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Expression profiling of genes in rheumatoid fibroblast-like synoviocytes regulated by tumor necrosis factor-like ligand 1A using cDNA microarray analysis

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Abstract. Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation in synovial tissues. Hyperplasia of synovial tissue leads to the formation of pannus, which invades joint cartilage and bone resulting in joint destruction. Tumor necrosis factor-like ligand 1A (TL1A), a member of the tumor necrosis factor superfamily (TNFSF15), contributes to the pathogenesis of autoimmune diseases, including RA. In the present study, a cDNA microarray was used to search for genes whose expression in rheumatoid fibroblast-like synoviocytes (RA-FLS) were regulated by TL1A. Four individual lines of primary cultured RA-FLS were incubated either with recombinant human TL1A protein or phosphate-buffered saline, as an unstimulated control, for 12 h. Gene expression was then detected through the microarray assay. The results revealed the expression profiles of genes in RA-FLS regulated by TL1A. The present study also demonstrated the functions of those genes whose expression in RA-FLS was regulated by TL1A. Among the genes in this profile, the present study focused on the following genes: Spectrin repeat-containing nuclear envelope 1, Fc receptor-like 2, PYD (pyrin domain)-containing 1, cell division cycle 45 homolog, signal transducer and activator of transcription 5B, and interferon regulatory factor 4. These genes may affect the pathogenesis of RA, including proliferation, regulation of B cells and T cells, inflammation, and cytokine processing. The present study revealed for the first time, to the best of our knowledge, the expression profile of genes in RA-FLS regulated by TL1A. The data indicate that TL1A may regulate the gene expression of various key molecules in RA-FLS, thus affecting the pathogenesis of RA. Further investigations of the genes detected in the current profiles may provide a deeper understanding of the pathogenesis and a novel target for the treatment of RA.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation in synovial tissues. Hyperplasia of synovial tissue leads to the formation of pannus, which invades joint cartilage and bone, resulting in joint destruction. Previous reports have indicated that a number of features of transformed long-lived cells are observed in the hyperplastic synovial tissues of patients with RA, including oncogene expression, resistance to apoptosis and the presence of somatic mutations (1-3). Several explanations for the resistance of RA-FLS to apoptosis have been suggested, including deregulation of the Bcl-2 family of proteins critical to intrinsic pathway regulation, deregulation of the nuclear factor (NF)-κB signaling pathway, p53 mutations and a low expression of PUMA, found in the RA synovium and FLS, which provides an explanation for the lack of p53-induced FLS apoptosis (4).

Tumor necrosis factor (TNF)-like ligand 1A (TL1A)/TNFSF15, a member of the TNF superfamily, is expressed by endothelial cells (5), macrophages (6,7), T cells (8,9), monocytes (10,11), dendritic cells (11), chondrocytes (12) and synovial fibroblasts (12), and contributes to the pathogenesis of cancer and autoimmune diseases via the apoptotic, stress, mitogenic and inflammation pathways by binding to death receptor 3 (DR3) and decoy receptor 3 (DcR3) (5,13). Previous studies have reported that the expression of TL1A is increased in the synovial fluid and serum from patients with RA (12,14), and that TL1A increases the production of interleukin (IL)-6 on rheumatoid fibroblast-like synoviocytes (RA-FLS) (15). In a previous *in vivo* study, it was demonstrated that TL1A treatment increased the severity of arthritis and destruction of bone in a collagen-induced arthritis mouse model of RA (12).

DcR3/TR6/M68/TNFRSF6b, a member of the TNF receptor superfamily, binds to three ligands, Fas ligand

(FasL), LIGHT and TL1A, which are members of the TNF superfamily (16). The overexpression of DcR3 may benefit tumors by enabling them to avoid the cytotoxic and regulatory effects of FasL (17,18), LIGHT (19) and TL1A (5). In our previous studies, it was demonstrated that DcR3 is expressed in RA-FLS (20), and that DcR3 binds to TL1A expressed on RA-FLS, resulting in the negative regulation of cell proliferation induced by inflammatory cytokines (21). The expression profiles of genes regulated by DcR3 in RA-FLS were further revealed, which were obtained through the use of a cDNA microarray (22). Based on these profiles, it was suggested that DcR3-TL1A signaling is involved in the pathogenesis of RA (23-25).

