF9	Mm	Up	Induced during differentiation; no good d/t data.	7656983	1
FGFR2	FGFR-2	Hs	Dn	Suppressed during differentiation; no good d/t data.	7680553	1
FGFR3	FGFR-3	Hs	Dn	Suppressed during differentiation; no good d/t data.	7680553	1
FGFR4	FGFR-4	Hs, Mm	Dn	Suppressed during differentiation; no good d/t data.	7680553; 8077293	1
FGR	fgr	Hs	Up	Induced during differentiation; no good d/t data.	1987282	1
FKBP1A	FKBP12	Hs	Up	No good d/t data; increased during differentiation; mRNA data lacking.	0009472103	1
FOLR2	FR-β	Hs	vrs	No good d/t data; late induction in some leukemic, non-APL lines; some differentiation controls; no motif found.	11071651	1
Fos	c-fos	Rn, Mm, Gg	vrs	Very little good d/t data for mRNA; no significant change reported (but data not shown) in one short-term mRNA study; several indirect mechanisms proposed (including SRE and mRNA stability); other NRs.	3691668; 2108933; 2163931; 1909429; 0001400313; 1568207; 8336949; 8226882; 0007999013; 7851664; 0010395942; 10479451	1
Foxa2	HNF-3 β	Mm	Up	Delayed induction during differentiation.	7925656; 9260895	1
Fshr	FSH-R	Ss, Rn	vrs	No good mRNA d/t data using RA alone.	3118982; 0010699459	1
Fut4	CD15, Lewis x, SSEA-1	Rn	vrs	No good d/t data; generally observed only as a marker; other NRs.	0001362196; 7905817; 8621726; 9678720	1
FXYD3	RA28	Hs	Up	No good d/t data.	0010667226	1
Fyn	fyn	Mm, Hs	Up	No good d/t data.	8643689; 1987282	1
GAP43[hh]	GAP-43	Hs	Up	Induction (sometimes very rapid) during differentiation; some differentiation controls; requires protein synthesis, at least in some systems.	1645738; 7649373; 8679712; 11120388	1
GATA2	GATA-2	Hs	vrs	No good d/t data.	1370462; 7738198	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Gata4	GATA-4	Mm, Rn, Cj	Up	No good d/t data; other NRs; evidence from receptor knockouts; evidence from dietary studies.	8455608; 0008007990; 7823950; 9986733	1
Gata6	GATA-6	Mm	Up	No good d/t data; induced in Gata4 −/− animals.	9256344	1
Gck	glucokinase	Rn	Up	No good d/t data.	1537314; 9220022; 10385401	1
Gfra1	GFRα-1	Rn	Up	No good d/t data.	0010751444	1
Gfra1	GFRα-1	Rn	Up	No good d/t data.	0010751444	1
Gjb3	connexin31	Rn	Dn	No good d/t data.	8806447	1
Gpcr13	H218	Mm	Dn	Suppressed during differentiation; no good d/t data.	9521849	1
Grasp	GRASP	Mm	Up	Induction (partially inhibited by cyclohexamide).	10828067	1
GRP	GRP	Hs	Up	No good d/t data.	0009468588	1
HCK	Hck	Hs	Up	No good d/t data.	8018933; 7512079; 8995234	1
HNF4A	HNF4α	Hs	vrs	No good d/t data; DR1 binding site, may be RXRE.	0009792724; 11027556	1
HOXC5	HOX3D	Hs	Up	Delayed induction; motif.	0001346761	1
Hoxd10	Hoxd-10	Mm	Dn	Shared regulatory silencing region that binds RARs and COUPs; no good d/t data; brings inappropriate expression when mutated in transgenics.	0008824591	1
Hoxd11	Hoxd-11	Mm	vrs	Shared regulatory silencing region that binds RARs and COUPs; no good d/t data; brings inappropriate expression when mutated in transgenics.	0008824591; 8792611	1
Hoxd13	Hox D13	Gg, Mm, Rn	Dn	No good d/t data.	7958440; 8792611; 10633866	1
HSD11B2	11β-HSD2	Hs	Up	Induction data at 6 hours "detectable" but not statistically significant.	10026096	1
Hsp86-1	HSP86, HSP90, HSPCA	Mm, Hs	vrs	Up or down during differentiation or apoptosis; regulation within hours in some cases; some differentiation controls; induction, at least, is thought to be independent of RA.	2806771; 1655528; 8612676; 11146166; 10718371	1
ICAM1	ICAM-1	Hs, Rn	Up	No good d/t data; late induction; functional binding site (and functional GAS sites); may be secondary to calmodulin, CaM kinase II, or other activity.	0001983003; 0001680399; 0007914515; 0007913411; 0007737364; 0007647034; 0007913411; 0010411124	1
ICAM3	CD50, ICAM-3	Hs	Up	No good d/t data for mRNA.	9497494; 11261782	1
Igf1r	IGF-IR	Rn	Up	No good d/t data; other NRs.	9048627	1
IGFBP2	IGFBP-2	Hs	vrs	No good d/t data.	0001382963; 0008640300	1
IGFBP3	IGFBP-3 (42–46kD)	Hs, Bt	vrs	Increase in most cases, but late decrease in Bt cells and at extreme dose/time points in Hs cells; associated with growth inhibition; specific ligands; early, rapid increase appears to require protein synthesis.	0001382963; 0008620495; 0008655603; 0009153223; 0010580834; 0010364250	1
IGFBP5	IGFBP-5	Hs, Rn	vrs	No good d/t data; generally decreased, but there may be an opposing increase in mRNA stability.	0007536661; 0008603611; 0009368678	1
IL6	IL-6	Hs	Dn	No good d/t data.	0010704257; 10785230	1
IL6R	IL-6R	Hs	Dn	Repressed during inhibition of proliferation; no good d/t data.	0002033252; 0007949175	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
INHBA	Activin A	Hs	vrs	No good d/t data.	1690989; 8774352	1
INS[ii]	proinsulin, insulin	Rn, Hs	Up	No good d/t data; there is a binding site in the uniquely Hs insulin-linked polymorphism.	1537314; 0007639703; 0009260196	1
ITGAL	CD11a	Hs	Up	No good d/t data; some differentiation controls.	7512079; 8774361	1
ITGAM	CD11b, MAC-1	Hs	vrs	Motifs; no good d/t data; some differentiation controls; specific ligands; other NRs.	0001347945; 7512079; 8025272; 0010704061; 11426618; 11339831	1
Itgav	Integrin α v, vitronectin receptor, CD51	Mm, Hs, Gg, Oc	Up	No good d/t data.	1939209; 7529599; 0008891892; 10520221	1
ITGB2	CD18	Hs	Up	No good d/t data; motifs.	2901419; 0001346252; 9337080; 10641747	1
Itgb4	β 4 integrin	Mm	vrs	No good d/t data.	0008287622; 0008875079	1
Jun	c-jun	Mm, Rn	Up	Rapid induction probably indirect; no good d/t data for suppression.	1963081; 0001851295; 0001310930; 8670250; 0009436983; 0010395942; 10479451	1
JUNB	jun-B	Hs, Mm	Up	No good d/t data; some differentiation controls; report (data not shown) of no RA effect under low-dose, short-term conditions.	0001667479; 2113273; 10479451	1
KAI1	CD82	Hs	Up	No good d/t data; induced during differentiation.	10630309	1
KCNH2	HERG	Hs	Up	No good d/t data; induced during differentiation.	9535729; 10413451	1
Kitl	c-kit ligand, stem cell factor, SCF	Mm, Hs	Up	No good d/t data.	7537079; 8874749; 9827903; 11205272	1
KLK7	SCCE	Hs	Dn	No good d/t data; mRNA data lacking.	8105613	1
KRT10	K10	Hs, Oc	Dn	No good d/t data; region that responds to RA identified; RAR (only) binding demonstrated; hexamer motifs.	1712634; 1375251; 1284070; 10542138	1
KRT13	K13	Hs, Oc, Rn, Mm	Up	No good d/t data; induced during differentiation, but some differentiation controls have been done; potential response element found not to be active; AP-1 regulation; specific ligands.	6205395; 2470609; 7687243; 0007525098; 8634095; 0008853895	1
