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ORIGINAL ARTICLE

The expression of GAS5, THRIL, and RMRP lncRNAs is increased in T cells of patients with rheumatoid arthritis

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Abstract

Objective Long non-coding RNAs (lncRNAs) comprise a large and diverse group of non-coding RNAs (ncRNAs) with important regulatory roles in various biological processes, including the immune system regulation. Rheumatoid arthritis (RA) as an autoimmune disease initiates inflammation in the synovial joints. T cells infiltrating into the synovial membrane have an important role in the pathogenesis of RA. The aim of the current investigation was to analyze the expression of four lncRNAs in the T cells from RA patients and healthy controls.

Methods In the current study, we investigated the expression of GAS5, RMRP, IFNϒ-AS1, and THRIL lncRNAs in circulating T cells from 20 patients with RA and 18 healthy matched controls by quantitative real-time PCR. T cell isolation was accomplished using the MAC method. We also analyzed the correlation between lncRNA expression and clinical parameters. Also, the mRNA expression levels of IL-17 and TNF-α and the association between lncRNAs and these cytokines were examined.

Results The results indicate that T cells of RA patients display increased levels of GAS5 (3.31-fold, $p = 0.007$), RMRP (2.43-fold, $p = 0.02$), and THRIL (2.14-fold, $p = 0.03$) lncRNAs compared with those of controls. Furthermore, a positive correlation was found between RMRP expression and disease duration in RA. Receiver operating characteristic (ROC) curve of GAS5, RMRP, and THRIL has a discriminative value in comparing RA patients and controls.

Conclusion The results suggest lncRNAs may be involved in T cell dysfunction in RA. Further studies are required to see whether these lncRNAs have an effect on dysregulation of immune responses in RA disease.

Key Points

- *70% of non-coding sequences in the human genome are transcribed to RNA.*
- *A growing body of evidence shows the importance of lncRNAs in innate and adaptive immune cell differentiation and functions.*
- *Important recent works suggest a key role of immune cell lncRNAs in autoimmune processes and diseases including RA.*

Keywords GAS5 · IFNϒ-AS1 · lncRNA · Rheumatoid arthritis · RMRP · THRIL

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting the joints and leads to the destruction of the synovial membrane and cartilage and bone erosion [1]. In severe cases, RA is accompanied by extra-articular manifestations and the involvement of other internal organs of the body leading to disability and death. RA is known as one of the most common autoimmune diseases, affecting about 1% of the population worldwide. The disease is 2 to 4 times more prevalent among women [2]. Epidemiological studies demonstrated that the peak age of the disease is around the fourth decade of life [3]. Similar

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to the most autoimmune diseases, RA is a multifactorial disease affected by both genetic and environmental factors [4]. The studies on identical twins demonstrated that genetic factors are responsible for 60% liability to the RA disease indicating the importance of environmental factors (such as smoking and infection) [5]. The variants of several genes, particularly *HLA-DRB1*, have been demonstrated to increase the risk of RA [6].

Previously, B lymphocytes and immunoglobulins were considered the most important actors in RA pathogenesis [7]. However, new studies point at the importance of macrophages, T cells, and resident synovial membrane cells and their cytokines in the initiation and the development of inflammation and tissue damage [8]. It is known that some T cell subsets such as Th1, Th17, and Treg are involved in the pathogenesis of the RA [9]. Th17 cells through the production of IL-17 have been implicated in RA. For instance, the combination of the anti-TNF-α and monoclonal antibodies against IL-17 cytokine showed more efficacy in disease treatment [10]. The anti TNF-α is an effective biological agent for RA patient treatment. Recently new Treg-manipulating approaches have provided promising results in the treatment of RA in pre-clinical models [11, 12]. Besides, the strong association between class II MHC and the development of RA indicates the importance of T cells in RA.