Although the gene expression profiles regulated by DcR3 were revealed in our previous study, how TL1A, one of the ligands of DcR3, contributes to the pathogenesis of RA remains to be fully elucidated. As the functions of TL1A are diverse, it was hypothesized that TL1A controls the expression of genes potentially involved in the pathogenesis of RA.

In the present study, a search was performed to identify those genes whose expression in RA-FLS is regulated by TL1A through use of a cDNA microarray. The gene expression profiles revealed a series of genes that may serve a significant role in the pathogenesis of RA in the TL1A-DcR3/DR3 signaling pathway.

Materials and methods

Isolation and culture of synovial fibroblasts. RA-FLS were obtained from four patients (samples 1-4) with RA who fulfilled the 1987 criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (26) during total knee replacement surgery. The patients were four women aged 73.0±11.2 years old. Their C-reactive protein levels and erythrocyte sedimentation rates were 2.04±2.16 mg/dl and 60.0±22.1 mm/h, respectively. In terms of drug therapy for RA, two patients were administered oral methotrexate (MTX; average dose, 3.00±1.41 mg/week), one was administered salazosulfapyridine (1 g/day), and one was administered mizoribine (150 mg/day). Prednisolone (PSL) was used in the treatment of all four patients (average dose, 3.63±2.14 mg/day). The patients had never been treated with biological disease-modifying anti-rheumatic drugs or Janus kinase inhibitors.

Synovial samples were collected from the patients, who provided informed written consent to their involvement in the 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 the Ethics Committee of Kobe University Graduate School of Health Sciences (Kobe, Japan; approval no. 308). The tissue specimens were minced and digested in Dulbecco's modified Eagle's medium (DMEM; Merck KGaA, Darmstadt, Germany) containing 0.2% collagenase (Merck KGaA) for 2 h at 37˚C with 5% CO_2. The dissociated cells were cultured in DMEM supplemented with 10% fetal bovine serum (Merck KGaA) and 100 U/ml of penicillin/streptomycin (Meiji Seika Pharma Co., Ltd., Tokyo, Japan). Following incubation overnight and the removal of non-adherent cells, the adherent cells were further incubated in fresh medium. All experiments were performed using cells from passages 3-4 (20).

RNA extraction. Four individual cell lines (samples 1-4) of primary cultured RA-FLS ($2x10^6$ cells/well) were incubated with 1.0 μg/ml of recombinant human TL1A protein (R&D Systems, Inc., Minneapolis, MN, USA) or were left untreated with OPTI-MEM medium (Thermo Fisher Scientific, Inc., Waltham, MA, USA) for 12 h at 37˚C with 5% CO_2. Following incubation, RNA was extracted with QIAshredder (Qiagen GmbH, Hilden, Germany) and RNeasy Mini kit (Qiagen GmbH) according to the manufacturer's protocol. The extraction of total RNA was performed for each sample separately.

Gene expression profiling and data analysis. Gene expression was detected by microarray assay (Human Genome U133 Plus 2.0, GeneChip® 3' Expression Array; Thermo Fisher Scientific, Inc.). The labeling of RNA probes, hybridization and washing were performed according to the manufacturer's protocol.

Avadis 3.3 Prophetic software (Strand Life Sciences, Bangalore, India) was used for statistical analysis (27). Differentially expressed genes were extracted using a paired t-test with $P<0.05$ 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. Values are expressed as the mean ± standard deviation unless otherwise indicated.

Results

Microarray analysis for gene expression profiling of RA-FLS stimulated by TL1A. The microarray analysis performed in the present study (Human Genome U133 Plus 2.0, GeneChip® 3' Expression Array) detected the expression of 54,613 genes. The entire microarray data obtained were deposited in the NCBI Gene Expression Omnibus (GEO) and are accessible through GEO series accession no. GSE118958 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse118958).