KRT14	K14	Hs, Oc	vrs	No good d/t data; associated with differentiation (or inhibition of differentiation); upstream region responsible for RA effect (suppression) identified; in vitro RAR binding; AP-1 regulation; other NRs.	1700022; 1711202; 1375251; 0001281867; 10713177	1
KRT16	K16	Hs, Oc	vrs	During differentiation (or inhibition of differentiation); no good d/t data; upstream region responsible for RA effect identified.	2470609; 1711202; 1375251; 8977666	1
KRT17	K17	Hs	Up	No good d/t data; an upstream cluster of hexamers that can bind RAR (weakly) and suppress a CAT reporter has been found; other NRs.	1708801; 8977666; 0009326392	1
KRT2A	K2e	Hs	Dn	No good d/t data.	10692107	1
KRT3	K3	Hs, Oc	Dn	No good d/t data; upstream region responsible for RA effect identified.	1375251	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
KRT6A[ij]	K6	Mm, Hs	vrs	Recent duplications make it difficult to be sure which K6 gene is being studied in many papers; there appear to be significant difference between RA effects in vitro and in vivo, with up-regulation perhaps the most likely in vivo effect; both positive and negative motifs have been proposed; AP-1 regulation; no good d/t data in vivo.	2439609; 1711202; 0007682522; 0007545670; 0009326392; 9790766; 10887174	1
KRT7	K7	Hs	Up	No good d/t data.	2459129; 7505756	1
Laptm5	E3	Mm	Up	Rapid induction with high RA dose during differentiation in receptor-modified cells; no good d/t data for other cells; binding motif in region responsible.	0008839844	1
Lep	leptin, ob	Rn, Hs	Dn	No good d/t data; other NRs.	9659286; 9514867; 10381155; 10902807; 11479138; 11369444	1
Lgals1	14.5-D lectin, L-14	Mm, Hs, Rn	vrs	Differentiation associated; no good d/t data; no likely binding site found.	2555043; 8135794; 7954433; 9865605; 10760565	1
Lgals3	34-kD lectin, L-34	Hs, Mm	vrs	Differentiation associated; no good d/t data.	2555043; 2537146; 9865605	1
LGALS7	Galectin-7	Hs	Dn	No good d/t data.	7729568	1
LOR	Lorcrin	Hs	Dn	No good d/t data.	0001710017; 0002007780; 0001378029; 0007516397	1
LPA	apolipoprotein(a), apo(a)	Hs, Mf	Dn	No good d/t data; motif.	0009299449; 0009535807; 0010423167	1
Ltf	lactoferrin	Mm	Up	No good d/t data for RA; induction at 6 h with 9-cis; functional binding site; other NRs.	8113151; 0007623814; 0009828118; 0010505667	1
Mapk1	Erk2	Hs, Mm	Up[kk]	No good d/t data for mRNA; region at least partially responsible for RA effect identified; no apparent response element.	0009261178; 9679985; 10548434	1
MAX	max	Hs	vrs	Delayed induction in some studies; no change in others.	0008239509; 8134128; 8570225; 0009804832	1
Mc1r	melanocyte-stimulating hormone receptor	Mm, Hs	vrs	No good d/t data for mRNA; specific ligands.	0002265702; 0008168086; 9610863	1
Meox1	Mox1	Mm	Up	Late induction during differentiation.	7649373	1
MLN64[ll]	MLN/CAB1	Hs	Dn	Data not shown.	11146166	1
MME	CD10, NEP	Hs	vrs	No good d/t data; differentiation associated change; mRNA data lacking.	7528753	1
MMP13	MMP-13	Bt, Ss, Hs	vrs	No good t/d data.	10548534; 10429942	1
MMP2	gelatinase A	Hs, Gg	vrs	Early studies of enzyme activity (not mRNA) showed a decrease with high dose/long exposure conditions; later studies have shown late increases; upstream region conferring RA effect identified; probably indirect.	6279711; 8314305; 0008858101; 9664142; 9407317; 0010329442	1
MSX1	Msx-1	Mm, Hs, Gg	vrs	No good d/t data; motif in Mm not Hs; required binding region for induction in Hs; possibility of indirect action discussed.	0007916326; 0007866431; 0007650517; 0009045990; 9870533	1
Msx2[mm]	Msx-1	Gg, Cj	Dn	No good d/t data; whole animal evidence for RA effect.	0001685987; 0007650517; 0009045990	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Mt3	MT-3	Mm	Up	No good d/t data.	0010712606	1
MUC2	MUC2	Hs, Mf	vrs	Induced or inhibited, but no good d/t data; down-regulated following maintenance in retinoid-depleted culture; specific ligands.	0008179918; 0008997274; 0009870916; 0010024510; 11200589	1
Muc3	RMUC176	Rn	Up	No good d/t data.	0008297336	1
MUC5AC	MUC5AC	Hs, Rn	Up	No good d/t data; down-regulated after maintenance in retinoid-deprived culture; down-regulated in vitamin A deficient animals; specific ligands.	0008997274; 0009870916; 0010024510; 11200589; 0010634605	1
MUC5B	MUC5B	Hs	Up	No good d/t data; specific ligands; down-regulated in retinoid-depleted culture.	0009870916; 0010024510; 11200589	1
MYBL2	B-myb	Hs	Dn	Inhibition during differentiation; no good d/t data.	8598228	1
MYCL1	L-myc	Hs	vrs	No good d/t data for repression; induction may be rapid, but data unclear; induction blocked by cyclohexamide.	8123593; 8934535; 0010074929	1
NCF2	p67-phox	Hs	Up	No good d/t data; other NRs.	7578267; 9145335; 9447831	1
NDRG1	RTP, Drg1, Ndr1	Hs	Up	Induced during differentiation; no good d/t data.	0010395947	1
Ngp	F1	Mm	Up	Rapid induction with high RA dose during differentiation in receptor-modified cells.	0008839844	1
NME1	nm23-H1	Hs	Up	No good d/t data.	0010664247	1
NOS1	n-NOS, nNOS	Hs, Mm	Up	No good d/t data; induced during differentiation.	8929985; 10820202	1
Nos2	iNOS, NOS2	Hs, Rn	vrs	No good d/t data.	9635256; 0010772914	1
NOS3	eNOS	Hs	Dn	Down-regulated late in differentiation; no good d/t data.	9635256	1
Notch1	Notch-1	Mm	vrs	No good d/t data.	7615640; 11414696	1
NPY	NPY	Hs	Dn	No good d/t data; no motif found.	10854907	1
NR3C1	GR	Hs, Mm	vrs	No good d/t data (or d/t conditions not described).	6611455; 8339256; 7994082; 7854351; 11146166	1
NR4A2	Nurr1	Hs	Up	Data hard to interpret at early time points.	9070291	1
Nr6a1	GCNF, RTR	Hs, Mm	vrs	Transient induction followed by repression during differentiation; no good d/t data.	9134503; 0009563832; 10524192	1
Ntrk2	Trkb	Rn, Hs	Up	Induced during differentiation; no good d/t data.	7988722; 0008817533	1
NTRK3	TrkC	Hs	Up	Induced during differentiation; no good d/t data.	0008817533	1
Olr1^{nn}	LOX-1	Rn	Up	No good d/t data; rapid induction with high dose.	11181072	1
PCDH11	PCDHX	Hs	Dn	No good d/t data (but only a qualified claim is made in the paper).	11003707	1
PCDH22	PCDHY	Hs	Dn	No good d/t data.	11003707	1
Pdgfrb	PDGF receptor β	Mm	Up	No good d/t data.	2155144; 8180134	1
PECAM1	PECAM-1, CD31	Hs, Mm	vrs	Motifs; regulated during differentiation, but some controls have been done; no good d/t data.	0008955189; 9678720; 10830620; 11397002	1
