# Decoy receptor 3 regulates the expression of various genes in rheumatoid arthritis synovial fibroblasts

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**Abstract.** Decoy receptor 3 (DcR3), a member of the tumor necrosis factor (TNF) receptor (TNFR) superfamily, lacks the transmembrane domain of conventional TNFRs in order to be a secreted protein. DcR3 competitively binds and inhibits members of the TNF family, including Fas ligand (FasL), LIGHT and TNF-like ligand 1A (TL1A). We previously reported that TNFα-induced DcR3 overexpression in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) protects cells from Fas-induced apoptosis. Previous studies have suggested that DcR3 acting as a ligand directly induces the differentiation of macrophages into osteoclasts. Furthermore, we reported that DcR3 induces very late antigen-4 (VLA-4) expression in THP-1 macrophages, inhibiting cycloheximide-induced apoptosis and that DcR3 binds to membrane-bound TL1A expressed on RA-FLS, resulting in the negative regulation of cell proliferation induced by inflammatory cytokines. In the current study, we used cDNA microarray to search for genes in RA-FLS whose expression was regulated by the ligation of DcR3. The experiments revealed the expression profiles of genes in RA-FLS regulated by DcR3. The profiles showed that among the 100 genes most significantly regulated by DcR3, 45 were upregulated and 55 were downregulated. The upregulated genes were associated with protein complex assembly, cell motility, regulation of transcription, cellular protein catabolic processes, cell membrane, nucleotide binding and glycosylation. The downregulated genes were associated with transcription regulator activity, RNA biosynthetic processes, cytoskeleton, zinc finger region, protein complex assembly, phosphate metabolic processes, mitochondrion, ion transport, nucleotide binding and cell fractionation. Further study of the genes detected in the current study may provide insight into the pathogenesis and treatment of rheumatoid arthritis by DcR3-TL1A signaling.

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*Key words:* rheumatoid arthritis, fibroblast-like synoviocytes, decoy receptor 3, microarray assay, gene expression profile

## Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease characterized by hyperplasia of the synovial tissue and formation of pannus, which grows invasively into the cartilage, causing cartilage and bone destruction. Analyses of hyperplastic synovial tissue of patients with RA have revealed a number of features of transformed long-living cells, such as the presence of somatic mutations, expression of oncogenes and resistance to apoptosis (1-3).

We previously reported that the decoy receptor 3 (DcR3)/TR6/M68/tumor necrosis factor receptor (TNFR) superfamily member 6 (TNFRSF6b) is expressed in rheumatoid fibroblast-like synoviocytes (RA-FLS), and that DcR3 expression induced in RA-FLS by TNFα protects cells from Fas-induced apoptosis (4). DcR3, a member of the TNFR superfamily, lacks the transmembrane domain of conventional TNFRs and thus can be a secreted protein (5). DcR3 is typically overexpressed in tumor cells, including lung and colon cancers (5), gliomas, gastrointestinal tract tumors (6) and virus-associated leukemia (7). In addition, as previous studies have demonstrated, DcR3 is expressed in some normal tissues, including the colon, stomach, spleen, lymph nodes, spinal cord, pancreas and lungs (5,6). However, DcR3 is not expressed in NIH3T3 human fibroblast cells (8). DcR3 has 3 ligands, Fas ligand (FasL), LIGHT and TNF-like ligand 1A (TL1A), which are members of the TNF superfamily (9). The overexpression of DcR3 may benefit tumors by helping them avoid the cytotoxic and regulatory effects of FasL (5,10), LIGHT (11) and TL1A (12). In a previous study, we suggested that DcR3 is one of the key molecules that regulate the proliferation of RA-FLS (4).