The microarray analysis revealed that TL1A upregulated or downregulated the expression of various genes in RA-FLS. The NCBI UniGene database (https://www.ncbi.nlm.nih.gov/UniGene/clust.cgi?ORG=Hs&CID=55682) was used to identify the gene names, with gene symbols representing abbreviations of the gene names. The fold change is the ratio of each gene expression in the TL1A-stimulated group compared with that in the control group. Among the 100 most differentially upregulated genes by TL1A, 67 genes were annotated in the database, and 21 of these 67 genes upregulated by TL1A are shown in Table I. Gene annotations of 58 of the 100 most differentially downregulated genes by TL1A were also annotated in the database, and 21 of the 58 genes downregulated by TL1A are shown in Table II. The results of hierarchical clustering analysis for the 100 most upregulated genes and the 100 most downregulated genes are illustrated in Figs. 1 and 2, respectively.

Functional annotation. The 100 genes most regulated by TL1A were significantly classified into 14 categories registered in the Database for Annotation, Visualization and Integrated

Table I. List of the 21 genes upregulated by tumor necrosis factor-like ligand 1A.

Gene symbol	Fold-change	P-value	Gene name
SYNE1	15.3	0.013391	Spectrin repeat-containing, nuclear envelope 1
PDE11A	14.40000186	0.013724	Phosphodiesterase 11A
MGC15705	12.6299996	0.006738	Hypothetical protein MGC15705
COG2	12.61445783	0.016001	Component of oligomeric golgi complex 2
FCRL2	11.97633136	0.000003	Fc receptor-like 2
RAD21L1	11.82758621	0.007302	RAD21-like 1 (*S. pombe*)
PPP4R1L	10.1975316	0.005913	Protein phosphatase 4, regulatory subunit 1-like
MIER3	9.72072035	0.048129	Mesoderm induction early response 1, family member 3
LOC100505801	9.711538484	0.029304	Hypothetical LOC100505801
C12orf74	9.576924282	0.008377	Chromosome 12 open reading frame 74
CCNE2	9.118012422	0.039656	Cyclin E2
LOC100288507	9.064056744	0.009929	Hypothetical protein LOC100288507
USH2A	8.986842105	0.048673	Usher syndrome 2A (autosomal recessive, mild)
SEZ6L	8.7578125	0.002512	Seizure related 6 homolog (mouse)-like
LOC100133308	8.376812174	0.026850	Ras suppressor protein 1 pseudogene
MLL	8.357512953	0.007109	Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*)
SYTL3	8.348148148	0.038552	Synaptotagmin-like 3
GAGE12F///GAGE12G/// GAGE12I///GAGE5///GAGE7	8.124137931	0.018128	G antigen 12F///G antigen 12G///G antigen 12I///G antigen 5/// G antigen 7
FRMD4A	7.891089109	0.044768	FERM domain-containing 4A
LOC404266	7.725807116	0.003327	Hypothetical LOC404266
PYDC1	5.42662116	0.006955	PYD (pyrin domain)-containing 1

Table II. List of the 21 genes downregulated by tumor necrosis factor-like ligand 1A.

Gene symbol	Fold-change	P-value	Gene name
CDC45	0.08	0.006927	Cell division cycle 45 homolog (*S. cerevisiae*)
STAT5B	0.10	0.019873	Signal transducer and activator of transcription 5B
BEND4	0.11	0.026734	BEN domain-containing 4
ALAS2	0.11	0.004251	Aminolevulinate, δ-, synthase 2
LOC728743	0.11	0.031562	Similar to GLI-Kruppel family member HKR1
LOC100130815	0.12	0.037456	Hypothetical LOC100130815
LOC255130	0.12	0.020509	Hypothetical LOC255130
RBM25	0.12	0.032102	RNA-binding motif protein 25
PARP15	0.12	0.028820	Poly (ADP-ribose) polymerase family, member 15
SUFU	0.12	0.025031	Suppressor of fused homolog (*Drosophila*)
MUC7	0.12	0.045462	Mucin 7, secreted
VPS35	0.12	0.013976	Vacuolar protein sorting 35 homolog (*S. cerevisiae*)
GKN1	0.13	0.013159	Gastrokine 1
KRT77	0.13	0.030364	Keratin 77
GOT1L1	0.14	0.047977	Glutamic-oxaloacetic transaminase 1-like 1
DEFA5	0.14	0.005483	Defensin, α5, Paneth cell-specific
SLC13A3	0.14	0.041769	Solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3
C10orf137	0.15	0.030915	Chromosome 10 open reading frame 137
PRTN3	0.15	0.001312	Proteinase 3
RASGRP1	0.15	0.038526	RAS guanyl-releasing protein 1 (calcium and DAG-regulated)
IRF4	0.22	0.027305	Interferon regulatory factor 4

