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ULOGA RETINOIČNE KISELINE U REGULACIJI TRANSKRIPCIJE GENA

Romana Popović, 6628/N

Sažetak: Retinoidi, uključujući retinoičnu kiselinu, su spojevi odgovorni za regulaciju normalnih bioloških procesa poput embrionskog razvoja, diferencijacije stanica, metabolizma, reprodukcije, vida. All-trans retinoična kiselina (aTRA) kao glavna signalna molekula i ligand regulira transkripciju gena vežući se na retinoidne receptore (RAR i RXR) unutar stanične jezgre. Vezanje liganda uzrokuje konformacijsku promjenu receptora, korepresorski proteini su potom disocirani što omogućava regrutaciju koaktivatora. Posljedično, receptor se veže na tzv. element odgovora retinoične kiseline (RARE) smješten u promotorskoj regiji ciljnih gena i tako pozitivno ili negativno regulira transkripciju. Također, često se u proces regulacije transkripcije ubrajaju fosforilacija i ubikvitin-proteosom sistem kao daljnji procesi. Identifikacijom gena koji sadrže RARE u promotoru i analizom funkcija proteina kodiranih tim genima utvrđeno je da je značajan udio uključen u proces diferencijacije stanica, kao i metabolizam. No, potrebna su daljnja istraživanja kako bi se opisale i druge uloge retinoida u staničnom metabolizmu kojih očito ima još.

Ključne riječi: receptor, retinoična kiselina, geni, transkripcija

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ROLE OF RETINOIC ACID IN REGULATION OF GENE TRANSCRIPTION

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Abstract: Retinoids, including retinoic acid, are compounds responsible for normal biological processes such as embrionic development, cell differentiation, metabolism, reproduction, vision. All-trans retinoic acid (aTRA) as the main signal molecule and ligand regulates gene transcription by binding retinoid receptors (RAR and RXR) within cell nucleus. Binding of the ligand induces conformational change of receptor, corepressor proteins are then dissociated enabling coactivators to recruit. Consequently, receptor binds to so called retinoic acid response element (RARE) located in the promoter region of target genes and thus up-regulates or down-regulates transcription, respectively. Phosphorylation and ubiquitin-proteasome system are also involved as further processes in regulation of transcription. By identifying genes containing RARE in its promoter and analysing functions of encoded proteins, it has been found that majority is involved in cell diferentiation and metabolism. Still, further studies are needed to describe other roles of retinoids in cell metabolism which are apparently present.

Keywords: receptor, retinoic acid, genes, transcription

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1 UVOD

Retinoidi, skupni naziv za prirodne i sintetske derivate vitamina A, reguliraju kompleksne biološke funkcije poput embrionskog razvoja, organogeneze, formiranja kostiju, metabolizma, vida i reprodukcije. Na staničnom nivou, ove regulacije su postignute, između ostalog, modulacijom proliferacije, diferencijacije i apoptoze.

Preciznije govoreći, all-trans retinoična kiselina (aTRA) ponašajući se kao transkripcijski modulatorni faktor, regulira transkripciju gena povezanih s tim normalnim staničnim procesima. Dakle, retinoična kiselina ima važnu ulogu u organizmu budući da je ekspresija velikog broja gena upravo regulirana nuklearnim receptorima za koje retinoična kiselina predstavlja ligand (Al tanoury et al., 2013).

Počevši s istaživanjima kasnih 1960- ih , s vremenom je narastao velik interes za opisivanjem utjecaja diferencijacije i tumor-potiskujućih funkcija retinoida na genetski mehanizam. Koliko se dosad zna, Blalock i Gifford su bili prvi koji su pružili dokaz o povezanosti retinoida i genske aktivnosti 1977. godine kad su pokazali da sinteza interferona može biti potisnuta na transkripcijskom nivou od proteina induciranog all-trans retinoičnom kiselinom (Blalock i Gifford, 1977).

Dosad je identificirano više od 500 gena koji su definirani kao ciljni geni signalnog puta retinoida, odnosno retinoične kiseline. Pregledni članak Balmera i Blomhoffa iz 2002. godine je obuhvatio dotad objavljene studije i tablično su popisana i klasificirana 532 različita gena s obzirom na vrstu regulacije transkripcije, bilo direktnu ili indirektnu, te jačinu dokaza (Balmer i Blomhoff, 2002).

U nastavku ovog rada, pojašnjen je mehanizam regulacije transkripcije putem retinoidnih receptora, jednih od najvažnijih faktora, uz naravno retinoičnu kiselinu kao početnu signalnu molekulu te je tablično prikazan popis gena koji sadrže funkcionalno vezno mjesto za retinoičnu kiselinu.

2 RETINOIDI

Pojam retinoidi obuvaća i spojeve strukturno slične vitaminu A, kao i one koji pokazuju biološku aktivnost vitamina A. Osnovna struktura hidrofobne retinoidne molekule se sastoji od cikličke krajnje grupe, polienskog bočnog lanca i polarne krajnje grupe. Konjugirani sustav formiran od naizmjeničnih dvostrukih ugljikovih veza (C=C) u polienskom bočnom lancu je odgovoran za boju retinoida (tipično žuta, narančasta ili crvena). Stoga, mnogi retinoidi su kromofori. Izmjenjivanje bočnih lanaca i krajnjih grupa stvara različite razrede retinoida.

Retinoidi nastaju iz prehrambenog vitamina A (all-trans retinol). Jedini izvor vitamina A je biljni karotenoidni pigment (β-karoten), ali glavni unos vitamina A kod mesoždera potječe iz dugolančanih retinil estera prisutnih u namirnicama životinjskog porijekla (jaja, mlijeko, maslo, ulje riblje jetre). Vitamin A podilazi nekoliko metaboličkih konverzija u crijevima. Retinol u mukoznim stanicama je re-esterificiran s dugolančanim masnim kiselinama. Retinil esteri su potom inkorporirani, zajedno s drugim lipidima, u kilomikronske čestice koje se izlučuju u limfu. Cijepanjem retinil estera se oslobađa retinol koji zatim oksidira u retinal i retinoičnu kiselinu (RA). Također je bitno naglasiti da je vrlo mali udio retinola u plazmi i tkivu pretvoren u all-trans retinoičnu kiselinu (aTRA), glavni signalni retinoid (Bender et al., 2003).

Više metabolita obnašaju više signalizirajućih funkcija. Jedan metabolit, 4-okso-retinoična kiselina djeluje kao specifikator položaja tijekom embriogeneze (Pijnappel et al., 1993). Drugi retinoid, 1,4-hidroksi-4,14-retro-retinol regulira rast T limfocita i izgleda da djeluje direktno u interakciji s protein kinazom C. Naposljetku, tu je raprava o podrijetlu i signalizirajućoj funkciji 9-cis izomera all-trans retinoične kiseline, 9-cis retinoične kiseline, što je zanimljivo zbog visokog afiniteta za receptore retinoične kiseline druge vrste (RXR). Važno je istaknuti da produkcija all-trans retinoične kiseline u organizmu mora biti usko regulirana za pravilnu organogenezu jer preniska koncentracija vitamina A ili previsoka koncentracija retinoične kiseline uzrokuje ozbiljne razvojne malformacije (Lee et al., 2004).

Inače se koriste u medicini pri tretmanu brojnih različitih bolesti i pokazali su se učinkovitima u liječenju raznoraznih dermatoloških stanja poput upalnih kožnih poremećaja, psorijaze, raka kože, fotostarenja. No, toksični efekti se javljaju kod produženog i povišenog unosa u organizam. Medicinski znak kroničnog trovanja jest prisutnost bolnih oteklina na dugim

kostima. Također, kronično predoziranje uzrokuje povećanu labilnost bioloških membrana i vanjskog sloja kože (Bushue i Wan, 2010).