Previous studies have suggested that DcR3 directly induces osteoclast formation from monocytes (13), and that DcR3 triggers the enhanced adhesion of monocytes via reverse signaling (14). We have also reported that DcR3 induces very late antigen-4 (VLA-4) expression in THP-1 macrophages, inhibiting cycloheximide-induced apoptosis (15). As for RA-FLS, in a recent study, we reported that DcR3 binds to membrane-bound TL1A expressed on RA-FLS, resulting in the negative regulation of cell proliferation induced by inflammatory cytokines (16). Therefore, we hypothesized that DcR3 plays a role in the pathogenesis of RA, not only as a decoy receptor, but also as a ligand via TL1A on RA-FLS. However, the function of DcR3 as a ligand in RA-FLS is not yet well understood. In the current study, we searched for genes in RA-FLS whose expression was regulated by the ligation of DcR3 using cDNA microarray. The gene expression profiles may reveal the possible target molecules that play a significant role in the DcR3-TL1A signaling pathway in the pathogenesis of RA.

## Materials and methods

*Isolation and culture of synovial fibroblasts*. RA-FLS were obtained during total knee replacement surgery from 4 patients (samples 1-4) with RA who fulfilled the 1987 criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (17), who had never been treated with biological drugs. Synovial samples were collected from the patients who provided written consent in order to participate in this study in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The protocol, including consent procedures, was approved by Kobe University Graduate School of Medicine Ethics Committee. Tissue specimens were minced and digested in Dulbecco's modified Eagle's medium (DMEM; Gibco BRL, Grand Island, NY, USA) containing 0.2% collagenase (Sigma, St. Louis, MO, USA) for 2 h at 37˚C with 5% $CO_2$. The dissociated cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS; BioWhittaker, Walkersville, MD, USA) and 100 U/ml of penicillin/streptomycin. Following overnight culture, the non-adherent cells were removed, and the adherent cells were subsequently incubated further in fresh medium. All experiments were conducted using cells from passages 3 to 4 (4).

*RNA extraction*. Four individual lines (samples 1-4) of primary cultured RA-FLS ($2x10^6$ cells/well) were incubated with 1.0 $\mu$g/ml of recombinant DcR3-Fc protein or control human IgG1 (R&D Systems, Minneapolis, MN, USA) for 12 h at 37˚C with 5% $CO_2$. Following incubation, RNA was extracted using a QIAshredder and the RNeasy Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Extraction of total RNA was performed for each sample separately.

*Gene expression profiling and data analysis*. Gene expression was detected by microarray (Human Genome U133 Plus 2.0, GeneChip® 3' Expression Array; Affymetrix, Santa Clara, CA, USA). The labeling of RNA probes, hybridization and washing were carried out according to the manufacturer's instructions.

Avadis 3.3 Prophetic software (Strand Life Sciences, Bangalore, India) was used for statistical analysis. Differentially expressed genes were extracted by a paired t-test, with a P-value <0.05 considered to indicate a statistically significant difference, and fold change >1.4, and ordered into hierarchical clusters using the Euclidean algorithm as the distance measure, and the complete algorithm as the linkage method.

Microarray data have been deposited in NCBIs Gene Expression Omnibus (GEO) and are accessible through GEO series accession no. GSE45665.

## Results

*Microarray analysis (gene expression profiling of RA-FLS stimulated by DcR3-Fc)*. Microarray data analysis revealed that DcR3 upregulated or downregulated the expression of various genes in RA-FLS. We identified the 100 most differentially regulated genes in the DcR3-stimulated group compared with the control IgG1-stimulated group. Among these, 45 genes were upregulated (Table I) and 55 genes were downregulated (Table II).

*Hierarchical clustering analysis*. The upregulated and downregulated genes were classified into 7 and 10 categories according to their biological functions, respectively (Fig. 1). The upregulated genes were associated with protein complex assembly, cell motility, regulation of transcription, cellular protein catabolic processes, cell membrane, nucleotide binding and glycosylation. The upregulated genes belonging to each cluster are listed in Table III. The downregulated genes were associated with transcription regulator activity, RNA biosynthetic processes, cytoskeleton, zinc finger region, protein complex assembly, phosphate metabolic processes, mitochondrion, ion transport, nucleotide binding and cell fractionation. The downregulated genes belonging to each cluster are listed in Table IV.