Non-coding RNAs (ncRNA) are a group of RNA molecules that code no proteins. Non-coding RNAs, based on their length, are divided into two groups: short ncRNAs and long non-coding RNAs (lncRNA) [13]. Short ncRNAs such as micro-RNAs, piwi-interacting RNAs, small nucleolar RNAs, and many others encompass less than 200 nucleotides. lncRNAs are a type of ncRNAs with a length of more than 200 nucleotides that mostly are transcribed by RNA polymerase II, which subsequently are capped, spliced, and polyadenylated [14]. lncRNAs are categorized in different classes based on their genomic location, including intergenic non-coding RNAs (lincRNAs), natural antisense transcripts (NATs), and intronic lncRNAs [15]. lncRNAs have different biological functions from epigenetic regulation to protein metabolism through interactions with DNA, RNA, and proteins. Many studies have reported the key role of lncRNAs in the regulation of gene expression, differentiation, and development of innate and adaptive immune cells [16, 17]. T cells, as one of the components of the adaptive immune system, express specific lncRNAs to regulate their function [18]. Recently, dysregulation of lncRNAs in various autoimmune diseases, including RA, has been reported [19]. In the present study, we investigated the expression of lncRNAs including growth arrest specific 5 (GAS5), the RNA component of mitochondrial RNA processing endoribonuclease (RMRP), TNF-α- and hnRNPL-related immunoregulatory lincRNA (THRIL), and interferon gamma antisense RNA 1 (IFNϒ-AS1) in circulating T cells from RA patients. Moreover, the association between the expression of these lncRNAs, clinical manifestations of the disease, and two important cytokines, TNF-α and IL-17, involved in the disease was examined.

Materials and methods

Patients and control participants

In this study, 20 RA patients and 18 sex- and age-matched healthy controls were enrolled. Patient diagnostics were accomplished by a rheumatologist based on the American College of Rheumatology (ACR) criteria for RA [20]. The control subjects enrolled in current project were not affected by any autoimmune or rheumatic diseases nor did have a family history of any autoimmune disease. Informed consent was obtained from all participants. All steps are performed according to the revised ethical principles of the Declaration of Helsinki in 2000. Control and patient's clinical and demographic information is presented in more detail in Table 1. Clinical parameters including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and disease activity scores of 28 joints (DAS-28) were measured after blood withdrawal. RA patients were receiving methotrexate and prednisolone drugs but not anti-TNF-α treatment.

T cell isolation and RNA extraction

Peripheral blood was taken from the participants. Two milliliters of the blood was used to measure ESR, and 4 ml of blood serum was extracted for determining rheumatoid factor (RF) and CRP. Peripheral blood mononuclear cells (PBMCs) were obtained from 7 ml blood using Ficoll (Lympholyte-H, Cedarlane, Canada, CL5020) density gradient centrifugation. T cells were purified from PBMCs by negative selection using a magnetic-activated cell (MAC) isolation kit and magnetic-activated cell sorter columns (all from Miltenyi Biotec, Germany, cat no 130-042-401), according to the manufacturer's instructions. Total RNA was extracted by RiboEx™

Table 1 Clinical characteristics of RA patients and healthy controls

Characteristics	RA patients (*n* = 20)	Healthy controls (*n* = 18)
Male/female	16 (80%)/4 (20%)	14 (70%)/4 (30%)
Age (years)	48 ± 11.98	45 ± 9.03
ESR (mm/h)	23.65 ± 18.72	NA
CRP (μg/ml)	17.54 ± 15.86	NA
DAS-28 ESR score	4.21 ± 1.27	NA
Disease duration	8.25 ± 4.19	NA
Medication (no. of patients)		
Methotrexate	20	0
Prednisolone	20	0
Biological agents	0	0

RA rheumatoid arthritis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS-28 ESR* Disease Activity Score-28 erythrocyte sedimentation rate, *NA* not applicable

(GeneAll, Korea, cat no. 301-902). Purity and concentration of isolated RNA were determined with a nano-spectrophotometer (NanoDrop Technologies, USA).

cDNA synthesis and real-time PCR

Two micrograms of RNA was used for complementary DNA (cDNA) synthesis by 2x RT pre-mix (Biofact, Korea, BR631-096) and random hexamers. Gene expression analysis was carried out using the 2X Real-Time PCR Master Mix (Biofact™, Korea, cat no. DQ383-40H) and the Magnetic Induction Cycler real-time PCR apparatus system (Bio Molecular Systems, Australia). The *B2M* gene was used for normalization. Primers for the genes were designed and blasted using the Primer3 online software and the National Center for Biotechnology Information (NCBI) database. Primer sequences are shown in Table 2. The comparative CT method ($2^{-\Delta CT}$) was used to analyze the relative changes in mRNA expression.

Statistical analysis

All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 6. Data distribution was identified by the Shapiro–Wilk test. The Mann–Whitney *U* test was used for the analysis of the relative gene expression. Correlation between clinical parameters and relative gene expression was tested with the Spearman correlation test. The receiver operating characteristic (ROC) curve was plotted to assess the dysregulated THRIL, IFNϒ-AS1, RMRP, and GAS5 lncRNAs for RA diagnosis. *p* values less than 0.05 were considered significant.