2.1 Retinoična kiselina

Retinoična kiselina ili drugim imenom poznata i kao tretinoin, molekulske formule $C_{20}H_{28}0_2$, je kristalni prah žuto do svijetlonarančaste boje, praktički netopljiv u vodi, topljiv u hidrofobnim otapalima, nestabilan u otopini u kojoj je prisutan jak oksidirajući agens. (National Center for Biotechnology Information. Retinoic acid., 2015)

Neophodna je kod svitkovaca, što uključuje sve više organizme od ribe do čovjeka. Tijekom ranog embrionskog razvoja retinoična kiselina proizvedena u specifičnoj regiji embrija pomaže odrediti položaj duž embrionske prednje/stražnje osi služeći kao unutarstanična signalna molekula koja predvodi razvoj prednjeg dijela embrija (Duester et al., 2008).

Osim dobro poznatog utjecaja na vid, većina efekata deficijencije vitamina A uključuje probleme kod proliferacije i diferencijacije stanica (skvamozna metaplazija i keratinizacija epitela), dediferencijaciju i gubitak cilijarnog epitela. Retinoična kiselina ima glavnu ulogu u rastu te specifičnu morfogenetsku ulogu u razvoju i diferencijaciji tkiva. Ove funkcije su rezultat genomskih akcija, modulacije genske ekspresije aktivacijom nuklearnih receptora. Retinoična kiselina ima specifičnu morfogeničku uloge u razvoju udova. Također može biti važna u razvoju centralnog živčanog sustava (Bushue i Wan, 2010).

Gledano na farmakološkoj razini, retinoična kiselina pojačava ekspresiju neveznog proteina 1 (termogenina) u smeđem masnom tkivu i smanjuje ekspresiju leptina u bijelom masnom tkivu, sugerirajući da može imati utjecaj na energetsku homeostazu, ali nije poznato da li su utjecaji relevantni na fiziološkoj razini (Kumar et al., 1999). Retinoična kiselina također potiče sintezu glukokinaze u jetrenim stanicama beta-Langerhansovih otočića. Povećani metabolizam glukoze kao rezultat glukokinazne aktivnosti je odgovoran za početak inzulinske sekrecije kao odgovora na povećanu koncentraciju glukoze u krvi (Brigelius-Flohe i Joost, 2006).

3 NUKLEARNI RECEPTORI

Nuklearni receptori su skupina proteina unutar stanice koji su odgovorni za djelovanje steroidnih i tiroidnih hormona, kao i određenih drugih molekula. Kao takvi, receptori djeluju s drugim proteinima kod regulacije ekspresije specifičnih gena, kontrolirajući razvoj, homeostazu i metabolizam organizma. Oni imaju sposobnost direktnog vezanja na molekulu DNA i reguliranja ekspresije gena, pa se zato klasificiraju i kao transkripcijski faktori (Evans et al., 1998).

Regulacija ekspresije gena preko nuklearnih receptora općenito se odvija samo kad je ligand-molekula koja utječe na receptorsko ponašanje- prisutan. Točnije, vezanje liganda na nuklearni receptor uzrokuje konformacijsku promjenu receptora koja aktivira receptor i rezultira pozitivnom ili negativnom regulacijom ekspresije gena. Jedinstvena osobina nuklearnih receptora koja ih razlikuje od drugih vrsta receptora jest njihova mogućnost da direktno djeluju i kontroliraju ekspresiju genomske DNA. Posljedično, oni igraju ključnu ulogu i u embrionskom razvoju kao i u homeostazi odrasle jedinke.

Nuklearni receptori se mogu podijeliti u sljedeće četiri mehanističke kategorije (Novac et al. 2004) :

1) tip 1- vezanje liganda uzrokuje disocijaciju proteina, homodimerizaciju, translokaciju iz citoplazme u staničnu jezgru gdje se vežu na specifične sekvence DNA koje se sastoje od dva dijela mjesta vezanja odvojena promjenljivom duljinom lanca, pri čemu drugio dio sadrži sekvencu obrnutog redoslijeda od prvog dijela („inverted repeats“).
2) tip 2- za razliku od tipa 1, oni ostaju u jezgri usprkos statusu vezivanja liganda i vežu se kao heterodimeri, uglavnom i najčešće s RXR, na DNA. U odsutnosti liganda, tip 2 su često u kompleksu sa korepresorskim proteinima. Vezanje liganda uzrokuje disocijaciju korepresorskih i regrutaciju koaktivatorskih proteina. Dodatni proteini uključujući RNA polimerazu su potom regrutirani na receptor/DNA kompleks koji prepisuje DNA na mRNA.
3) tip 3-slični tipu 1 jer se vežu na DNA kao homodimeri, ali je razlika što se vežu na istosmjerna ponavljanja, a ne na obrnuta ponavljanja elemenata odgovora hormona
4) tip 4- vežu se kao monomeri ili dimeri, ali samo jedna DNA- vezujuća domena receptora se veže na jedno half-site elementa odgovora hormona

Retinoidni receptori spadaju u skupinu nuklearnih receptora tip 2.

4 RETINOIDNI RECEPTORI

Receptor retinoične kiseline je tip nuklearnog receptora koji se također može ponašati i kao transkripcijski faktor koji je aktiviran i all-trans retinoičnom kiselinom i 9-cis retinoičnom kiselinom (Allenby et al., 1993). Iako biološki aktivni ligandi za receptore retinoične kiseline uključuju i 9-cis retinoičnu kiselinu među ostalim, ipak cirkulirajuća koncentracija iste je puno niža od koncentracije all-trans retinoične kiseline i fiziološki značaj izomerizacije mora biti potvrđen. Nedavno su to i pokazali Kane et al. (2010) kad su identificirali 9-cis retinoičnu kiselinu u stanicama pankreasa gdje ima ulogu u regulaciji inzulinske sekrecije stimulirane glukozom.

Postoje tri vrste receptora i svaka izoforma ima nekoliko varijanti različitog splajsinga: 2 za RARα, 4 za RARβ i 2 za RARγ.

Kao što je slučaj i kod drugih nuklearnih receptora tipa 2, RAR čini heterodimer sa RXR i u odsutnosti liganda, RAR/RXR dimer se veže na elemente odgovora hormona u ovom slučaju zvane elementi odgovora retinoične kiseline (RARE) u kompleksu sa korepresorskim proteinom. Vezanje agonista liganda na RAR uzrokuje disocijaciju korepresora i regrutaciju proteina koaktivatora koji potiče nizvodnu transkripciju ciljnog gena u mRNA i na kraju u protein (Germain et al.2006).

4.1 Podjela retinoidnih receptora

Retinoidni receptori mogu biti klasificirani na dva načina, prema mehanizmu ili homologiji. Promatrajući podjelu prema sekvencijskoj homologiji koja je uspostavljena 1990. godine (Nuclear Receptors Nomenclature Committee) retinoidni receptori se ubrajaju u skupinu sličnih receptora tiroidnih hormona, a nazivaju se receptori retinoične kiseline (RAR)- RARα, RARβ, RARγ za koje kodiraju geni RARA, RARB, RARG , dok su ligandi vitamin A i slični spojevi. Druga skupina su retinoid X receptori (RXR) i slični- RXRα, RXRβ, RXRγ za koje kodiraju geni RXRA, RXRB, RXRG, a ligandi su specifični oblici vitamina A, od kojih je najvažniji 9-cis retinoična kiselina.

Receptor β retinoične kiseline je član porodice receptora tiroidnih/ steroidnih hormona. Lokaliziran je u citoplazmi i u subnuklearnim odjeljcima. Veže retinoičnu kiselinu, koja posreduje staničnu signalizaciju u embrionskoj morfogenezi, staničnom rastu i diferencijaciji.