## Discussion

Among the 3 ligands of DcR3, TL1A (TNFSF15) is expressed by endothelial cells (12), macrophages (18,19), T cells (20,21), monocytes (22,23), dendritic cells (23), chondrocytes (24) and synovial fibroblasts (24), and contributes to the pathogenesis of cancer and autoimmune diseases via the apoptotic, stress, mitogenic and inflammation pathway by binding death receptor 3 (DR3) and DcR3 (12,25). The 3 ligands of DcR3 have been reported to contribute to the pathogenesis of RA (4,24,26,27). In these studies, DcR3 was considered a decoy receptor for ligands. We previously demonstrated that DcR3 binds to membrane-bound TL1A expressed on RA-FLS when it acts as a ligand in the pathogenesis of RA (16).

Genome-wide gene expression cDNA microarray is a powerful technique used to investigate the pathophysiology of a variety of diseases, including tumors (28-30), immune-mediated diseases (31,32) and inflammatory diseases (33-35). Using microarray, Chang *et al* revealed that genes characteristically expressed by tumor-associated macrophages were upregulated by DcR3 (30). In the current study, we first demonstrated the expression profiles of genes in RA-FLS regulated by DcR3.

We demonstrated that DcR3 regulates the expression of genes that are mainly associated with the upregulation of the

Table I. The 45 genes upregulated by DcR3.

| Gene symbol | Representative public ID | P-value | Fold change | Gene title |
|---|---|---|---|---|
| --- | AW612461 | 0.002695443 | 2.0972981 | --- |
| CDH2 | NM_001792 | 0.0327261 | 1.9276143 | Cadherin 2, type 1, N-cadherin (neuronal) |
| AGPAT9 | BC006236 | 0.006782195 | 1.9184313 | 1-Acylglycerol-3-phosphate O-acyltransferase 9 |
| LOC440944 | BC036698 | 0.039432783 | 1.8932389 | Hypothetical protein LOC440944 |
| BIVM | BC039587 | 0.012760683 | 1.6798534 | Basic, immunoglobulin-like variable motif-containing protein |
| ZC3H3 | D63484 | 0.02914655 | 1.6767992 | Zinc finger CCCH-type containing 3 |
| IL12B | NM_002187 | 0.008306135 | 1.6463093 | Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40) |
| NUB1 | AK026433 | 0.045851827 | 1.6456505 | Negative regulator of ubiquitin-like proteins 1 |
| LTV1 | AW236214 | 0.002476914 | 1.6453595 | LTV1 homolog (*S. cerevisiae*) |
| DMRT2 | AF284225 | 0.033502746 | 1.6123677 | Doublesex and mab-3 related transcription factor 2 |
| SUZ12P | AI820796 | 0.021593563 | 1.5686668 | Suppressor of zeste 12 homolog pseudogene |
| ZBTB1 | BU950380 | 0.039786864 | 1.5227357 | Zinc finger and BTB domain containing 1 |
| --- | N29716 | 0.00277571 | 1.5223095 | --- |
| --- | AK090762 | 0.034467466 | 1.5185958 | --- |
| --- | BG398977 | 0.015083793 | 1.5135463 | --- |
| RANBP17 | NM_022897 | 0.021518266 | 1.5035642 | RAN binding protein 17 |
| GAS5 | BF336936 | 0.041366957 | 1.499078 | Growth arrest-specific 5 (non-protein coding) |
| --- | BC031996 | 0.011258653 | 1.4903411 | --- |
| REPS2 | AI984607 | 0.012121066 | 1.4882914 | RALBP1 associated Eps domain containing 2 |
| LOC645158 | BC018088 | 0.013921799 | 1.4854323 | Hypothetical protein LOC645158 |
| --- | AI332454 | 0.012677074 | 1.4752275 | --- |
| CCDC138 | AU152965 | 0.022518823 | 1.4711432 | Coiled-coil domain containing 138 |
| hCG_1749898 | BC012486 | 0.002276273 | 1.471024 | KRTAP2-4 protein |
| --- | AI693281 | 0.0196566 | 1.4607961 | --- |
| TUBB2B | AL533838 | 0.006628409 | 1.4584572 | Tubulin, beta 2B |
| SLC9A9 | AA029791 | 0.004298657 | 1.4567653 | Solute carrier family 9 (sodium/hydrogen exchanger), member 9 |
| --- | AA505135 | 0.023416178 | 1.4560933 | --- |
| SLC16A6 | AI873273 | 0.032126337 | 1.4534916 | Solute carrier family 16, member 6 (monocarboxylic acid transporter 7) |
| --- | AL080112 | 0.035647828 | 1.4486992 | --- |
| LOC100128988 | AI761436 | 0.035967685 | 1.4464797 | Similar to hCG2018847 |
| ZNF252 | AU145662 | 0.015798416 | 1.4447424 | Zinc finger protein 252 |
| FGFR1OP2 | R91766 | 0.021976791 | 1.4398756 | FGFR1 oncogene partner 2 |
| --- | R26931 | 0.03931969 | 1.4398652 | --- |
| ZBTB10 | BG483802 | 0.006168698 | 1.4324573 | Zinc finger and BTB domain containing 10 |
| C3AR1 | U62027 | 0.031616967 | 1.4275972 | Complement component 3a receptor 1 |
| ZER1 | NM_006336 | 0.000529948 | 1.4270489 | Zer-1 homolog (*C. elegans*) |
| THRB | BF431989 | 0.027043225 | 1.4229552 | Thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian) |
| FLJ35220 | AI311040 | 0.008202907 | 1.422941 | Hypothetical protein FLJ35220 |
| CDH10 | NM_006727 | 0.018871933 | 1.4211183 | Cadherin 10, type 2 (T2-cadherin) |
| PEX13 | BC040953 | 0.00670011 | 1.4182297 | Peroxisomal biogenesis factor 13 |
| C7orf58 | NM_024913 | 0.04462639 | 1.4087468 | Chromosome 7 open reading frame 58 |
| DOK3 | BC004564 | 0.039809346 | 1.4068991 | Docking protein 3 |
| --- | CA776505 | 0.038875684 | 1.4046313 | --- |
| EGR3 | NM_004430 | 0.008657368 | 1.4038599 | Early growth response 3 |
| ZNF681 | BG281940 | 0.009279283 | 1.4019198 | Zinc finger protein 681 |