PLAU	u-PA	Hs, Bt, Mm	Up	Induction by RA alone is slow or during differentiation; in other assays, RA appears ineffective by itself; no motif found; probably indirect.	0008491555; 0008385052; 0008404615; 0009560322; 0010361124	1
Pou4f2	Brn-3.2	Mm	Dn	No good d/t data for RA alone; inhibition rapid if cAMP is present.	0007904822	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Pou5f1	Oct-3, Oct-4, Oct3/4	Mm, Hs	vrs	No good d/t data; indirect repression through the upstream 1.2 kb region (no RARE motif); reporter induction through proximal RARE motif; indirect repression through proximal RARE motif; indirect repression through the upstream 2 kb region; other NRs.	0001915274; 0008289783; 0008289793; 0008152920; 0007823919; 0008832901; 0008631309; 0010512201; 0010692469	1
PPP3CA	calcineurin A	Hs	Up	No good d/t data; increased during differentiation; mRNA data lacking.	0009472103	1
PPP3CB	calcineurin B	Hs	Up	No good d/t data; increased during differentiation; mRNA data lacking.	0009472103	1
PRAM-1[oo]	PRAM-1	Hs	Up	No good d/t data in non-APL cells.	11301322	1
PRKCB1	PKC β 1	Hs, Rn, Mm	vrs	No good d/t data for mRNA; some differentiation controls; other NRs.	3422643; 1868031; 0001550338; 7961696; 9145335; 8732669; 9486851	1
PRKR	p68 kinase	Hs	Up	No good d/t data.	9393879	1
PRLR	PRL-R	Hs	Dn	No good d/t data for RA, but protein synthesis not required; specific ligands; rapid reduction with 9-cis.	0009888458	1
PRNP	PrP	Hs	vrs	No good d/t data.	7984043; 9473220	1
PTEN	PTEN	Hs	Up	No good d/t data; increased during differentiation but some controls have been done.	11290607	1
Ptgds	PGDS	Rn	Up	No good d/t data; contains a functional TRE that can act as an RARE in vitro.	0009582446; 9579690; 10650953	1
Ptgs1	Cyclooxygenase-1, COX-1, PGHS1	Mm, Rn, Hs	vrs	No good d/t data; induction (when it occurs) may be blocked by cyclohexamide.	7851378; 8967521; 8948503; 11299304	1
PTGS2	TIS10, COX-2, PGHS2	Hs, Mm, Rn	vrs	Modest induction using RA or platelet-activating factor alone; stronger induction with RA + PAF; binding region for RA + PAF activation contains no obvious motif, but no site for independent RA activity sought elsewhere in the gene; most studies use long incubation periods or high doses.	0008202477; 7851378; 8967521; 8948503; 9569236	1
Pth	Pth	Bt	Dn	No good d/t data; other NRs.	8377475; 0008113407	1
Pthr	Pthr	Rn, Mm	vrs	Delayed suppression; no good time data for induction; a DR1 is involved in induction but it is not sufficient; other NRs.	0001660713; 0009792954; 0010406468	1
PTK2	focal adhesian kinase, FAK	Hs	vrs	No good d/t data for mRNA; various non-transcriptional effects have been demonstrated.	9566310; 9590130; 9989778; 11369141	1
PTMA	ProT α	Hs	vrs	No good d/t data or data not shown.	8416800; 11146166	1
PTPN13	CD95	Hs	Dn	No good d/t data.	0009792441	1
Rai2	RAI2	Mm, Hs	Up	No good d/t data in Mm; Hs ortholog proposed only by analogy.	0008314004; 0010049581	1
RARRES1	TIG1	Hs	Up	No good d/t data; tested only with synthetic retinoids and specific ligands.	0008601727	1
RARRES2	TIG2	Hs	Up[pp]	No good d/t data; tested only with synthetic retinoids and specific ligands.	0009204961	1
Rbp2	CRBPII	Rn, Mm, Hs	Up	Induction controversial; motifs; no good d/t data; other NRs; possibly an RXR.RXR system; physiological relevance of RA questioned.	0001651173; 0008288643; 0009040537	1
RET	ret	Hs, Rn	Up	Induced during differentiation; no good d/t data; motif not found.	1766678; 7867726; 0009426223; 0009843911; 0010751444	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Rho	Rod-specific opsin, rhodopsin, Rh1	Mm, Dr, Dm	Up	No good d/t data; evidence from transgenics; evidence from dietary studies.	8681798; 8917585; 8994352; 10711716	1
RNPEP	aminopeptidase-B	Hs	Dn	Late increase; specific ligands.	0009049835	1
Rrg1	NN8-4AG	Mm	Up	Induction seems to occur rapidly but RA activity is blocked by protein synthesis inhibitors (9-cis activity is not); motif binds RAR.RXR and RXR.RXR; RA induction is probably at least partly indirect.	0008754834	1
RTN1	NSP-A	Hs, Rn	Up	No good d/t data.	9560466	1
RTN3	NSP-C	Hs, Rn	Up	No good d/t data.	9560466	1
Rxra	RXR α	Mm	Up[qq]	No good d/t data; other NRs; AP-1 regulation; message may be superinduced by cyclohexamide.	8269997; 8806431; 0008940178; 10403834; 0009717711	1
S100A8	MRP-8	Hs	Dn	No good d/t data; tested only with synthetic retinoids.	0010319995	1
SAG	arrestin	Hs, Mm	Up	No good t/d data; partially conserved motif; the Mm site binds RAR.RXR, but the Hs site is "inefficient"; the Mm site drives a heterologous reporter construct, but the Hs site (which is identical to the Bt site) does so only poorly; may be primarily COUP regulation.	0007708064; 9068616	1
SALF[rr]	SALF	Rn	Up	No good d/t data; rapid induction with high dose.	11181072	1
SCD	SCD	Hs	Up	No good d/t data; specific ligands.	11397803	1
SCYA2	MCP-1	Hs, Rn	vrs	No good d/t for RA but rapid induction with 9-cis; other NRs; suppression, when it occurs, is probably through AP-1.	7919389; 10479651; 11274229	1
SDC2	HSPG	Hs	Up	No good d/t data; increased during differentiation.	0009109513	1
SELL	L-selectin	Hs	Dn	No good d/t data.	0010704061	1
SERPINC1	antithrombin III	Hs	Up	No good d/t data; motifs are responsive to RXRs and THR; both T3 and RA induce in some systems.	8192147; 7531260; 0008761481	1
SERPINE1	PAI-1, plasminogen activator inhibitor 1	Hs	vrs	Induced during differentiation; short term studies report no effect.	0001905574; 1908141; 0001935958; 0008491555	1
SFTPC	SP-C	Hs, Rn, Mm	vrs	No good d/t data; possible mRNA stability effect.	0008404646; 0008944731; 9458794	1
Slc18a3	VAChT, vesicular acetylcholine transporter	Mm, Rn, Hs	Up	No good d/t data.	0007673184; 7616258; 0009237624; 10960602; 11306187	1
Slc2a2	GLUT 2	Rn	Up	No good d/t data; other NRs.	11494305	1
Slugh	Slug	Gg	Dn	No good d/t data; possibly indirect (TGFb2 signaling is involved in some cases).	9303343; 10864463	1
SOD2	MnSOD	Hs, Rn	Up	Late increase in protein; mRNA studies (using RA alone) are lacking.	10702810	1
Sox9	SOX9	Mm	Up	No good d/t data.	0010753864	1
SP100	Sp100	Hs	Up	No good d/t data in non-APL cells.	9393879	1
Sparc	SPARC, osteonectin	Mm, Gg	Up	Slow (or differentiation associated) induction; evidence from receptor knockouts.	1310471; 1584226; 8344389; 0008105479	1
SPN	CD43	Hs	Up	No good d/t data; motifs.	0009174604	1
SPRR1B[ss]	Spr1, cornifin	Hs, Mf, Oc	Dn	No good d/t data; during differentiation or growth arrest; specific ligands; other NRs.	1627333; 7769256; 8631988; 8950452; 10615070	1