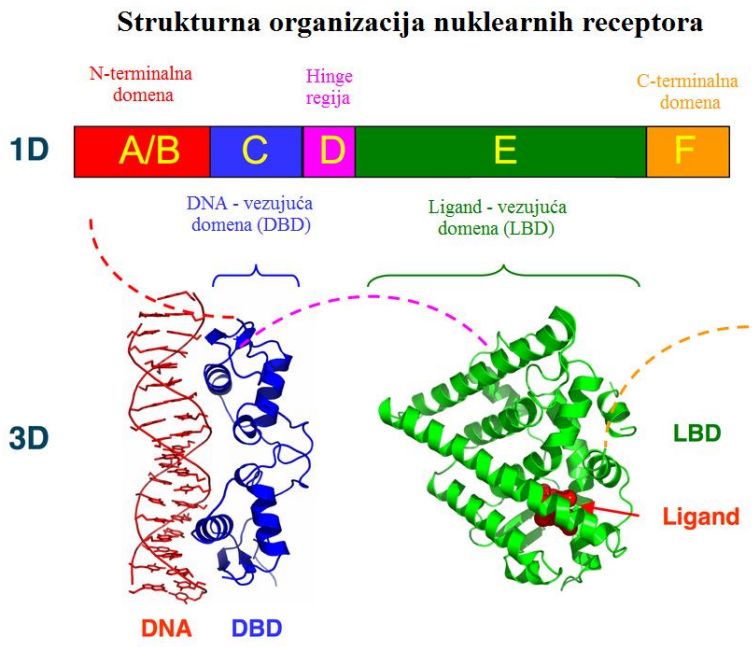
Smatra se da ovaj protein ograničava rast brojnih tipova stanica reguliranjem genske ekspresije.

Postoje tri tipa RXR, ali da stvar bude još kompliciranija RXR su heterodimer partneri za raznorazne nizove ligand-ovisnih i –neovisnih nuklearnih receptora ili transkripcijskih faktora, uključujući tiroidni hormon i receptore vitamina D, i manje poznate poput receptora jetre X (LXR). Nadalje, ne smije se preskočiti činjenica da RAR i RXR tipovi mogu imati varijabilne N-terminalne transkripcijske aktivacijske domene kao rezultat upotrebe različitih promotora i alternativnog splajsinga te razumijevanje uloge N-terminalnih varijanti u diferencijalnoj genskoj ekspresiji ostaje izazov za budućnost.

4.2 Struktura retinoidnih receptora

Retinoidni receptor sadrži sljedeće domene (Kumar et al., 1999) (Slika 1.) :

a) N-terminalna regulatorna domena- sadrži aktivacijsku funkciju 1 (AF-1)
b) DNA-vezujuća domena (DBD)- visoko konzervirana domena s dva cinkova prstena koji se vežu na specifične sekvence DNA zvane „hormon-response elements“ (HRE)
c) hinge regija- fleksibilna domena koja povezuje DNA-vezujuću i ligand-vezujuću domenu te utječe na intracelularni promet i subcelularnu distribuciju
d) ligand-vezujuća domena (LBD)- umjereno konzervirana u sekvenci i visoko konzervirana u strukturi između različitih nuklearnih receptora; struktura domene se referira kao 'sendvič' alfa zavojnica u kojem su tri anti paralelne alfa zavojnice okružene dvjema alfa zavojnicama s jedne strane i trima s druge strane;
ligand vezujuća šupljina je unutar domene; zajedno s DNA-vezujućom domenom doprinosi dimerizaciji receptora i dodatno, veže koaktivatorske i korepresorske proteine; sadrži i aktivacijsku funkciju 2 (AF-2) čija je aktivnost ovisna o prisutnosti vezanog liganda
e) C-terminalna domena- visoko varijabilna u sekvenci između različitih receptora



Slika 1. Strukturna organizacija RAR i RXR
Podijeljeni su u pet regija: amino-terminalni kraj A/B s AF-1 ligand neovisnom, ali stanično-ovisnom transkripcijskom aktivnošću; DNA-vezujuća domena (C) s dva cinkova prstena uključena u prepoznavanje RARE u promotorima ciljnih gena; ligand-vezujuća domena s AF-2 ligand-ovisnom transkripcijskom aktivnošću i domena za dimerizaciju receptora; D vezna domena. Fosforilacija B i E je nužna za učinkovitost AF-1 i AF-2 funkcija. U odsutnosti liganda, korepresorski kompleks ostaje vezan na dimer i inhibira transkripciju. Vezanje liganda potiče konformacijsku promjenu koja zamjenjuje korepresor s koaktivatorskim kompleksom i transkripcija započinje (izvor: https://commons.wikimedia.org/wiki/File:Nuclear_Receptor_Structure.png, preuzeto 22 kolovoza 2015.)

Ligand-vezujuća domena je formirana od 12 konzerviranih alfa zavojnica i beta okreta, koji su odvojeni petljama i namotani u tri slojevita, paralelna helična sendviča (Chambon et al. 1996). Jedna od najvažnijih karakteristika domene je konformacijska fleksibilnost C-terminalne zavojnice/heliksa (H12), koji usvaja različite konformacije. Druga karakteristika jest funkcionalna kompleksnost pošto je uključena u vezanje liganda, dimerizaciju, interakciju s brojnim koregulatorima. Ligand-vezujući džep obuhvaća hidrofobne ostatke uglavnom od zavojnica H3, H5, H11 (Bourguet et al. 2000). Koregulator-vezujuće površine uključuju većinom znane hidrofobne ostatke zaslužne za vezanje korepresora/koaktivatora.

5 KOREGULATORNI PROTEINI

Nuklearni receptori vezani na elemente odgovora hormona regrutiraju značajan broj drugih proteina (referiranih kao transkripcijski koregulatori) koji olakšavaju ili inhibiraju transkripciju udruženih ciljnih gena na mRNA. Funkcije su različite i uključuju remodeliranje kromatina čineći ciljni gen više ili manje dostupnim transkripciji, ili funkciju premošćivanja da se stabilizira vezanje drugih koregulatornih proteina.

Pod koregulatorne proteine su ubrajaju koaktivatori i korepresori. Za koaktivatorske proteine je karakteristično da vezanje agonista liganda na receptor potiče njegovu konformacijsku promjenu, a koji inače preferirano veže koaktivatorske proteine. Ti proteini često imaju unutarnju histon acetiltransferaznu aktivnost (HAT) koja otežava asocijaciju histona na DNA i tako promovira gensku transkripciju. Korepresorski proteini su posebni po tome što vezanje antagonista liganda na receptor suprotno potiče konformacijsku promjenu receptora koja preferirano veže korepresorske proteine. Ti proteini regrutiraju histon deacetilaze (HDAC) koje jačaju asocijaciju histona na DNA i tako potiskuju gensku transkripciju.

Signalizacija retinoidom je provođena od strane dviju vrsta nuklearnih receptora, receptora retinoične kiseline i receptora X retinoida, koji tvore RXR/RAR heterodimere. U odsutnosti liganda, RXR/RAR vezan na DNA potiskuje transkripciju regrutiranjem korepresora jezgreni receptor korepresor 1 (NCOR1)- transkripcijski koregulatorni protein koji regrutira histon deacetilazu na DNA promotorsku regiju., dakle pomaže u negativnoj regulaciji genske ekspresije. Stišavajući posrednik za receptore retinoida ili tiroidnih hormona (SMRT ili NCOR2) služi kao korepresor kod više puteva transkripcijskog faktora i histon deacetilaze. Kad se ligand veže na kompleks, uzrokuje konformacijsku promjenu dopuštajući regrutaciju koaktivatora, histon acetiltransferaze i osnovne transkripcijske mašinerije. No, primjerice RIP140 je korepresorski protein koji se veže na RAR na kojem je već vezan ligand, radije nego na apo-RAR/RXR kompleks koji tipično regrutira korepresore. RIP140 inhibira transaktivacijsku funkciju nekoliko ligand-vezujućih nuklearnih receptora.

6 PRIJENOS RETINOIČNE KISELINE U JEZGRU

Endogena koncentracija aktivnog retinoida je ključna i pod uskom homeostatskom kontrolom, jer i viša razina retinoida kao i retinoidna deficijencija imaju teratogene učinke.