DcR3, decoy receptor 3.

Table II. The 55 genes downregulated by DcR3.

| Gene symbol | Representative public ID | P-value | Fold change | Gene title |
|---|---|---|---|---|
| TPH1 | NM_004179 | 0.022398373 | 2.4520018 | Tryptophan hydroxylase 1 |
| TREML4 | AK090633 | 0.028559439 | 1.9765018 | Triggering receptor expressed on myeloid cells-like 4 |
| CEP70 | AI285884 | 0.038745213 | 1.8690827 | Centrosomal protein 70 kDa |
| CCNB2 | AK023404 | 0.040380865 | 1.8138049 | Cyclin B2 |
| CCDC121 | NM_024584 | 0.023371078 | 1.8025432 | Coiled-coil domain containing 121 |
| ZNF563 | NM_145276 | 0.01811626 | 1.7816929 | Zinc finger protein 563 |
| PANK2 | AV703394 | 0.025317192 | 1.769196 | Pantothenate kinase 2 |
| --- | N46436 | 0.047841128 | 1.7669531 | --- |
| ZFP28 | AW590434 | 0.011407225 | 1.7393188 | Zinc finger protein 28 homolog (mouse) |
| LOC284926 | BG828817 | 0.04181046 | 1.7324702 | Hypothetical protein LOC284926 |
| SLC24A1 | AF026132 | 0.001774447 | 1.7150456 | Solute carrier family 24 (sodium/potassium/calcium exchanger), member 1 |
| --- | AU146924 | 0.04154287 | 1.699999 | --- |
| SOS2 | L20686 | 0.019266233 | 1.6804754 | Son of sevenless homolog 2 (*Drosophila*) |
| UBE3B | AL096740 | 0.048379965 | 1.6700492 | Ubiquitin protein ligase E3B |
| ELL | AL521391 | 0.03850427 | 1.6655054 | Elongation factor RNA polymerase II |
| SEZ6L2 | AF131749 | 0.008593195 | 1.6527929 | Seizure related 6 homolog (mouse)-like 2 |
| MB | NM_005368 | 0.024074124 | 1.650637 | Myoglobin |
| --- | BC040628 | 0.049794715 | 1.6501505 | --- |
| MCOLN3 | NM_018298 | 0.030422723 | 1.6494503 | Mucolipin 3 |
| --- | AK021551 | 0.04994646 | 1.6114371 | --- |
| --- | BF062156 | 0.03806778 | 1.5880637 | --- |
| FBXL17 | AW002273 | 0.003356424 | 1.5799221 | F-box and leucine-rich repeat protein 17 |
| ZNF117 | BF107006 | 0.048431396 | 1.5662925 | Zinc finger protein 117 |
| C1orf230 | AV746331 | 0.007892164 | 1.5605123 | Chromosome 1 open reading frame 230 |
| --- | AA650017 | 0.049496956 | 1.5536357 | --- |
| VKORC1L1 | NM_173517 | 0.01724287 | 1.5391829 | Vitamin K epoxide reductase complex, subunit 1-like 1 |
| MIR155HG | BG231961 | 0.026413728 | 1.5365719 | MIR155 host gene (non-protein coding) |
| KCNAB1 | L39833 | 0.024623908 | 1.534346 | Potassium voltage-gated channel, shaker-related subfamily, beta member 1 |