Table 2 Primer sequences and product size of the selected genes

Gene	Primer	Sequence (5′–3′)
GAS5	Forward Reverse	CTTCTGGGCTCAAGTGATCCT TTGTGCCATGAGACTCCATCAG
RMRP	Forward Reverse	ACTCTGTTCCTCCCCTTTCC CTTCTTGGCGGACTTTGGAG
THRIL	Forward Reverse	GGTGATCCATACTCCTCGGC TGGGCAAGGGAGTTTCAGAA
IFNϒ-AS1	Forward Reverse	ACGAACTAGCACAACGAGG TGACTTCTCCTCCAGCGTTT
IFN-ϒ	Forward Reverse	TCCTTTGGACCTGATCAGCT TATGGGTCCTGGCAGTAACA
IL-17	Forward Reverse	TGTGATCTGGGAGGCAAAGT CCCACCGGACACCAGTATCTT
TNF-α	Forward Revers	AGGACCAGCTAAGAGGGAGA CCCGGATCATGCTTTCAGTG
B2m	Forward Reverse	CCTGAATTGCTATGTGTCTG TGATGCTGCTTACATGTCTCGA

Result

In order to study the expression of four lncRNAs, 20 RA patients along with 18 age- and sex-matched healthy controls were employed. In this study, according to DAS-28 data, patients were divided into two groups: severely (DAS-28 > 5) and mildly ($5.1 > \text{DAS-28} > 3.2$) affected patients. The expression of the four selected lncRNAs (GAS5, RMRP, IFNϒ-AS1, and THRIL) was measured in isolated T cells from RA patients and controls using the quantitative real-time PCR method. The results show a significant increase in the levels of GAS5 with 3.31-fold change ($p = 0.007$), RMRP with 2.43-fold change ($p = 0.02$), and THRIL with 2.14-fold change ($p = 0.03$) in RA patients in comparison with controls (Fig. 1). The results show no significant changes in IFNϒ-AS1 expression ($p > 0.05$) between RA patient T cells and healthy subjects.

Next, we studied the association between the expression of lncRNAs and RA clinical manifestations. Clinical parameters included DAS-28, ESR, CRP, age, and disease duration. We found a positive correlation between RMRP lncRNA expression and disease duration ($p = 0.04$, $r = 0.59$) using the Spearman correlation test (Fig. 2). There was no significant association between lncRNA expression and clinical parameters.

TNF-α and IL-17 are two important cytokines produced by T cells involved in RA disease. We measured the expression of these two cytokines in T cells of RA patients in comparison with healthy controls. TNF-α and IL-17 expression showed a 3.02-fold ($p = 0.04$) and 2.86-fold ($p = 0.01$) increase in T cells of RA versus controls (Fig. 1e, f). Then, we examined whether there was a correlation between these cytokine expressions and the expressions of lncRNAs (Fig. 3a–f). There was no correlation between the expression of lncRNAs and TNF-α and IL-17 expression.

The ROC curve was drawn to evaluate the diagnostic value of GAS5, RMRP, IFNG-AS1, and THRIL lncRNAs in RA disease. The area under the curve (AUC) of GAS5, RMRP, and THRIL were 0.75 (95% CI 0.59–0.92, $p = 0.006$), 0.71 (95% CI 0.55–0.88, $p = 0.02$), and 0.7(95% CI 0.52–0.87, $p = 0.03$), respectively (Fig. 4). This indicates a clear distinction between the RA and control groups and could provide better diagnostic efficiency. However, IFNG-AS1 lncRNA with an AUC 0.61 (95% CI 0.41–0.82) and a *p* value of 0.2 lacked a predictive value for RA (Fig. 4).