Intracelularna koncentracija vitamina A je održana zahvaljujući celularnim retinol vezujućim proteinima (CRBP) i celularnim retinoična kiselina vezujućim proteinima (CRABP-I i CRABP-II). CRBP su povezani s transportom i pohranom retinil estera dok se CRABP ponašaju kao pratioci retinoične kiseline. CRABP-II prenosi retinoičnu kiselinu iz citosola u jezgru. To je mali citosolni protein koji specifično veže retinoičnu kiselinu i prenese ju u jezgru gdje se veže na receptor putem direktnih protein-protein interakcija (Dong et al. 1999). Rezultirajući kompleks povezuje put retinoične kiseline od vezujućeg proteina do receptora i olakšava formiranje kompleksa ligand-receptor. Direktnim prijenosom liganda do receptora, CRABPII povećava njegovu transkripcijsku aktivnost i učini stanice osjetljivijima na biološku aktivnost retinoične kiseline.

Nedavne studije su pokazale da u određenim tipovima stanica, retinoična kiselina se veže i na FABP5, protein koji inače veže masne kiseline. Vezanje retinoične kiseline aktivira staničnu translokaciju FABP5, koji zatim prenosi ligand do PPAR β/δ podtipa (Schug et al. 2007).

Osim za RAR i RXR receptore, retinoična kiselina djeluje kao ligand za peroksisom proliferator-aktivirani receptor PPAR β/δ, nuklearni receptor koji potiče gene za preživljavanje stanica. Masne kiseline-vezujući protein 5 (FABP5) se ponaša kao pratilac pri prijenosu retinoične kiseline do PPAR β/δ receptora. Rapodjela retinoične kiseline do RAR i PPAR β/δ je regulirana preko prijenosnih proteina CRABP-II i FABP5, te povećana ekspresija FABP5 premješta prijenos na PPAR β/δ.

7 TRANSKRIPCIJA I EKSPRESIJA GENA

Genska ekspresija je proces u kojem je genska sekvenca pretvorena u zreli genski produkt ili produkte- proteine ili RNA. To uključuje nastanak RNA transkripta kao i bilo koji drugi proces nastanka zrelog RNA produkta ili mRNA (za protein-kodirajuće gene) te translaciju mRNA u protein. Maturacija proteina je uključena kad je potrebno formiranje aktivnog oblika produkta iz neaktivnog prekursorskog oblika.

Klasični put regulacije ekspresije gena od strane retinoične kiseline ima četiri specifična koraka, premda sekvence u koracima nisu identične za sve gene.

Transkripcija posredovana retinoičnom kiselinom je definirana kao (Dupe et al., 1997):

i. Vezanje retinoične kiseline ili drugog retinoidnog liganda na ligand-vezujuće mjesto
ii. Dimerizacija receptora (nastanak RAR/RXR heterodimera)
iii. Vezanje receptorskog heterodimera na molekulu DNA (RARE)
iv. Transkripcijska modulacija gena, putem kromatinskog remodeliranja i regrutacije transkripcijske mašinerije

Kad je represivni kromatin dekondenziran, dogodi se zamjena koregulatora kako bi se dopustilo heterodimerima vezanima na RARE da sudjeluju pri ulasku RNA-polimeraze II i generalnih transkripcijskih faktora (GTF) u preinicijacijski kompleks (Malik et al. 2000). Nakon što koaktivatori disociraju, tada retinoidni receptori mogu regrutirati transkripcijsku mašineriju preko njihove asocijacije s tzv. SMCC (Srb i Mediator protein sadržavajući kompleks) posrednički kompleks. Potom posrednik ubrzava dolazak transkripcijske mašinerije do promotora kroz interakciju s holoenzimom RNA-polimerazom II.

Jednom kad je transkripcija započeta, RNA-polimeraza II putuje niz gen koji treba biti 'prepisan'. Ovaj proces uključuje remodelaciju kromatina i modifikacijske aktivnosti obdarene podjednicama elongacijskih faktora koji slijede RNA-polimerazu II. (Orphanides et al., 2000.)

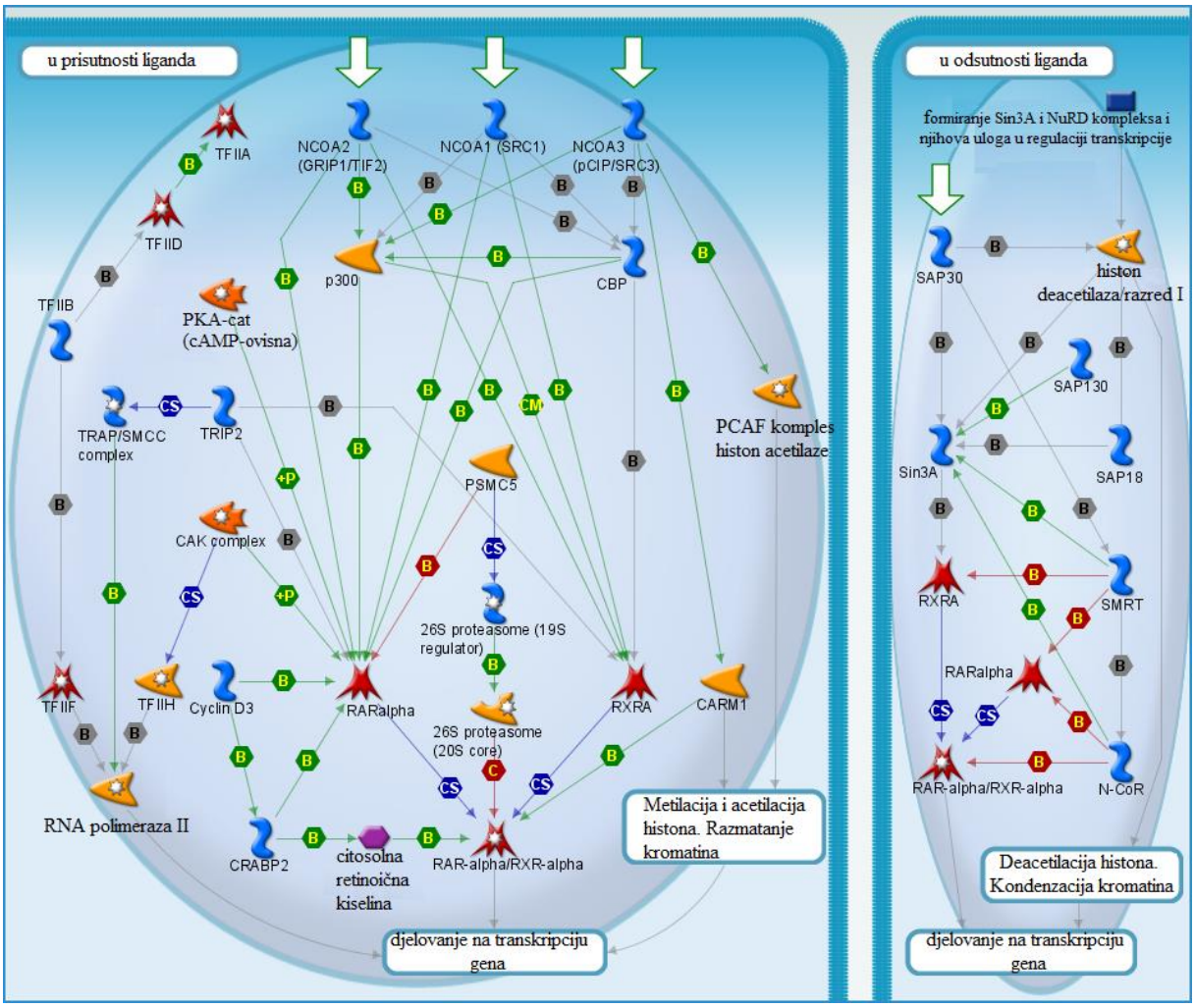
Kad geni nisu aktivirani, DNA je zapakirana u organiziranu i kompaktnu nukleoproteinsku strukturu zvanu kromatin koji ometa sve korake transkripcije. Osnovna jedinica kromatina je nukleosom koji se sastoji od DNA omotane oko proteinske jezgre sadržavajući dvije kopije svakog od četiri histonska proteina.