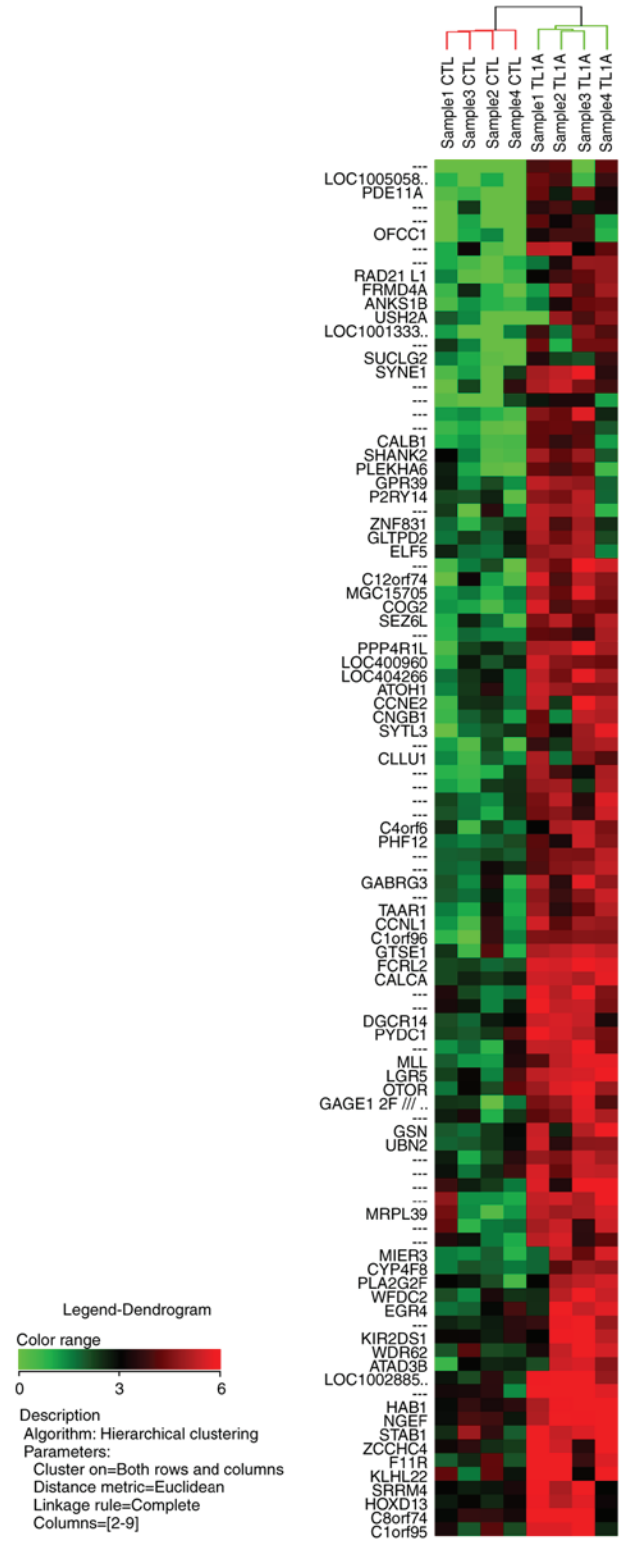

Figure 1. Cluster analysis and heat map of 100 probe sets significantly upregulated by TL1A. The heat map shows expression values mapped to a color gradient from low (green) to high expression (red). Experiments are arranged according to a hierarchical clustering dendrogram. The horizontal dendrogram shows the similarity of functions between neighboring genes. The vertical dendrogram shows the similarity of gene expression between neighboring samples. TL1A, tumor necrosis factor-like ligand 1A; CTL, control.