| --- | AI870634 | 0.048582062 | 1.5243825 | --- |
| YTHDC2 | AW975818 | 0.008661097 | 1.5151424 | YTH domain containing 2 |
| CCNO | BC004877 | 0.012114909 | 1.5041811 | Cyclin O |
| C5orf24 | AW068615 | 0.029783456 | 1.5023562 | Chromosome 5 open reading frame 24 |
| --- | AV648424 | 0.032394256 | 1.5009412 | --- |
| ADRBK2 | NM_005160 | 0.034059193 | 1.4894675 | Adrenergic, beta, receptor kinase 2 |
| PIH1D2 | AI744716 | 0.0245486 | 1.477943 | PIH1 domain containing 2 |
| --- | BF224218 | 0.036218014 | 1.4755102 | --- |
| --- | BF591554 | 0.042058036 | 1.474276 | --- |
| GRIN2A | N48896 | 0.006276551 | 1.4638788 | Glutamate receptor, ionotropic, N-methyl D-aspartate 2A |
| RABL2A///RABL2B | NM_007082 | 0.00963415 | 1.4549305 | RAB, member of RAS oncogene family-like 2A///RAB, member of RAS oncogene family-like 2B |
| MYH14 | BC000676 | 0.009328251 | 1.4530606 | Myosin, heavy chain 14 |
| LOC727820 | AW340595 | 0.018635018 | 1.4494766 | Hypothetical protein LOC727820 |
| --- | AW074143 | 0.04609772 | 1.448378 | --- |
| ATP5G2 | X69909 | 0.005548685 | 1.4429137 | ATP synthase, $H^+$ transporting, mitochondrial F0 complex, subunit C2 (subunit 9) |
| MDM4 | AW269813 | 0.031021323 | 1.4353052 | Mdm4 p53 binding protein homolog (mouse) |
| C11orf84 | AI866590 | 0.02536254 | 1.433334 | Chromosome 11 open reading frame 84 |
| STYX | AW968935 | 0.000515506 | 1.4238193 | Serine/threonine/tyrosine interacting protein |

Table II. Continued.

| Gene symbol | Representative public ID | P-value | Fold change | Gene title |
|---|---|---|---|---|
| S100A14 | NM_020672 | 0.03042584 | 1.4226245 | S100 calcium binding protein A14 |
| --- | BE549780 | 0.020434508 | 1.4224106 | --- |
| NEURL4 | AL136870 | 0.03654641 | 1.4173305 | Neuralized homolog 4 (*Drosophila*) |
| --- | AI803010 | 0.009107939 | 1.4132907 | --- |
| ETV7 | AF218365 | 0.007053576 | 1.4130081 | Ets variant 7 |
| RBBP9 | AL121893 | 0.01381168 | 1.4109538 | Retinoblastoma binding protein 9 |
| --- | AI298755 | 0.048068948 | 1.4096705 | --- |
| LOC100130855 | AK093077 | 0.008585751 | 1.4052048 | Hypothetical protein LOC100130855 |
| TSFM | AI796813 | 0.005840706 | 1.4036938 | Ts translation elongation factor, mitochondrial |

DcR3, decoy receptor 3.