continued

Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
SULT2B1[tt]	cholesterol sulfotransferase	Oc	Dn	mRNA studies lacking.	3477542	1
SUPT4H1	SUPT4H	Hs	Up	No good d/t data; increased during differentiation.	0009109513	1
TAF2S	TF CA150	Hs	Up	Data not shown.	11146166	1
TAT	TAT	Rn	vrs	Down-regulation, when it occurs, may be due to decreased mRNA stability; no good d/t data in either direction; other NRs.	1350056; 0008100575; 7734399; 0009449205	1
Tcf1	HNF-1 α	Mm, Hs	Up	Induced late in differentiation; RXR.RXR binding site.	2065662; 11027556	1
Tcf2	HNF-1 β	Mm	Up	Induced late in differentiation.	2065662; 7649373	1
TFAP2A	AP-2	Hs	Up	No good d/t data; upregulated during differentiation; no motif found up to −1.7 kb.	0003063603; 0002482225; 0008190633; 0008687453	1
TFRC	CD71, TfR	Hs	Dn	No good d/t data; mRNA stability may be involved in some systems; reduction during differentiation or growth arrest.	6573952; 2702640; 2404770; 9491782	1
TGFA	TGF-α	Hs, Mm	vrs	Regulated during differentiation (or growth arrest) but some controls have been done; upstream region conferring increased expression in vitro identified; no motif found; no good d/t data for RA but suppression can be rapid for synthetics; specific ligands; other NRs.	3215396; 2087681; 0001922084; 7536865; 8619789	1
TGFB1	TGF-β 1	Hs, Rn	vrs	No good d/t data; suppression (when it occurs) is probably through AP-1; no RARE found; other NRs; some differentiation controls have been done.	2909528; 1848114; 1334692; 0008264664; 0008557772	1
Tgfb2	TGF-β 2	Mm, Hs, Gg	Up	Induction but d/t borderline; possible mRNA stability effect; upstream region responsible for RA effect probably identified; no RARE found; evidence of other transcription factor changes following RA treatment; specific ligands; other NRs; some differentiation controls have been done.	2519621; 2084113; 1734039; 7654367; 0008557772; 0009153223	1
Tgm1	TGase K, TGase1	Oc, Hs, Rn[uu]	Dn	No good d/t data; decreased during differentiation; gene can be induced in vitro by RA; AP-1 and AP2 response elements; intronic negative DR5 alluded to.	2876994; 1356818; 1355099; 0008097865; 8537408; 10321835	1
Th	TH	Rn	Up	No good d/t data.	0008522994	1
Thrsp	S14	Mm, Rn	Up	No good d/t data; other NRs.	0001322331; 0007997231; 0010187832	1
Tnc	Tn-C	Mm, Rn, Hs	vrs	No good d/t for increase; rapid[vv] reduction possible; other NRs.	8528505; 10502285; 10078937; 10651229	1
TOP2A[ww]	TopoII	Hs	vrs	No good d/t data; generally studied in differentiating systems; probably indirect.	7954372; 9763571	1
TRA1	gp96	Hs	Up	No good d/t data.	9641219	1
Trpm2	Sgp-2, clusterin	Rn	Dn	No good d/t data; motif.	1350056; 0009547504	1
Tshb	TSH β	Rn, Mm	Dn	No good d/t data; dietary evidence; upstream binding region responsible for RA effect identified and found distinct from T3-responsive region; possibly 9-cis, RXR system; evidence from transgenics.	0007835286; 0009296372; 10880050	1
Tyr	tyrosinase	Mm	vrs	No good d/t data for mRNA; motifs that drive reporter induction identified; other NRs.	6260817; 2983883; 2107263; 0007620342	1
Ucp2	UCP2	Rn	Dn	No good d/t data.	10694373	1