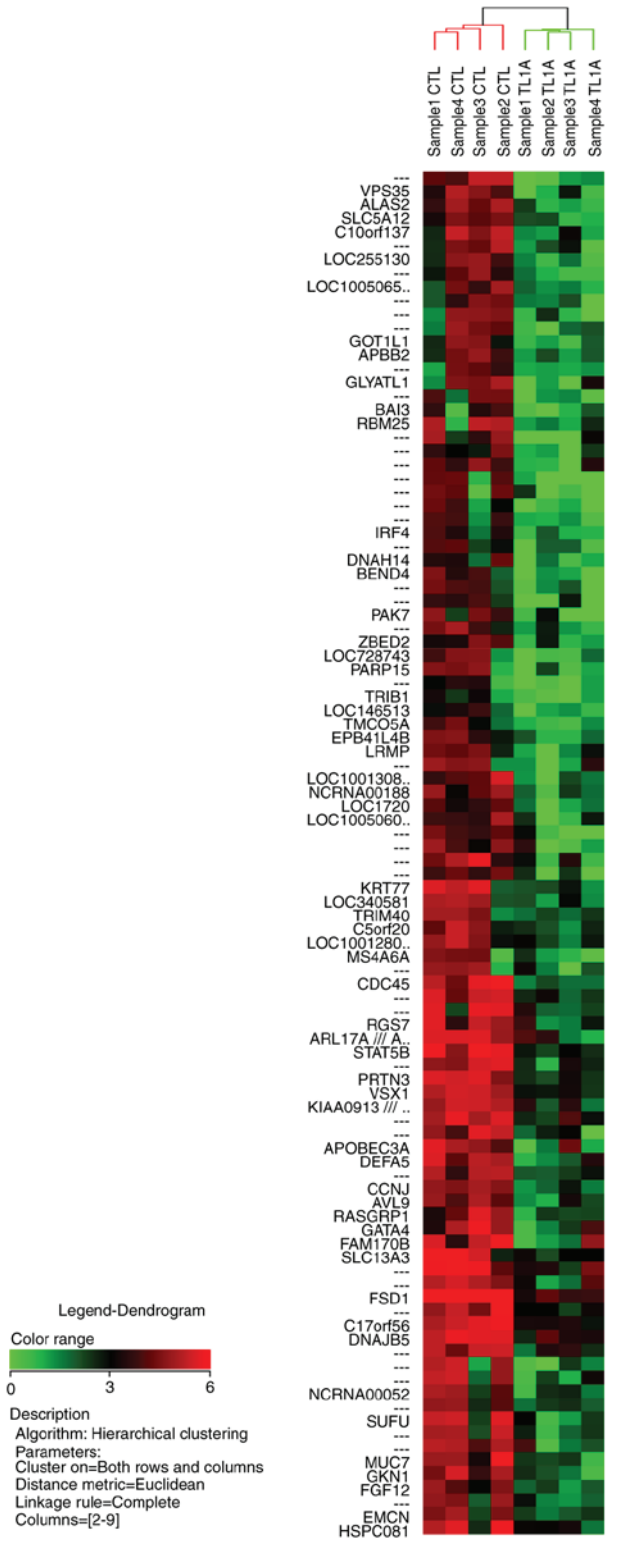

Figure 2. Cluster analysis and heat map of 100 probe sets significantly downregulated by TL1A. The heat map shows expression values mapped to a color gradient from low (green) to high expression (red). Experiments are arranged according to a hierarchical clustering dendrogram. The horizontal dendrogram shows the similarity of functions between neighboring genes. The vertical dendrogram shows the similarity of gene expression between neighboring samples. TL1A, tumor necrosis factor-like ligand 1A; CTL, control.

Discovery bioinformatics database (https://david.ncifcrf.gov/) according to their biological functions; alternative splicing, splice variant, coenzyme A, regulation of cytokine production, Cyclin; N-terminal, Cyclin, Pleckstrin homology-type, CYCLIN, transcription from RNA polymerase II promoter, cyclin, compositionally biased region:Ser-rich, postsynaptic

Table III. Functions of the 100 most regulated genes classified into 14 categories with statistical significance.