Discussion

Around 2% of the human genome comprises protein-coding genes, and at least around 70% of non-coding sequences are

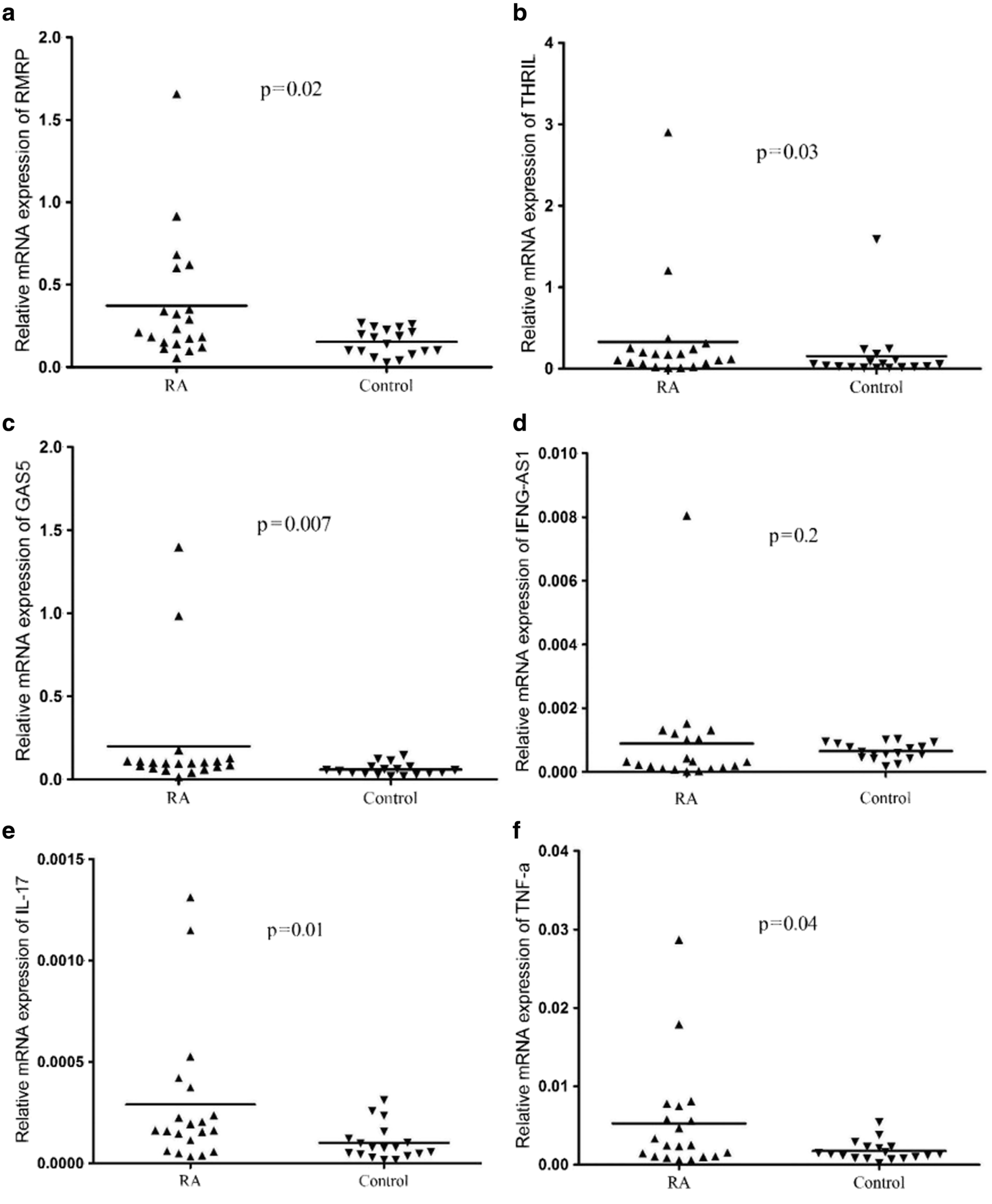

Fig. 1 The selected lncRNA expression in T cells of RA vs healthy controls. A significant increase in the relative expression of RMRP (2.43-fold change, $p = 0.02$) (**a**), THRIL (2.14-fold change, $p = 0.03$) (**b**), GAS5 (3.31-fold change, $p = 0.007$) (**c**), TNF-α (3.02-fold change, $p = 0.04$) (**e**), and IL-17 (2.86-fold change, $p = 0.01$) (**f**) was observed. Data are shown as the mean ± SEM. The Mann–Whitney *U* test was carried out, and *p* values below 0.05 were considered significant