Za aktiviranje ekspresije gena, retinoidni receptori se moraju natjecati s represivnim kromatinskim strukturama kako bi dopustili regrutaciju transkripcijske mašinerije. U tom pogledu, ligand-inducirana konformacijska promjena u receptorima će uzrokovati disocijaciju korepresora i koordiniranu i/ili kombiniranu regrutaciju koaktivatora koji će odmotati represivni kromatin i olakšati postavljanje transkripcijske mašinerije na promotor.

Ako je ligand vezan na ligand-vezujuću domenu RXR-a, konformacijska promjena je nedovoljna za prestići regrutaciju korepresora. Ta nemogućnost aktivacije RXR-a da inicira put receptora se zove subordinacija RXR-a ili apo-RAR stišavanje.

Alternativno, kad je retinoična kiselina ili drugi retinoid vezan na odgovarajuću domenu, konformacija proteina se mijenja dovoljno da pretvori kompleks iz regrutacije korepresora u regrutaciju koaktivatora. Ako vezujuće domene RAR-a i RXR-a imaju vezane ligande, namatanje proteinskog kompleksa je naglašeno.

Raznovrsnost u kontroli genske ekspresije signalima retinoida je ostvarena kroz kompleksnost na različitim razinama puta signaliziranja. Glavni izvor te raznosvrsnosti potječe iz postojanja dviju skupina receptora retinoične kiseline, tri RAR izotipa i tri RXR izotipa te njihovih brojnih izoformi, koji se vežu kao RXR/RAR heterodimeri na polimorfne cis-djelujuće elemente odgovora ciljnih gena retinoične kiseline. Mogućnost unakrsne modulacije sa signalizirajućim putevima receptora na staničnoj površini, kao i činjenica da RAR i RXR međusobno djeluju sa višestrukim pretpostavljenim koaktivatorima i/ili korepresorima, čini dodatnu razinu kompleksnosti (Olefsky et al., 2001).



Slika 2. Prikaz ligand-ovisne transkripcije ciljnih gena retinoida u prisutnosti i odsutnosti liganda (preuzeta s web stranice http://www.kegg.jp/kegg-bin/show_pathway?map07223, 15.kolovoza 2015)

7.1 Element odgovora retinoične kiseline (RARE)

Element odgovora retinoične kiseline (RARE) nađen u promotorima brojnih gena sastoji se od varijabilnih direktnih ponavljanja sekvence PuGGTCA razmaknutih s pet nukleotida (DR5) (Mader Leroy et al., 1993).

Asimetrična priroda direktnog ponavljanja RARE nalaže da se RAR i RXR prije vežu na jednu polovicu veznog mjesta nego na drugu. Studijom je pokazano da RXR okupira 5' uzvodno polumjesto, a RAR 3' nizvodno polumjesto direktnog ponavljanja kod DR2 i DR5 RARE (Laudet et al., 2001). Također, regija susjedna regiji cinkovog prstena RAR i RXR je esencijalna za specifično i kooperativno vezanje peptida DNA-vezujuće domene na RARE.

Drukčija upotreba ovih determinanti posreduje vezanje RAR/RXR heterodimera na DR2 i DR5 RARE.

Vezanje heterodimera na RARE se odvija sa specifičnom polarnošću, a RAR partner okupirajući nizvodnu poziciju stimulira transkripciju djelujući sa transkripcijskim preinicijacijskim kompleksom na ligand-ovisan način.

Elementi odgovora retinoične kiseline su identificirani u promotorima velikog broja ciljnih gena retinoida koji obuhvaćaju širok raspon funkcija. Klasični DR5 elementi su nađeni u promotorima RARB gena, cyp26 i nekoliko Hox i HNF gena (Dupe et al., 1997). DR2 elementi su identificirani u CRBP i CRABP- II promotorima. Jedini prirodni DR1 element je nađen u CRBP- II promotoru štakora. Međutim, i novi geni koji se povezuju s elementom odgovora retinoične kiseline su nedavno otkriveni putem *in-silico* studija, čak je u nekim slučajevima i nekoliko elemenata povezano s istim genom (Lavelee et al. 2011).

7.2 Kromatinska remodulacija

Proteini koaktivatori steroidnih receptora (SRC) i p160 proteini sa histon acetiltransferaznom aktivnošću (HAT) se mogu vezati na ligand.vezujuću domenu RAR-a ili RXR-a u pristunosti liganda. SRC koaktivatori acetiliraju lizinske aminokiselinske ostatke u jezgri histona blizu DNA vezujućeg mjesta, neutralizirajući naboj histona i oslabljujući interakciju s kromatinom. Kromatin se opusti i postane dostupniji za mehanizam transkripcije DNA.

ATP- ovisni proteini kromatinske remodulacije poput SWI/ SNF koriste energiju hidrolize ATP-a za repoziciju vezanja nukleosoma na promotorsku regiju gena, formirajući regije slobodne ili razmaknute od nukleosoma i pružajući pristup transkricijskoj mašineriji. Primjer dodatnih koaktivirajućih ili kointegrirajućih proteina je p300/CRB protein. U putu signaliziranja retinoidima funkcionira tako što regrutira dodatne generalne transkripcijske faktore (GTF) na promotorskoj regiji i povezuje se sa transkripcijskom mašinerijom na mjestu inicijacije.

Nakon remodeliranja kromatina, koaktivatori disociraju, i moguće je da budu degradirani u proteosomu. Zatim retinoidni receptori regrutiraju SRB i kompleks koji sadržava posrednika (SMCC). Posrednički kompleks olakšava ulazak transkripcijske mašinerije, koja uključuje

RNA-polimerazu II (Pol II), ključni enzim u genskoj transkripciji, na startno mjesto promotora gena. Kromatinsko remodeliranje također olakšava vezanje dodatnih transkripcijkih faktora. Retinoična kiselina započinje vezanje NF-kB inducirano TNF-a i radi sinergistički s TNF-a u regrutaciji i stimulaciji fosforilacije polimeraze II koja je povezana s aktivacijom enzima.

7.3 Fosforilacija kao proces u regulaciji transkripcije

Fosforilacija je proces od važnosti pošto izoforme RAR i RXR mogu funkcionirati kao supstrati za mnoštvo kinaza (Gianni et al., 2006).

Još važnije, zbog njihove interakcije s TFIIH, RAR (α i γ) su fosforilirani na N-terminalnoj A/B regiji od strane cdk7 podjedinice TFIIH-a koji ima ciklin- ovisnu kinaznu aktivnost. Ovaj fosforilacijski proces ima kritičnu ulogu u retinoidnom odgovoru. Da TFIIH fosforilira AF-1 domenu kad su GTF regrutirani na promotor, pretpostavka da fosforilacija pomaže ligand-ovisnu regrutaciju koaktivatora i modifikatori kromatina bi bila nedostižna. Umjesto toga, fosforilacija može olakšati regrutaciju komponenti transkripcijske mašinerije i tako stabilizirati formaciju receptorskog kompleksa. Nije ni isključeno to da fosforilacija može prije olakšati disocijaciju RAR od inhibitora transkripcije ili cjelokupne mašinerije da bi dopustila nastavak elongacije. Za razliku od drugih transkripcijskih aktivatora, fosforilacija AF-1 domene RAR ne utječe na ubikvitinaciju ni proteosomalnu degradaciju RAR.

Nadalje, može sudjelovati u degradaciji proteosomom i utjecati na sposobnost povezivanja holo-RAR/RXR kompleksa s koregulatorima i generalnim transkripcijskim faktorima. Fosforilacija serinskog ostatka RARγ se pokazala da kontrolira RARγ transaktivacijsku funkciju kao i degradaciju.

U posebnom slučaju RARγ izotipa, fosforilacija od strane TFIIH, iako je potrebna, nije dovoljna. RARγ mora biti fosforiliran i na dodatnom susjednom kraju od strane p38MAPK, za čim slijedi aktivacija putem retionida (Gianni et al., 2006). Iako se mislilo da je fosforilacija TFIIH-om i p38MAPK-om krucijalna i za transkripcijsku aktivnost i degradaciju RARy, još uvijek je nedovoljno poznat mehanizam tih procesa.