Term	P-value	Genes
Alternative splicing	0.004007	KIAA0913, ELF5, C17ORF56, FCRL2, PDE11A, FGF12, CNGB1, LGR5, GLYATL1, C10ORF137, CCNE2, PPP4R1L, ATAD3B, GSN, MIER3, KLHL22, MRPL39, USH2A, ANKS1B, BEND4, CCNJ, AVL9, CCNL1, TRIM40, SEZ6L, UBN2, PARP15, LRMP, WFDC2, PLA2G2F, EMCN, RAD21L1, DNAH14, OFCC1, EPB41L4B, SUFU, CALCA, RASGRP1, MS4A6A, C1ORF96, RBM25, NGEF, MLL, TMCO5A, PHF12, SHANK2, VSX1, SYNE1, ARL17B, ARL17A, WDR62, STAB1, RGS7, SLC13A3, SYTL3, IRF4, APBB2, DNAJB5, SLC5A12
Splice variant	0.00425	KIAA0913, ELF5, C17ORF56, FCRL2, PDE11A, FGF12, CNGB1, LGR5, GLYATL1, C10ORF137, CCNE2, PPP4R1L, ATAD3B, GSN, MIER3, KLHL22, MRPL39, USH2A, ANKS1B, BEND4, CCNJ, AVL9, CCNL1, TRIM40, SEZ6L, UBN2, PARP15, LRMP, WFDC2, PLA2G2F, EMCN, RAD21L1, DNAH14, OFCC1, EPB41L4B, SUFU, CALCA, RASGRP1, MS4A6A, C1ORF96, RBM25, NGEF, MLL, TMCO5A, PHF12, SHANK2, VSX1, SYNE1, ARL17B, ARL17A, WDR62, STAB1, RGS7, SLC13A3, SYTL3, IRF4, APBB2, DNAJB5, SLC5A12
Coenzyme A	0.011118	SAT1, ALAS2, SUCLG2
Regulation of cytokine production	0.013645	CALCA, STAT5B, GATA4, IRF4, PYDC1
Cyclin, N-terminal	0.01396	CCNE2, CCNJ, CCNL1
Cyclin	0.020121	CCNE2, CCNJ, CCNL1
Pleckstrin homology-type	0.025198	ANKS1B, NGEF, PLEKHA6, FRMD4A, EPB41L4B, APBB2
Cyclin	0.025934	CCNE2, CCNJ, CCNL1
Transcription from RNA polymerase II promoter	0.031469	ATOH1, MLL, ELF5, GATA4, HOXD13
Cyclin	0.033221	CCNE2, CCNJ, CCNL1
Compositionally biased region: Ser-rich	0.036248	SYNE1, SRRM4, KIAA0913, FRMD4A, C17ORF56, C5ORF20, UBN2
Postsynaptic membrane	0.036429	ANKS1B, GABRG3, SYNE1, SHANK2
Positive regulation of transcription from RNA polymerase II promoter	0.04068	ATOH1, MLL, STAT5B, GATA4, HOXD13, IRF4
Synapse	0.042545	ANKS1B, GABRG3, RAD21L1, SYNE1, APBB2, SHANK2

membrane, positive regulation of transcription from RNA polymerase II promoter, and synapse. The regulated genes belonging to each cluster are listed in Table III.

Discussion

Genome-wide gene expression cDNA microarrays provide a useful way of investigating the pathophysiology of a variety of diseases, including tumors (28-30), immune-mediated diseases (31,32), and inflammatory diseases (33-35). Using microarrays, our previous study revealed the expression profiles of genes in RA-FLS regulated by DcR3 (22). Subsequently, based on that profile, the significance of the regulation of IL-12B p40 (23), tryptophan hydroxylase 1 (24), and centrosomal protein 70 kDa (25) by DcR3 in RA-FLS was investigated in detail.

The present study is the first, to the best of our knowledge, to demonstrate the expression profiles of genes in RA-FLS regulated by TL1A. Among the genes in this profile, the following genes were of note: Spectrin repeat-containing nuclear envelope 1 (SYNE1), Fc receptor-like 2 (FCRL2), PYD (pyrin domain)-containing 1 (PYDC1), cell division cycle 45 homolog (CDC45), signal transducer and activator of transcription 5B (STAT5B), and interferon regulatory factor 4 (IRF4), as these genes were highly regulated by TL1A and belong to major functional clustering categories.