Table III. Functional categories of the 45 upregulated genes classified into 7 categories.

| Functional category | Genes |
|---|---|
| Protein complex assembly | CDH2, RANBP17, REPS2, TUBB2B, PEX13 |
| Cell motility | CDH2, IL12B, PEX13 |
| Regulation of transcription | CDH2, ZC3H3, NUB1, DMRT2, ZBTB1, REPS2, SLC9A9, ZBTB10, THRB, CDH10, EGR3, ZNF681 |
| Cellular protein catabolic processes | ZER1 |
| Cell membrane | CDH2, AGPAT9, RANBP17, SLC9A9, SLC16A6, C3AR1, CDH10, PEX13, DOK3 |
| Nucleotide binding | RANBP17, TUBB2B, |
| Glycosylation | CDH2, IL12B, SLC9A9, C3AR1, CDH10, C7orf58 |

Table IV. Functional categories of the 55 downregulated genes classified into 10 categories.

| Functional category | Genes |
|---|---|
| Transcription regulator activity | ZNF563, ZFP28, ELL, ZNF117, CCNO, MDM4, ETV7, TSFM |
| RNA biosynthetic processes | ELL, ZNF117, ETV7, TSFM |
| Cytoskeleton | Cep70, CCNB2, GRIN2A, MYH14 |
| Zinc finger region | TPH1, ZNF563, ZFP28, SLC24A1, SOS2, ELL, MB, ZNF117, KCNAB1, GRIN2A, MDM4, S100A14, ETV7, RBBP9, TSFM |
| Protein complex assembly | MDM4 |
| Phosphate metabolic processes | ADRBK2, ATP5G2, STYX |
| Mitochondrion | PANK2, ATP5G2, TSFM |
| Ion transport | TREML4, SLC24A1, SEZ6L2, MB, MCOLN3, VKORC1L1, KCNAB1, GRIN2A, ATP5G2 |
| Nucleotide binding | PANK2, YTHDC2, ADRBK2, RABL2A///RABL2B, MYH14 |
| Cell fractionation | CCNB2, SLC24A1, GRIN2A |

protein complex assembly, cell motility and the regulation of transcription, and the downregulation of transcription regulator activity, RNA biosynthetic processes and cytoskeleton. We then focused on the following genes: cadherin 2, type 1, N-cadherin (neuronal) (CDH2), interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40) (IL12B), tryptophan hydroxylase 1 (TPH1), centrosomal protein 70 kDa (Cep70) and Zinc finger proteins