Ono što je zanimljivo, transkripcijske aktivnosti RARα i RARγ mogu također biti modulirane fosforilacijom od strane drugih kinaza kao odgovor na raznolikost signala. Tako fosforilacija

PKA na serinskom aminkiselinskom ostatku, između H9 i H10, djeluje pozitivno na transkripcijsku aktivnost RARa (Chambon, 1996) ili fosforilacija PKC signaliziranjem pogoduje dimerizaciji te vezanju heterodimera na molekulu DNA.

Mora biti istaknuta i činjenica da različiti putevi prijenosa signala se isto preklapaju s transaktivacijom retinoidnih receptora preko fosforilacije koaktivatora i korepresora. Fosforilacija korepresora poput SMRT-a korelira s inhibicijom njihove interakcije sa RAR i njihova redistribucija iz jezgre u citoplazmu. Histoni su također fosforilirani, povećavajući učinkovitost HAT i HMT da acetiliraju ili metiliraju susjedne lizinske aminokiselinske ostatke. Isto zapažanje je za GTF i RNA-polimerazu II (Orphanides et al., 2002). Svi ovi fosforilacijski procesi teže k tome da transkripcijski inicijacijski kompleks bude efikasno formiran i da odgovor bude maksimalno kontroliran.

7.4 Ubikvitin-proteosom sistem

Dosad je utvrđeno da je transkripcijska aktivnost retinoidnih receptora, kao transkripcijskih faktora, također regulirana putem ubikvitin-proteosom sistema. Glavna uloga tog sistema je degradirati transkripcijske aktivatore. U tom procesu, slijedeći signal, protein supstrat je označen ubikvitinom (višestruko ubikvitiliran) na aminokiselinskom ostatku lizin i zatim određen za uništenje od strane 26S proteosoma. 19S kompleks proteosoma prepoznaje ubikvitilirani supstrat, uklanja grupe ubikvitina, razmotava supstrat i nastali nestrukturirani lanac premješta u 20S katalitičku jezgru proteosoma gdje se degradira.

Ubikvitin-proteosom sustav može imati dvojaku ulogu, s jedne strane kontrolirajući funkcionalnost RAR/RXR heterodimera tako što pomaže regrutaciju transkripcijske mašinerije, a s druge strane ubikvitinaciju i posljedično degradaciju heterodimera. Takvu dvojaku ulogu regulira dinamičko spajanje/ razdvajanje retinoidnih receptora na promotor ciljnih gena, kao što je prethodno demonstrirano za druge nuklearne receptore poput receptora estrogena i androgena (Reid et al., 2003).

Pregledi puta retinoične kiseline često uključuju ubikvitinaciju i fosforilaciju kao daljne procese koji su presudni u genskoj regulaciji i transkripciji. Degradacija RAR/RXR

protesomom nakon ubikvitinacije završava retinoidnu signalizaciju, tako da jednim dijelom ubikvitinacija sudjeluje u transkripciji pokretanjem procesa terminacije.

8 IDENTIFIKACIJA CILJNIH GENA REGULIRANIH RETINOIČNOM KISELINOM

Retinoična kiselina kao signalna molekula utječe na transkripciju velikog broja različitih gena, kao što je prethodno navedeno. Cilj rada je prikazati ulogu retinoične kiseline identifikacijom gena koji u promotorskoj regiji sadrže genetički element na koji se veže retinoična kiselina (RARE) te pokušati utvrditi funkcije proteina kodiranih tim genima u različitim staničnim procesima.

U nastavku je prikazana tablica 1. koja prikazuje identificirane gene, a nastala je korištenjem baze sekvencija ljudskog genoma „FLJ Human cDNA database“ (http://flj.lifesciencedb.jp/v032/cgi/). Uz kraticu i službeni puni naziv gena odobren od strane HGNC-a (Human Gene Nomenclature Committee), u tablici 1. se nalazi i ID gena Nacionalnog centra za biotehnološke informacije te funkcija proteina za koji određeni gen kodira. Popisivanjem gena za koje je dokazano da sadrže element odgovora retinoične kiseline u promotoru dobio se rezultat od sveukupno 61 gena na koji retinoična kiselina definitivno utječe regulacijom same transkripcije.

Rezultati su uspoređeni s podacima objavljenim u radu Balmera i Blomhoffa (2002) koji su sumirani u tablici 2. (Prilog 1.), a koji sadrže sve gene za koje je različitim metodama utvrđeno da bi mogli biti neposredno ili posredno regulirani retinoičnom kiselinom. Vidljivo je da se 61 gen nađen pretraživanjem nalazi i u tablici 2. U svojoj studiji, Balmer i Blomhoff su istražili i pregledali dotad objavljene podatke o 532 različita gena regulirana retinoičnom kiselinom. Njihova analiza literature je uključila procjenu gena koji su imali jak dokaz regulacije klasičnim putem. Samo 27 gena je čvrsto identificirano kao regulirani klasičnim putem, od kojih je 26 pozitivno regulirano, a jedan je reguliran promjenljivo. Gena koji su regulirani retinoičnom kiselinom, bez obzira na put, ima sveukupno 311; njih 212 su ili negativno ili promjenljivo regulirani.

Klasični direktni put, iako pruža uvid u funkciju retinoične kiseline, nije jedini način na koji ista utječe na ekspresiju. Geni koji odgovaraju klasičnom putu signaliziranja su nazvani

'direktni', dok su drugi koji odgovaraju na prisutnost retinoične kiseline drugim molekularnim mehanizmima, ali isto odgovaraju, nazvani 'indirektni'.

Konstruiranje klasifikacijske tablice je pokušaj započinjanja procesa razumijevanja uloge retinoične kiseline kod određivanja koji regulatorni događaji se odvijaju u staničnim krugovima. Pregledan je 1191 objavljeni člana s eksperimentalnim dokazima i na temelju toga pripremljena primarna kategorizacija ciljnih gena retinoične kiseline s obzirom na stupanj dokaza; stupanj koji pokazuje da li određeni dokaz podržava ili se protivi pojmu direktne regulacije u barem jednom staničnom kontekstu. Gdje je dokaz vrlo jak, taj gen se smješta u kategoriju broj 3. Gdje dokaz demonstrira indirektnu regulaciju, gen je svrstan u kategoriju broj 0. Kategorije 1 i 2 su smješteni između dvije prethodno navedene, od kojih, naravno, kategorija 2 je poduprta nešto jačim dokazom.

Tablica 1. Popis gena reguliranih retinoičnom kiselinom koji sadrže funkcionalno vezno mjesto odnosno motiv elementa odgovora (RARE) u promotorskoj regiji

Kratica gena	Naziv gena	ID gena	Funkcija kodiranog proteina
ADH1C	Alcohol dehydrogenase class 1, gamma polypeptide	126	Enzim koji metabolizira raznorazne supstrate uz etanol kao najvažniji (retinol, hidroksisteroide)
CD38	CD38	952	Multifunkcionalni ektoenzim sudjeluje u staničnoj adheziji, prijenosu signala (Ca)
Cdx1	Cdx1	1044	Kaudalni tip homeobox 1; regulira diferencijaciju enterocita
CEBPE	C/EBP epsilon	1053	Esencijalan za diferencijaciju i maturaciju progenitorskih granulocita
CRABP2	Cellular retinoic acid binding protein-II	1382	Veže retinoičnu kiselinu i prenosi ju iz citosola u jezgru
Cryab	B-crystallin/small HSP	1410	Molekularni pratioc držeći proteine u velikim topivim agregatima
Drd2	dopamine D2 receptor	1813	Inhibira adenilil ciklaznu aktivnost
Egr1	early growth response 1	1958	Transkripcijski regulator kod diferencijacije i mitogeneze
ETS1	v-ets avian erythroblastosis virus E26 oncogene homolog 1	2113	Transkripcijski aktivatori/represori, uključeni u razvoj matičnih stanica, starenje I smrt stanica te tumorigenezu
Foxa1	Forkhead box A1	3169	Hepatocitni transkripcijski aktivatori za speceifične transkripte za jetru (albumin)