SYNE1 in RA-FLS was upregulated by TL1A in this gene expression profile. SYNE1 is a member of the spectrin family that is expressed in various tissues (36,37). It is reported to be associated with cytokinesis in HeLa cells (38), and the proliferation and apoptosis of mesenchymal stem cells (39).

FCRL2 was upregulated in this profile and is a member of the Fc receptor-like molecules superfamily. It is predominantly expressed by memory B cells and can influence B-cell signaling due to having both immunoreceptor tyrosine-based activation and inhibitory motifs (40-42). Jackson *et al* suggested that FCRL2 may serve as a negative regulator of the memory B cell response (43). FCRL2 has been reported to be expressed at high levels in B-cell chronic lymphocytic leukemia cells, affecting

disease progression and survival rates (42,44,45), and is associated with the inflammatory marker and disease activity of RA (46).

PYDC1 was upregulated in this profile. PYD-containing proteins have been reported to be involved in the activation of NF-κB and caspase-1, which regulates the processing of IL-1β and IL-18, and is associated with inflammation and apoptosis (47-49).

CDC45 was downregulated in this profile. CDC45 serves a critical role in DNA replication (50), and has been reported to be overexpressed in cancer cells (51) and cancer-derived cell lines (52). The expression of CDC45 is significantly suppressed by the knockdown of IL-1 receptor-associated kinase 1 in endometrial carcinoma (53). The expression of CDC45 is closely associated with proliferating cell populations in cancer (52).

STAT5B was downregulated in this profile. STATs regulate gene transcription to influence cellular functions, including proliferation, apoptosis, differentiation, reproduction and lipid metabolism, and have biological roles in several diseases, including autoimmune disease (54-60). The expression and activity of STATs can contribute to the onset, progression and severity of RA (61).

IRF4 was downregulated in this profile. IRF4 has been reported to be an RA risk locus, as identified by GWAS data analysis (62). IRF4 is an IRF family member of transcription factors and is associated with the development and function of immune cells (63). Previous studies have found that IRF4 regulates autoimmunity (63,64). In addition, IRF4 regulates Th17 cell differentiation and the production of IL-17, which are important for modulation of autoimmunity, including RA (63,65).

Although neither SYNE1 nor CDC45 are reported to be associated with RA directly, SYNE1 is associated with cytokinesis, proliferation and apoptosis, and CDC45 serves a critical role in the cell cycle of proliferating cells, which are important factors in the pathogenesis of RA.

The limitations of the present study included its small sample size and that it examined microarray data only, without detecting mRNA or protein expression. The results of the present study revealed a series of genes whose expression is regulated by TL1A in RA-FLS using microarray analysis, however, each gene revealed through microarray analysis requires confirmation one by one with mRNA or protein analysis in a future study. In addition to the expression analysis of each genes, how these genes regulated by TL1A in RA-FLS are involved in combination in the pathogenesis of RA also requires investigation in a future study.

In conclusion, the present study is the first, to the best of our knowledge, to report the expression profile of genes in RA-FLS regulated by TL1A. The data demonstrate that TL1A may regulate the gene expression of various key molecules in RA-FLS, thus affecting the pathogenesis of RA, including proliferation, regulation of B cells and T cells, inflammation, and cytokine processing. Further investigations of the genes detected in this profile may provide a deeper understanding of the pathogenesis and novel targets for the treatment of RA.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the NCBI GEO repository and are accessible through GEO series accession no. GSE118958, (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse118958).

Authors' contributions

KF was involved in conception and design, data collection and analysis, manuscript writing and final approval of the manuscript; YM was involved in conception and design, data collection and analysis, manuscript writing and final approval of the manuscript. TM was involved in conception and design, data collection, and final approval of the manuscript. SH was involved in conception and design, data collection and final approval of the manuscript. RK was involved in conception and design, data collection, and final approval of the manuscript.

Ethics approval and consent to participate

The study protocol, including consent procedures, was approved by the Ethics Committee of Kobe University Graduate School of Health Sciences (approval no. 308).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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