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
VDR	VDR	Hs	Up	No good d/t data directly implicating an undiluted RA/RAR.RXR response; two regions drive reporters; autoregulation (potentially involving retinoid receptors); possibly indirect.	0009212063; 0010446999; 10919269	1
Vegfc	VEGF-C	Mm	Dn	No good d/t data.	11306173	1
VIM	vimentin	Hs, Mm	vrs	No good d/t data[xx]; late suppression (or induction) associated with differentiation or cell-cycle arrest; often observed primarily as a marker; no motif found; AP-1 involvement likely at least in some cases.	3467175; 2447102; 1352781; 0007790400; 0010631814; 11146166	1
VIPR1	VIP1 receptor, VIPR1, PACAP2 (Type II) receptor	Hs	Dn	No good t/d data; possibly a motif.[yy]	0007708752; 0009285932; 0009809989; 11150643	1
Wnt1	Wnt-1	Mm	vrs	No good d/t data; regulated during differentiation or development; region conferring RA effect in vitro isolated but its relevance to at least some in vivo systems has been questioned.	8441400; 7925022; 8626038; 9636087; 11414696	1
Wnt3a	Wnt-3a	Mm	Dn	No good d/t data, although inhibition may be rapid; evidence from receptor knockouts.	0009882496; 10473117	1
WT1	wt1	Hs, Mm	vrs	No good d/t data; regulated during differentiation, but some controls have been done.	8142654; 9040935	1
X17C[zz]	X17C	Xl	Up	No good d/t data.	0008861094	1
ZNF42	MZF-1	Hs	Up	No good d/t data; differentiation associated; region containing motifs can drive a reporter.	0001860835; 0008845378	1
Znfn1a1	Ikaros	Mm	Up	No good d/t data.	11092879	1
ADAMTS4[aaa]	Aggrecanase	Bt, Rn, Hs	Up	No good d/t data; many papers measure enzymatic activity only, so the gene(s) responsible are not clear; probably indirect.	7531436; 0007852317; 8603731; 10395742; 10936450	0
Adh1	Adh-1	Mm	–	No mRNA effect; no site found; possibly based on early confusion about the RA inducibility of the Hs gene previously known as ADH1.	0008018987	0
Afp	α-fetoprotein	Rn, Hs	Up	Delayed induction during differentiation; functional binding sites; some question about whether regulation is primarily by RXRs; other NRs; probably indirect although the –6327 site may mediate direct regulation.	0001379951; 0007528016; 0007525384; 0007512261; 0008945636; 0009792724; 0010025664	0
Agc	Aggrecan	Bt, Rn, Hs	vrs	Probably indirect.	8492742; 9779827; 0010753864	0
Agtr1a	angiotensin II type 1 receptor	Rn	Dn	Indirect.	0010642314	0
AHR	AhR	Hs	Dn	A normal increase during differentiation is inhibited by long-term, continuous RA; short-term exposure during differentiation has no effect; some differentiation controls; probably indirect.	8950195	0
Arhgap5[bbb]	p190 GAP-associated protein	Rn	Up	Dose and time unclear, but protein synthesis required; probably indirect.	10667225	0
ARNT	ARNT	Hs	Dn	A normal increase during differentiation is inhibited by long-term, continuous RA (1 μM); short-term RA exposure during differentiation has no effect; probably indirect.	8950195	0
Atp1a3	Na,K-ATPase	Rn	Up	No good d/t data; probably indirect.	0009925375	0
BGLAP	osteocalcin	Hs, Rn, Mm	Up[ccc]	Conflicting gene modulation data; motif (VDRE/AP-1) drives heterologous promoter and binds RAR; induction, when observed, is probably indirect, possibly through the induction of Srebf1 or through VDR.RAR or VDR.RXR dimers.	0002159384; 1820970; 0008395017; 0008466530; 8382933	0
BLR1	Blr1	Hs	Up	Induction during differentiation but some controls; probably indirect.	10640427; 11211936	0
Bmp7	BMP-7	Gg, Hs	Up	Probably indirect (protein synthesis).	0009621899; 11032177	0
BTK	BTK	Hs	–	Motifs; no other evidence.	7927535	0

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Cal1[ddd]	CT, CGRP	Rn	Dn	Long treatment required; probably indirect.	0001569964; 0008413210; 8061571; 9057102	0
CCND3	cyclin D3	Hs, Mm	Dn	Reduced during growth arrest or differentiation; no good d/t data; no significant change reported (but data not shown) in one short-term mRNA study; evidence from receptor knockouts; probably indirect.	9260897; 0009806360; 10479451	0
Cdrap	CD-RAP	Bt, Mm, Rn, Hs	Dn	Indirect.	8621736; 9097023; 0009478951; 10320524	0
Col1a1	α 1(I) collagen	Mm, Rn, Hs	vrs	No good d/t data; other NRs; putative response element (a DR37 or a single hexamer) shown to be spurious; probably indirect.	3919954; 2915650; 0010729205; 2019574; 7918630; 7988442; 0009077477	0
Col1a2	α 2(I) collagen	Mm, Hs, Gg	vrs	No good d/t data; regulation does not seem to be through the identified motif (an unusual DR6); probably indirect.	3919954; 2987306; 1429872; 0010729205; 3653521	0
Col4a1	collagen IV (α 1), α 1(IV)	Mm, Hs, Bt	Up	No good d/t data; now thought to be indirect.	0002981185; 0002842348; 0002327791; 9451807	0
COL7A1	type VII collagen	Hs	Dn	No good d/t data; probably indirect.	9130597	0
Cp	ceruloplasmin	Rn	Up[eee]	No good d/t data; probably indirect (protein synthesis).	11181072	0
CRH	corticotropin-releasing hormone	Hs	Up	Indirect.	0010446900	0
CSF1R	c-fms	Hs	Up	Induction; no motif found in the region sufficient to impart RA inducibility; regulation attributed to AP-1.RAR.	0010554038	0
CTNNB1	β-catenin	Hs	vrs	Probably indirect.	8754749; 9414661; 10607566	0
CTSD	cathepsin D	Hs	Up	Probably indirect.	0007547509; 0008639464	0
CTSG	cathepsin G	Hs	Dn	Probably indirect.	8558945	0
CTSL	cathepsin-L	Rn	Up	Delayed induction; probably indirect (protein synthesis).	11181072	0
Cyp7a1	CYP7A	Rn[fff], Mm	vrs	No good d/t data; largely transfection, cotransfection, or dietary studies; conserved binding motif, but RA response may not be conserved; many other NRs; probably indirect (possibly through RXR.LXR and FXR.RXR).	8656080; 0008753804; 0008831673; 0009799805; 10968783	0
DEFA1	promyelocytic defensin-1	Hs	Up	Probably indirect.	0009535850	0
EDN1	ET-1	Hs	Dn	Probably indirect.	0009809984	0
ENPP2	ATX	Hs	Up	No good d/t data; requires protein synthesis; probably indirect.	11346880	0
Etnmg1	ETnMG1	Mm	Dn	Repression probably due to decreased mRNA stability.	8863732	0
Evx2	evx2	Dr, Mm	vrs	No good d/t data; probably indirect (Hoxa-1).	0009879709; 10942599	0
FACL2	acyl-coA synthase, ACS	Hs, Rn	Up	Probably indirect; specific ligands.	0010777552	0
Fasn	FAS	Rn	vrs	No good d/t data; other NRs; probably indirect.	6164877; 7537465; 0009191201; 9070250; 9510066; 0009770474	0
Fbp1	Fru-1,6-P2ase, FBPase	Mm, Hs	Up	Slow induction during differentiation; no RA regulation seen in whole animal study; binding motif (DR3) is also a VDRE; other NRs; probably indirect.	9202079; 9556208; 0010731708	0
Fgf1	acidic FGF	Mm	Up	Induced during differentiation; indirect.	2544608	0