H1F0	H1 histone family, member 0	3005	Odgovoran za nukleosomsku strukturu u kromosomalnom vlaknu
Hoxa1	Homeobox A1	3198	Transkripcijski faktor koji regulira gensku ekspresiju, morfogenezu I diferencijaciju; uključen u smještanje stražnjeg mozga na pravilnu lokaciju
Hoxa4	Homeobx A4	3201	Regulira tijek embrionskog razvoja
Hoxb1	Homeobox B1	3211	Važna uloga u mofrogenezi svih višestaničnih organizama
Hoxb4	Homeobox B4	3214	Transkripcijski factor specifičan za sekvencu uključen u razvoj, razmnožavanje progenitorskih stanica
Hoxd4	Homeobox D4	3233	Važna uloga u određivanju pozicijskih vrijednosti kod razvoja udova
Pck1	Phosphoenolpyruvate carboxykinase 1	5105	Citosolni enzim koji katalizira reakciju pretvorbe oksaloacetata u fosfoenolpiruvat; glavna kontrolna točka u regulaciji glukoneogeneze
Pit1[d]	POU class 1 homeobox 1	5449	Regulira ekspresiju gena uključenih u razvoj hipofize i lučenja hormona
RARA	Retinoic acid receptor, alpha	5914	Ligand-ovisni transkripcijski faktor; regulira razvoj, diferencijaciju, apoptozu, granulopeozu
RARB	Retinoic acid receptor, beta	5915	Transkripcijski regulator kod embrionske morfogeneze, rasta stanica i diferencijacije
RARG	Retinoic acid receptor, gamma	5916	Transkripcijski regulator uključen u razvoj udova, rast skeletal I homeostazu matriksa
SFTPB	Surfactant protein B	6439	Esencijalan za funkciju pluća I homeostazu nakon rođenja
Tgm2	Transglutaminase	7052	Enzim koji katalizira povezivanje proteina glutamil lizin izopeptidnim vezama
ACADM	Acyl-CoA dehydrogenase	34	Enzim koji katalizira inicijalni korak u mitohodnrijskoj b-oksidaciji masnih kiselina
APOA1	Apolipoprotein A-I	335	Proteinska komponenta HDL- u plazmi, pospješuje izlaz kolesterola iz tkiva u jetru za izlučivanje
APOA2	apolipoprotein A-II	336	Drugi najveći protein HDL čestica
APOC3	apolipoprotein C-III	345	VLDL protein koji inhibira lipoproteinsku I jetrenu lipazu
CSH1	placental lactogen	1442	Važna uloga u kontroli rasta
CYP24	Cytochrome P450, family 24, subfamily A, polypeptide 1	1591	Katalizator brojnih reakcija metabolizma lijekova I sinteze kolesterola, steroida I drugih lipida; uloga u homeostazi Ca i D

Epo	Erythropoietin	2056	Regulira stvaranje crvenih krvnih stanica potičući sintezu hemoglobin
Gh1	Growth hormone 1	2688	Krucijalna uloga u regulaciji rasta organizma
GPX2	Glutathione peroxidase 2	2877	Odgovoran za glutation-ovisnu hydrogen peroksid- reducirajuću aktivnost u epitelu gastrointestinalnog trakta
GSTP1^{m}	Glutathione s-transferase pi 1	2950	Uloga u detoksifikaciji kataliziranjem konjugacije brojnih hidrofobnih I elektrofilnih spojeva
H2	major histocompatibility class I (H2K, -D, -L, and -Q, etc.)	6019	Endokrini hormon relaksin koji ima ulogu u reproduktivnom sustavu
Igfbp6	Insulin-like growth factor binding protein 6	3489	Posredna uloga u vezanju faktora rasta
Lamb1-1	laminin beta 1	3912	Glikoproteinski konstituent bazalnih membrana, uključeni u adheziju stanica, diferencijaciju, migraciju, signaliziranje, rast neurona I metastazu
Mdk^{p}	Midkine (neurite growth-promoting factor 2)	4192	Pospješuje rast stanica, migraciju, angiogenezu
MMP11	Matrix metallopeptidase 11	4320	Uključen u uništenje vanstaničnog matriksa u normalnim procesima poput embrionskog razvoja, reprodukcije, remodeliranja tkiva
NCX	Ncx protein	3196	Membranski protein koji uklanja Ca iz stanica; Na-Ca izmjenjivač
NES	Nestin	10763	Protein intermedijarni filamenta u živčanim stanicama
Pkca	Protein kinase C, alpha	5578	Uloga u staničnoj adheziji , transformaciji, provjeri staničnog ciklusa i kontroli volumena stanice
PLAT	Plasminogen activator, tissue	5327	Proteaza koja pretvara plazminogen u plazmin-fibrinolitički enzim; uloga u migraciji stanica i remodeliranju tkiva
PTAFR	Platelet-activating factor receptor	5724	Fosfolipid koji ima ulogu u onkogenskoj transformaciji, rastu tumora, angiogenezi, metastazi, proinflamatornim procesima
SLC10A1	Solute carrier family 10, member 1	6554	Kotransporter natrija/ žučne kiseline; sudjeluje u enterohepatskoj cirkulaciji žučne kiseline
CAMK2A	Ca/calmodulin- dependent protein kinase II alpha	815	Uloga u signaliziranju Ca; potreban za hipokampusno dugotrajno potenciranje I prostorno učenje
CYP4F2	Cytochrome P450, family 4, subfamily F, polypptide 2	8529	Monooksigenaza uključena u brojne reakcije metabolizma; započinje proces inaktiviranja i degradiranja leukotrien B4, posrednika upale

HNF4A	Hepatocyte nuclear factor 4, alpha	3172	Transkripcijski fakor koji ima ulogu u razvoju jetre, bubrega i crijeva
HOXC5	Homeobox C5	3222	Transkripcijski fakor koji ima važnu ulogu u morfogenezi višestaničnih oraganizama
ICAM1	Intercellular adhesion molecule 1	3383	Glikoprotein koji je tipično izražen na stanicama endotela i stanicama imuno sustava
ITGB2	Integrin, beta 2	3689	Protein na površini stanice koji sudjeluje u prijenosu signal te adheziji stanica
KRT3	Keratin 3, type II	3850	Sudjeluje u diferencijaciji jednostavnog ili slojevitog epitelnog tkiva
LPA	Lipoprotein , Lp (a)	4018	Serinska proteinaza koja inhibira aktivnost plasminogen aktivatora 1; fragmenti promiču trombogenezu
PECAM1	Platelet/ endothelial cell adhesion molecule 1	5175	Uključen u migraciju leukocita, angiogenezu, i aktivaciju integrina
Rbp2	Retinol binding protein 2, cellular	5948	Sudjeluje u unutarstaničnom metabolizmu vitamin A odgovornog za rast, reprodukciju, diferencjaciju epitelnog tkiva, vid
SPN	sialophorin	6693	Čini dio ligand-receptorsko kompleksa uključenog u aktivaciju T stanica; negativno regulatorna uloga u imuno sustavu
BTK	bruton agammaglobulinemia tyrosine kinase	695	Važna uloga u razvoju B stanica (limfocita)
Fbp1	Fructose-1,6-bisphosphatase 1	2203	Regulatorni enzim glukoneogeneze katalizira hidrolizu fru-1,6-bifosfata u fur-6-fosfat
FSCN2	Fascin actin-bundling protein 2, retinal	25794	Ugrađuje aktin u snopove filamenata; uloga u morfogenezi fotoreceptorskog diska
IBSP	Integrin-binding sialoprotein	3381	Strukturalni protein koštanog matriksa; veže se na Ca i hidroksiapatit te posreduje u prilaganju stanica
OAS3^{ppp}	2’-5’-oligoadenilat sintetaza 3	4940	Uloga u inhibiciji sinteze staničnih proteina i rezistenciji na virusne infekcije
Rxrg	Retinoid X receptor, gamma	6258	Uključen u posredovanje antiproliferativnog efekta retinoične kiseline