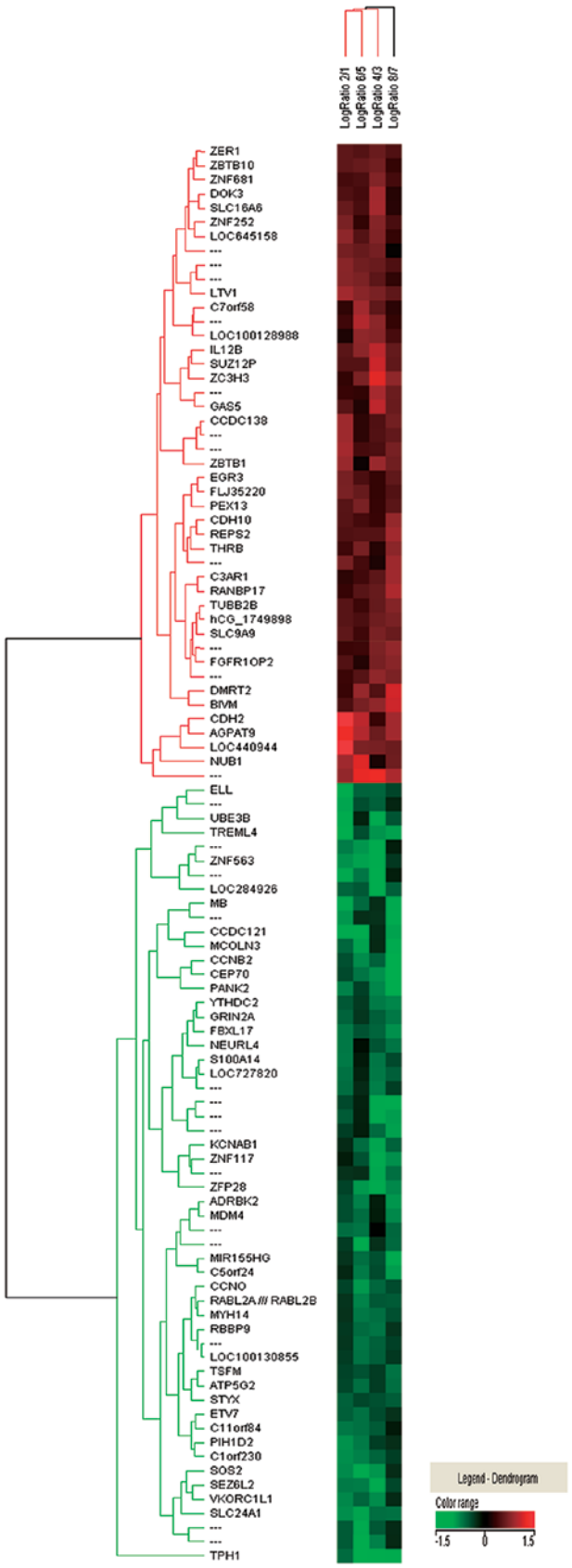


Figure 1. Cluster analysis and heat map of 100 significantly regulated probe sets. The heat map illustrates the expression values mapped to a color gradient from low (green) to high expression (red). Experiments are arranged according to a hierarchical clustering dendrogram. The horizontal dendrogram illustrates the similarity of functions between neighboring genes. The vertical dendrogram shows similarities in gene expression between neighboring samples.

as these genes were highly regulated, either upregulated or downregulated, and belonged to major functional clustering categories.

As for each gene, CDH2 has been reported to be associated with cell attachment and migration (36), metastatic potential (37), osteoblast differentiation (38) and the proliferation of RA-FLS (39).

IL12B encodes the IL-12B p40 subunit of IL-12 and IL-23 cytokines. IL-12 induces Th1 immune responses, and is thus linked with autoimmune diseases (40), while IL-23 is linked with autoimmune diseases via Th17 immune responses (41). IL-12 (42) and IL-23 (43,44) have also been reported to be involved in the pathogenesis of RA.

TPH1 is a rate-limiting enzyme involved in the synthesis of serotonin, and has been reported to be associated with the pathogenesis of RA through the inflammatory pathway (45) and bone biology (46-48).

Cep70 was discovered in a proteomic study of the centrosome (49). Centrosomal activity is indispensable for the execution of cytokinesis and the progression of the cell cycle (50). Cep70 is crucial for mitotic spindle assembly (51) and promotes microtubule polymerization by increasing microtubule elongation (52).

Zinc finger proteins are involved in a broad range of biological activities, including double-stranded DNA binding, single-stranded DNA and RNA recognition, as well as coordinating protein-protein interactions (53).

In the current study, we first reported the expression profiles of genes in RA-FLS regulated by DcR3. Combined with our previous findings that DcR3 serves as a ligand by binding to membrane-bound TL1A on RA-FLS, our data demonstrate that DcR3 may regulate the gene expression of various key molecules in RA-FLS by binding to TL1A, thus affecting the pathogenesis of RA, such as proliferation, apoptosis, inflammation and bone biology. Further studies on the genes detected in the current study may provide a deeper understanding of the pathogenesis and treatment of RA by DcR3-TL1A signaling.

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