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Fgf2	bFGF, basic FGF	Mm, Cf, Bt	vrs	No good d/t data; differentiation associated; specific ligands; probably indirect.	2544608; 10607884; 11230116	0
Fgf3	FGF-3	Mm	Up	Induced during differentiation; indirect.	8265348; 10358083	0
FGF4	K-FGF	Hs, Mm	Dn	Suppressed during differentiation; indirect.	2009969; 0001723621; 8844688	0
Fosl1	Fra-1	Mm, Hs	Up	Induction, probably indirect.	10217407	0
FSCN2	Retinal fascin	Hs	–	Motif; no other evidence.	10783262	0
Gja1	connexin43, Cx43	Mm, Hs, Rn	Up	Other NRs; probably indirect.	0002177604; 0001327514; 7954877; 0007720192; 8941706; 9428648; 10192774	0
GRIN1	NMDAR1	Rn, Hs	Up	No good d/t data; probably indirect.	8866697; 9219948	0
Grn[ggg]	Epithelin	Rn	Up	No good d/t data; probably indirect (protein synthesis).	11181072	0
Gsc	goosecoid	Xl, Dr, Mm	Dn	No good d/t data; generally studied in teratogenicity experiments; specific ligands; no motif found; probably indirect.	1684739; 7605750; 9207233; 10512193	0
Gsta4	GST 5.7	Mm	Dn	Decreased during differentiation[hhh]; no good d/t data; probably indirect.	0009806360	0
H19	H19	Hs	Up	No good d/t data; delayed induction; probably indirect.	0009720909	0
Ha1r[iii]	Hoxa-1 Regulating	Mm	Up	Probably indirect (Hoxa-1).	0010672899	0
HBP17	FGF-BP	Hs, Rn	Dn	No good d/t data; probably indirect.	8702908; 10831072; 11077050	0
HGF	hepatocyte growth factor	Hs	Dn	Rapid repression; specific ligands (in late-measurement studies); other NRs; probably indirect.	0009886825; 11223164	0
Hoxa5	Hoxa5	Mm	Up	Probably indirect.	0010679930	0
Htf9c	Htf9-c	Mm	–	In some cell types, RAR.RXR (as well as other RXR-containing complexes) bind to a DR1; no other evidence of RA regulation either way.	0009417108	0
IBSP	bone sialoprotein (BSP)	Hs	–	Motif; other NRs, but no direct evidence of RA involvement.	0008061918; 0008702678; 10900268	0
Ifng	IFN-γ	Mm, Hs	Dn	No good d/t data for RA alone; other NRs; probably indirect.	1907993; 0008900159; 0009808170	0
IGF2	IGF-II, IGF-2	Hs	vrs	Early induction, but the significance of the increase is not clear; mRNA decrease in some studies seems to be a late effect, probably indirect (possibly IGFBPs).	0001375906; 0008364891; 0007527270; 0009258346; 0009688937	0
IGFBP4	IGFBP-4	Hs, Ss	vrs	Generally studied during growth regulation; no good d/t data; other NRs; probably indirect (protein synthesis).	0007686749; 0008640300; 0008536624; 0010601968	0
Ihh	Ihh	Mm, Oc	Up	Rapid induction but probably indirect.	9242425; 11281644	0
Il12b	IL-12 p40	Mm	Dn	Probably indirect (NFκB); specific ligands.	10075655	0
IL2	IL-2	Hs	vrs	No good d/t data; specific ligands in some inhibition studies; probably indirect.	0001652063; 0007931079; 9130512	0
IL8	IL-8	Hs, Mf	Up	Probably indirect.	0007763262; 0010745031	0
Itga8[jjj]	α-8 integrin	Rn	Up	Delayed induction during differentiation; probably indirect (protein synthesis).	11181072	0
Itgb5[kkk]	β 5 integrin	Gg	Dn	Indirect.	0009893063	0
Itgb7	β 7 integrin	Mm	–	Motifs; no other evidence.	0008318458	0
IVL	involucrin	Hs	vrs	Differentiation associated; no good d/t; probably indirect (AP-1 in at least some systems).	3858572; 2463259; 0001378029; 0008853895; 0008959344	0

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Gene Table—*Continued*

Symbol	Name in REFS	Spp	Dir	Summary	Ref PMIDs	Cat
Kpna2[lll]	importin α	Rn	Up	No good d/t data; probably indirect (protein synthesis).	11181072	0
KRT1	K1	Hs	Dn	No good d/t data; there may be significant differences between in vitro and in vivo RA effects; AP-1 regulation; differentiation associated; probably indirect.	2440897; 7522960; 0007516397; 0007510286	0
KRT18	K18, EndoB	Mm, Oc, Hs	Up	Induced during differentiation (or growth inhibition), rapidly in some cell types; some proliferation controls have been done; specific ligands; probably indirect (AP-1, Ets2); RA-sensitive Alu in Hs gene.	1691021; 7514938; 0007526151; 0007667273; 8641545	0
KRT19	K19	Hs	Up	Probably indirect (mRNA stability and AP-1 have been discussed); other NRs.	6205395; 2414289; 0007505782; 0007506253; 8751982; 11026574	0
KRT4	K4	Hs	vrs	No good d/t data; probably indirect.	0008687453; 8751982; 8950195; 10692107	0
KRT8	K8, EndoA	Mm, Hs	Up	Induced during differentiation (or growth inhibition); induction rapid in some cell types; some proliferation controls; AP-1 regulation; specific ligands; probably indirect.	1691021; 7505756; 8641545; 11010814	0
Ldhb	LDH-B	Rn	Up	No good d/t data; during arrest or differentiation; probably indirect (protein synthesis).	11181072	0
lef1	lef1	Dr	Dn	Probably indirect.	11002347	0
Lmna	lamins A/C	Mm, Hs	vrs	Probably indirect.	1282809; 1281113; 0009828104; 0010694499	0
Lpl	LPL	Mm	–	No change in mRNA (but enzymatic activity decreased).	0001610391	0
Mbp	MBP	Rn	Up	Appears to be primarily a T3/TR system; may be activated by 9-cis/RXR in some cases.	0009889331	0
MMP1	collagenase	Hs, Oc	Dn	Indirect; several mechanisms proposed.	0002178224; 0001320254; 0007615643; 0008908199; 0009111003; 9537651; 0009888461	0
MMP3	Stromelysin	Rn, Hs, Bt, Ss	vrs	No good t/d data; possible differences between species in long term exposure; probably indirect.	0002176152; 10548534; 10429942	0
MMP9	92-kD gelatinase, MMP-9	Hs	Dn[mmm]	Probably indirect.	9565574; 9824620; 10646501; 11172606	0
MPO	MPO	Hs	vrs	Differentiation associated; no good d/t data; a binding site in the Alu includes an allelic Sp1 site that may be important in APL; probably indirect.	6321491; 0008662930; 0009326240	0
MST1	HGFL	Hs	Dn	No good d/t data; region responsible for RA inhibition identified; probably indirect.	0009886825	0
MUC4	MUC4	Hs	Up	No good d/t data; probably indirect (TGFb2 involved in some systems).	10938282	0
MYB	c-myb	Hs, Gc, Rn, Mm	vrs	Rapid induction by RA appears to be indirect; there is evidence of physical an RAR.MYB interaction (and mutual antagonism); inhibition appears to be indirect, but RXR-dependent.	3380093; 0001323819; 8670250; 8598228; 0009576918; 0009714701; 0010614788	0
NORPEG	NORPEG	Hs	Up	No good d/t data; probability of indirect mechanisms discussed.	11042181	0