9 ZAKLJUČAK

Pretraživanjem promotorskih regija svih gena humanog genoma u 61 promotoru nađen je genetički element za vezanje retinoične kiseline. Analizom poznatih funkcija nađenih proteina vidljivo je da je značajan udio tih proteina uključen, ili bi mogao biti uključen, u diferencijaciju stanica. Također, jedan dio tih proteina uključen je neposredno u metabolizam samih retinoida. Zanimljivo je, međutim, da se značajan dio reguliranih gena ne može dovesti u vezu niti sa jednim od ova dva procesa iz čega se može zaključiti da retinoidi imaju i druge, do danas neistražene uloge u stanici. Budući da je RXR u stanju formirati heterodimere s drugim nuklearnim receptorima, uključujući PPAR-ove, moguća je pojava unakrsnog preklapanja s drugim signalnim putevima posredovanim PPAR-om. 9-cis retinoična kiselina može služiti kao aktivirajući ligand za PPAR/RXR, a i drugi spojevi, specifični ligandi za RXR (rexinoidi), što govori o vrlo izraženoj kompleksnosti regulacijskih mehanizama u koje su retinoidi uključeni. Brojne tehnike,uključujući siRNA za eliminaciju specifičnih gena, RT-PCR za evaluaciju ekspresije gena, i kromatinsku imunoprecipitaciju, su ključne za proširenje znanja i razumijevanja klasičnog puta signaliziranja retinoičnom kiselinom. Iz toga se može zaključiti da su potrebne daljnje studije i novi rezultati koji bi rasvijetlili sve uloge retinoične kiseline i drugih retinoida u metabolizmu ljudskih stanica.

10 POPIS LITERATURE

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Prilog 1. Klasifikacijska tablica gena (Balmer i Blomhoff, 2002)

Symbol	Name in Refs	Spp	Dir	Summary	Ref PMIDs	Cat
ADH1C	ADH3	Hs		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	B-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-3	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
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	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-2	Hs, Mm, Tr	Up	Isoform 2 induction; conserved functional binding site.	2825025; 2825036; 0001658797; 0010452951	3
RARB	RAR	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	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
					continued	
ABCC2	mrp2	Hs, Rn[f]		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	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 posttranslational.	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	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
					continued	
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	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 tTG), however, induction may be direct; functional binding site.	8546677; or 0009407047; 0009679546; 0010536361	2
					continued	
H2	major histocompatibility class I (H2K, -D, -L, and -Q, etc.)	Mm, Hs, vrs[n]		No good d/t data; functional binding sites, one of them highly conserved.	0003467324; 0001736309; 0008413217; 0008604312; 0008618036; 0009758167; 0009790391	2
HSD17B2	17 -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	Mm, Hs	Up	Induction of pre-mRNA; may require additional special factors for processing.	0008083217; 0007763262	2

IL1B	IL-1	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	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	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
					continued	
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	PI3K	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
RARRES3	TIG3, RIG1			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[t] 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- 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
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	-skeletal actin	Mm	Dn	No good d/t data; other NRs.	8601621	1
Acta2	-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).	10995752	1
ALPI[w]	IAP	Hs	Dn	No good d/t data.	0010691970	1
Ambp	1-microglobulin	Rn	Up	No good d/t data.	0001371972	1

App	-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	3Gn-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
BCL2	Bcl-2		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); downregulated 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, -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	CaMKK	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
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; dif- ferentiation controls; functional binding motif; knockout evidence; other NRs; probably at least partly indirect.	7936668; 0008702678; 0008940196; 8895764; 0009490650; 10479451; 0010645889; 11032820	
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]	1(III) collagen	Gg	Up	No good d/t data.	3653521	1
Col4a2	collagen IV (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 2 on the basis of estimated weight following in vitro translation; 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 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 ,	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
DSG3	desmoglein 3		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-	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 shortterm 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	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
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	
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	GFR-1	Rn	Up	No good d/t data.	0010751444	1
Gfra1	GFR-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	HNF4	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	11-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
INHBA	Activin A		vrs	No good d/t data.	1690989; 8774352	
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 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	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 lowdose, 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
KRT6A[ii]	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	
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

continued

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
					continued	
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 vita-min 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	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
					continued	
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	
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 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	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
					continued	
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	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
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	Mm, Hs	Up	Induced late in differentiation; RXR.RXR binding site.	2065662; 11027556	1
Tcf2	HNF-1	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-	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- 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- 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	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
					continued	
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	-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 M); 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

Cal1[ddd]	CT, CGRP	Rn	Dn	Long treatment required; probably indirect.		
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.		
Cdrap	CD-RAP	Bt, Mm, Rn, Hs	Dn	Indirect.		
Col1a1	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.		
Col1a2	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.		
Col4a1	collagen IV (1), 1(IV)	Mm, Hs, Bt	Up	No good d/t data; now thought to be indirect.		
COL7A1	type VII collagen	Hs	Dn	No good d/t data; probably indirect.		
Cp	ceruloplasmin	Rn	Up[eee]	No good d/t data; probably indirect (protein synthesis).		
CRH	corticotropin-releasing hormone	Hs	Up	Indirect.		
CSF1R	c-fms	Hs	Up	Induction; no motif found in the region sufficient to impart RA inducibility; regulation attributed to AP1.RAR.		
CTNNB1	-catenin	Hs	vrs	Probably indirect.		
CTSD	cathepsin D	Hs	Up	Probably indirect.		
CTSG	cathepsin G	Hs	Dn	Probably indirect.		
CTSL	cathepsin-L	Rn	Up	Delayed induction; probably indirect (protein synthesis).		
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).		
DEFA1	promyelocytic defensin-1	Hs	Up	Probably indirect.		
EDN1	ET-1	Hs	Dn	Probably indirect.		
ENPP2	ATX	Hs	Up	No good d/t data; requires protein synthesis; probably indirect.		
Etnmg1	ETnMG1	Mm	Dn	Repression probably due to decreased mRNA stability.		
Evx2	evx2	Dr, Mm	vrs	No good d/t data; probably indirect (Hoxa-1).		
FACL2	acyl-coA synthase, ACS	Hs, Rn	Up	Probably indirect; specific ligands.		
Fasn	FAS	Rn	vrs	No good d/t data; other NRs; probably indirect.		
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.		
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

Fgf1	acidic FGF	Mm	Up	Induced during differentiation; indirect.		
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 RXRcontaining 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-	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 (NFB); 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]	-8 integrin	Rn	Up	Delayed induction during differentiation; probably indirect (protein synthesis).	11181072	0
Itgb5[kkk]	5 integrin	Gg	Dn	Indirect.	0009893063	0
Itgb7	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

Kpna2[lll]	importin	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; 11002347	0
lef1	lef1	Dr	Dn	Probably indirect.	1282809; 1281113; 0009828104; 0010694499	0
Lmna	lamins A/C	Mm, Hs	vrs	Probably indirect.	0001610391	0
Lpl	LPL	Mm	–		0009889331	0
Mbp	MBP	Rn	Up	No change in mRNA (but enzymatic activity decreased). Appears to be primarily a T3/TR system; may be activated by 9-cis/RXR in some cases.	0002178224; 0001320254; 0007615643; 0008908199; 0009111003; 9537651; 0009888461	0
MMP1	collagenase	Hs, Oc	Dn	Indirect; several mechanisms proposed.	0002176152; 10548534; 10429942	0
MMP3	Stromelysin	Rn, Hs, Bt, Ss	vrs	No good t/d data; possible differences between species in long term exposure; probably indirect.	9565574; 9824620; 10646501; 11172606	0
MMP9	92-kD gelatinase, MMP-9	Hs	Dn[mmm]	Probably indirect.	6321491;	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.		
MST1	HGFL	Hs	Dn	No good d/t data; region responsible for RA inhibition identified; probably indirect.		
MUC4	MUC4	Hs	Up	No good d/t data; probably indirect (TGFb2 involved in some systems).		
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.		
NORPEG	NORPEG	Hs	Up	No good d/t data; probability of indirect mechanisms discussed.	0008662930;	
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	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-	Mm	Up	No good d/t data; probably indirect.	0010509805	0
Pparg	PPAR-	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
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	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 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	preprothyrotropinreleasing 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