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Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Nppa	ANF, ANP	Rn, Hs[nnn]	Dn	No good d/t data; during growth or hypertrophy control; other NRs; responsive upstream region isolated; specific ligands; probably indirect.	7611385; 0007638203; 8601621	0
NPY1R	Y1R	Hs	Dn	Rapid decrease; at least partly due to decreased message stability; slowed by cyclohexamide; probably indirect.	8978705; 9165460	0
Nr2f1	COUP-TF1	Mm	Up	No good d/t data; delayed induction during differentiation in one study, but with some controls; probably indirect.	0008314004; 0007947324; 0008804707; 9831119	0
Nr2f2	ARP-1, COUP-TF II	Mm	Up	No good d/t data; delayed induction during differentiation in one study; some differentiation controls; probably indirect.	0007947324; 0008804707	0
NR4A1	NGFI-B, Nur77	Hs	Dn	The data from short-term work is hard to interpret but the level of repression is probably insignificant; longer-term work suggests an AP-1 intermediary.	9070291; 10772826	0
NRGN	RC3	Rn	Up	Evidence of induction and receptor binding in early papers; no longer thought to be directly regulated by RA.	0007898304; 0007730337; 0009282911	0
Ntrk1[ooo]	TrkA	Rn, Gg, Hs	vrs	Upregulation in most papers; various differentiation controls have been used; mRNA stability may be involved; probably indirect.	7988722; 0007496626; 7559588; 0008817533; 10784405	0
OAS3[ppp]	100-kD OAS	Hs	Up	No good d/t data; reporter induction; motif; probably indirect.	0006435868; 2472992; 1677311; 11112351	0
ODC1	ODC	Hs	Dn	Probably indirect (protein synthesis), but the mRNA is very short-lived.	2478272; 2295835	0
OPRD1	DOR	Hs, Rn	Up	No good d/t data; probably indirect.	7932156; 8866697; 9219948	0
Oprk1	KOR	Mm	vrs	Indirect.	11092879; 11222649	0
OPRM1	MOR	Hs	Up	No good d/t data; probably indirect.	7932156; 9219948	0
Otx2	Otx2	Mm, Xl, Gg	Dn	Promoter region conferring RA response identified, but no motif found; specific ligands (TTNPB repressed but TTNPB plus LG69 had no effect); physiological relevance of RA pathway questioned; expression normal in Aldh1a2 -/- embryos; probably indirect.	7607086; 7748789; 7720578; 7669695; 9006080; 10192400	0
PDGFA	PDGF-A	Hs, Mm	Dn	No good d/t data; down-regulated during differentiation; probably indirect.	3215396; 2155144; 8274456	0
Pdgfra	PDGF receptor α	Mm, Hs	Up	Region responsible for RA effect identified; no motif found; probably indirect (GATA-4 and Oct-4 have been discussed).	2155144; 2174116; 7731723; 0008552100; 0008662786	0
Pitx2	Pitx2	Mm	Up	Probably indirect.	0010331971; 11245568	0
Pk3	PK	Mm	Dn	Isoform M_2 decreased during differentiation[qqq]; no good d/t data; probably indirect.	0009806360	0
Plp	PLP	Rn	Up	Indirect.	1374482; 7503983	0
Ppara	PPAR-α	Mm	Up	No good d/t data; probably indirect.	0010509805	0
Pparg	PPAR-γ	Mm	Up	No good d/t data; probably indirect.	0010509805	0
Pthlh	PTHrP	Mm	Up	Probably indirect.	9280059	0
Ranbp1	Htf9-a/RanBP1	Mm	–	RAR.RXR binding to a DR1 in some cell types; the site is required for maximal transcription; no other information about RA regulation.	0009417108	0
RB1	Rb	Hs	Vrs[rrr]	No good d/t data; probably indirect.	0001511698; 8502481; 7889981	0
Rbbp7[sss]	pRbAp46	Rn	Up	Dose and time unclear, but protein synthesis required; probably indirect.	10667225	0
Rex2	Rex-2	Mm	Dn	Suppressed late in differentiation[ttt]; evidence from receptor knockouts; probably indirect.	0009806360	0

continued

Gene Table—*Continued*

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
Rex3	Rex-3	Mm	Dn	Suppressed late in differentiation[uuu]; evidence from receptor knockouts; probably indirect.	0009806360	0
Rsdr1[vvv]	RDH, retSDR1	Rn	Up	No good d/t data; probably indirect (protein synthesis).	11181072	0
Rxrg	RXR γ	Mm, Rn, Hs, Gg	Up	Many studies find no RA regulation; no good d/t data; other NRs; binding motif (prefers RXR.RXR); induction blocked by cyclohexamide; probably indirect.	8269997; 8294402; 0009006910; 9075714	0
Sara[www]	Sar1a	Rn	Up	Dose and time unclear but protein synthesis is required; probably indirect.	10667225	0
Sat	SSAT	Ss, Bt, Rn	Up	No good d/t data; probably indirect (protein synthesis).	9780334; 9831819; 11181072	0
Serpinh1	J6 serpin	Mm	Up	Promoter region responsible for RA effect identified; indirect (probably through GATA-4).	0002981185; 0002842348; 0001639782; 7717974	0
Shmt1[xxx]	shmt	Mm	Dn	Indirect; post-transcriptional.	8863732	0
SLA	SLAP	Hs	Up	Probably indirect.	0009020066; 11179692	0
SLC27A1	FATP	Hs, Rn	Up	Probably indirect; specific ligands.	0010777552	0
Slc2a3	GLUT 3	Mm	Dn[yyy]	Decreased during differentiation; no good d/t data; probably indirect.	0009806360	0
SLC9A1	Na+/H+ antiporter	Hs, Mm	Up	No good d/t data; induced during differentiation; probably indirect.	1315322; 8388633; 7737975; 11168401	0
Slc9a2	NHE-2	Rn	–	Motif; no other evidence.	0009804979	0
Sod1	Cu/Zn superoxide dismutase	Ss, Hs, Mm	Dn	The decrease during differentiation is probably indirect (Hoxa-1); other studies have reported no change in SOD activity.	2151307; 8389401; 10942599	0
TERT	hTERT	Hs	Dn	No good d/t data; late suppression during differentiation; some differentiation controls; probably indirect.	8709642; 10613358; 10786671	0
THYb10[zzz]	Thymosin β 10	Rn, Hs, Mm	Up	Probably indirect.	1846397; 0002059565; 0001315216; 8925915	0
TIMP1[aaaa]	Timp-1	Hs	Up	No good d/t data; probably indirect (protein synthesis).	0002824558; 1661164; 9664142; 10866818	0
TNFRSF6	CD95, Fas	Hs	Up	No good d/t data; some differentiation controls; specific retinoids; probably indirect.	0009792441; 10733098; 11103825	0
Tnfsf6	FasL, CD95 ligand	Mm, Hs	Dn	No good d/t data for RA; specific ligands; other NRs; probably indirect (NUR77).	0007565709; 0009792441; 11465095	0
Trh	preprothyrotropin-releasing hormone	Mm	Dn	Indirect.	0010537125	0
Trp53	p53	Mm, Hs	vrs	Regulated during differentiation (or other phenotypic change); specific ligands; probably indirect, several mechanisms discussed.	6287239; 2414665; 8484778; 7930673; 10327056; 11420666; 11526443	0
Vcam1	VCAM-1	Mm, Hs, Rn	Up	No good d/t data; probably indirect (protein synthesis).	7533155; 9022083; 11181072	0
VEGF	VEGF/VPF	Rn, Hs, Cp	Dn	Rapid inhibition; specific ligands; AP-1 sites identified; probably indirect.	8200985; 9804359; 0010617662; 10964585	0
VIP	VIP	Hs	Up	Slow increase during differentiation but some controls have been done; increase is prior to morphological change; probably indirect.	0001319016; 0007925107; 0009285932	0
Zfp42	Rex-1	Mm	Dn	No good d/t data; differentiation associated; probably indirect.	0002511439; 0008474450; 0009528758	0

[a] Hs only for apparent conservation of binding site.

[b] The function of the 5′ site remains problematic; in PMID 0007916164 it appears to be a negative element, but the authors offer alternative explanations; in PMID 0007831296 it appears to be positive, but requires a tissue-specific retinoid-dependent cofactor.

continued

[c] Called 17-β-HSD-II in PMID 0008013376.
[d] The Hs symbol and name is POU1F1: POU domain, class 1, transcription factor 1 (Pit1, growth hormone factor 1).
[e] It is not yet clear exactly what the active binding site(s) are. Orthologous control regions are definitely involved and there appears to be some degree of conservation in Mm and Rn.
[f] Rn promoter in Hs cells.
[g] See PMID 0010194513 for a brief review of RA and ApoA1.
[h] The sequence appears to come from chromosome 7 but may contain a large Line1 repeat.
[i] Figure 2B in PMID 0001700780 appears to show a data point which would satisfy our dose and time criteria. However, it is not discussed in the text.
[j] This is the Hs name. There is a 94% aa identity to rabbit OC2 according to OMIN.
[k] There has been some controversy about the metabolic products of the the gene(s) in different spp; also, Cyp26 may not be RA-inducible in some cells that nevertheless metabolize RA.
[l] It is not clear whether Stra7 and Gbx2 are different genes. The GB entries are virtually identical where they overlap. The Stra7 clone is effectively included in the Gbx-2 RefSeq.
[m] The allelic variant GGTP1*C used in some studies is thought not to effect the generality of the RA work.
[n] Site from 2nd intron and flanking exon more or less conserved in Hs, Rn, Ma, Oc, Cf, Ss, Gg, and cats.
[o] Mm symbol and name.
[p] This assumes the Ggal gene RIHB (NCBI GI 434357) is orthologous to Mm Mdk.
[q] Interim Hs name; no Rn assignment.
[r] Rn data mentioned but not shown.
[s] The ability of RA to counteract estrogen through the OTX ERE is discussed in PMID 0001655807, and the ERE was used as a "negative RARE" in combination with transfected RARa, JUN, and ER.
[t] The figure demonstrating this is not easy to interpret.
[u] Rn promoter and exogenous RAR/RXR in Hs cells.
[v] Interim symbol and name.
[w] Earlier papers that do not distinguish enzyme forms are not considered here.
[x] Interim symbol and name.
[y] Interim symbol and name.
[z] Mm symbol and name.
[aa] Name by analogy to mammalian crystallins.
[bb] We assume DDX1 is the gene in question; there are other DEAD box proteins, of course, but the paper does not clearly distinguish them.
[cc] Interim symbol and name.
[dd] To us, the figure showing rapid induction is unconvincing; no dose is given, either.
[ee] It is not clear what has happened between times 0 and 24 hours in Figure 2b of PMID 0010674883.
[ff] It is not clear what has happened between times 0 and 24 hours in Figure 2b of PMID 0010674883.
[gg] F3 is frequently studied in APL cells because it is thought to be involved in the pathology of the disease. Some of the work cited here is in APL lines.
[hh] Interim symbol and name.
[ii] Probably Ins2 in Rn.
[jj] KRT6A seems to be the predominantly expressed K6 gene in Hs; the paper cited for Bt (in whom there are 3 K6 genes) is concerned with K6b; the motifs in PMID 0009326392 BLAST identically (and with the same single mismatch) to the provisional refseqs for both Hs K6 genes, KRT6A and KRT6b; the Hs AP-1 work is on K6b.
[kk] Most investigations so far have dealt with Erk activation, not message induction.
[ll] Interim symbol and name.
[mm] The gene studied now appears to be the ortholog of Msx2, not Msx1 (as thought at the time).
[nn] Mm symbol and name.
[oo] Interim symbol and name.
[pp] Induced in 3-dimensional systems but not in 2-dimensional cultures of keratinocytes and fibroblasts.
[qq] The effects of 9-cis, which are not covered here, have also been investigated. Cf. PMID 10403834 and PMID 0009717711 for example.
[rr] Interim Hs symbol and name.
[ss] SPRR1A, SPRR2, and SPRR3 are covered in some of these papers; the RA situation is basically the same.
[tt] Probable name, see PMID 11416019.
[uu] Hs DNA in Rn cells.
[vv] Suppression at 8 hours (100 nM) is discussed in PMID 10502285, but Figure 1B suggests it is significant by 4 h.
[ww] Both TOP2A and TOP2B have been studied, but most of the RA work has concentrated on 2A.
[xx] The statistical significance of a slight decrease at 6 h in PMID 11146166 is not clear.
[yy] An RARE half site seems to be marked in a GenBank entry but neither the site nor RA is mentioned in the associated paper.
[zz] No official name or symbol; no curated orthologs.
[aaa] Aggrecanase-1 is an alias for ADAMTS4; some of the papers listed here cover ADAMTS5 (aggrecanse-2) as well. MMP3 and MMP13 (q.v.) may also be involved.
[bbb] Probable Mm ortholog; no Rn assignment.
[ccc] High consentrations of retinoic acid inhibit BGLAP induction by vitamin D, but a well-characterized AP-1 response element is contained in the VDRE. Some experiments found neither induction nor suppression by RA alone.
[ddd] There is no evidence that RA has different effects on the expression of the splicing alternates, calcitonin and calcitonin gene related peptide (CGRP).
[eee] Several studies have also been done in Rn and Hs using 9-cis. No good d/t data there, either.
[fff] Rn sequences in HepG2 cells; no RA regulation seen in hamster.
[ggg] Interim symbol and name.
[hhh] An altered transcription rate could not be shown in nuclear run-on experiments (although controls worked as expected); this was attributed to the highly stable mRNA.
[iii] Symbol and name pending.
[jjj] Interim symbol and name.
[kkk] Mm symbol and name.
[lll] Interim symbol and name.

continued

mmm Very long exposure may induce expression in some systems.
nnn Promoter constructs from Hs used in Rn cells.
ooo Mm symbol and name.
ppp The older articles study enzyme activity without distinguishing OAS1, -2, and -3.
qqq An altered transcription rate could not be shown in nuclear run-on experiments (although controls worked as expected); this was attributed to the highly stable mRNA.
rrr Many studies have looked at mechanisms by which RA influences RB phosphorylation. They are not included here.
sss Interim symbol and name.
ttt An altered transcription rate could not be shown in nuclear run-on experiments (although controls worked as expected); this was attributed to the highly stable mRNA.
uuu An altered transcription rate could not be shown in nuclear run-on experiments (although controls worked as expected); this was attributed to the highly stable mRNA.
vvv Interim Mm symbol and name.
www Probable Mm ortholog; no Rn assignment.
xxx It is not clear whether the repressed gene was Shmt1 or Shmt2.
yyy An altered transcription rate could not be shown in nuclear run-on experiments (although controls worked as expected); this was attributed to the highly stable mRNA.
zzz Interim symbol and name.
aaaa Studies do not necessarily distinguish members of the TIMP family.