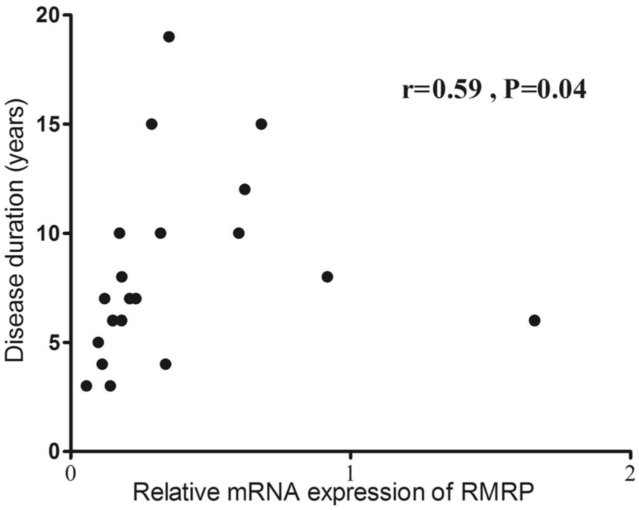

Fig. 2 Correlation between disease duration and RMRP expression. The Spearman test showed a positive correlation between RMRP expression and disease duration ($r = 0.59$, $p = 0.04$). p, p value; r, Spearman rank correlation coefficient

transcribed to RNA [21]. The most common of these ncRNAs are lncRNAs. The early findings on the existence and importance of lncRNA in immune cells derived from the study of inflammation in the innate immune system [22]. A growing body of evidence shows that adaptive immune cells including T lymphocytes express many lncRNAs in any phase of their development, differentiation, and activation. lncRNAs are versatile gene expression regulators indicating they regulate gene expression at different levels including transcription, post-transcription, translation, and post-translation and are involved in epigenetic modifications [23]. Important recent works suggest a key role of immune cell lncRNAs in autoimmune processes and diseases [24]. The most important lncRNAs in RA which are known to be deregulated include HOTAIR and H19 [25–27]. The higher expression of HOTAIR has been demonstrated in PBMCs and synovial fibroblasts and in serum exosomes of patients with RA. As such, H19 is highly expressed in the synovial tissue and it is suggested that H19 participates in inflammation and joint damage [27]. Despite the apparent importance of lncRNAs, our understanding about the role of lncRNAs in RA is still in its infancy. In this study, the expression of GAS5, RMRP, IFNΥ-AS1, and THRIL lncRNAs was analyzed for the first time in T cells of RA patients. Our finding indicates a significant increase in the expression of GAS5, THRIL, and RMRP in T cells of RA patients. We also measured the mRNA expression of TNF-α and IL-17 produced by T cells which both showed a significant increase in T cells of RA patients. Next, we investigated the association between the expression levels of lncRNAs and clinical parameters and expression levels of cytokines.

GAS5 is a lncRNA that was first identified as a tumor suppressor gene in cancer [28]. The studies have shown aberrant expression of GAS5 in several cancers and implicated this gene in cell cycle inhibition and apoptosis [29]. Notably, it has been reported that GAS5 acts as a repressor of glucocorticoid receptors (GRs) [30]. Glucocorticoids (GC) are most effective drugs used to treat inflammatory diseases. Evidence suggests that GAS5 binds to the DNA binding domain of glucocorticoid receptors and prevents GRs from interacting with DNA [30]. One can hypothesize that the observed increased expression of GAS5 in immune cells would prevent glucocorticoid activity and thereby contribute to the development of autoimmune diseases including RA. On the other hand, higher level of GAS5 may contribute to the resistance of GC treatment in RA and other diseases [31]. Also, we did not find any meaningful association between the expression of TNF-α and IL-17 cytokines and the GAS5 expression.

The lncRNA RMRP was first identified as part of the mitochondrial enzymatic complex that cleaves mitochondrial RNAs [32]. Increasing evidence shows that the expression of RMRP is deregulated in several cancers including lung adenocarcinoma and gastric cancer [33, 34]. More recently, RMRP is identified as a partner of RORΥt transcription factor in Th17cells [35]. RORΥt regulates Th17 differentiation and transcription of selective Th17 genes including IL-17 and demonstrated to be needed for inflammatory pathologies caused by Th17 cells [35]. Huang et al. discovered that RMRP, along with a RNA helicase called DDX, is required for promoting assembly and regulating RORΥ transcriptional activity in Th17 cells [35]. IL-17 produced by Th17 cells has strong proinflammatory and joint-destructive activities [10, 36]. Here there was a significant increase in RMRP and IL-17 levels; nonetheless, no significant correlation was found between them. There was also a significant correlation between the expression of RMRP and the duration of the disease.

IFNΥ-AS1, also known as Tmevpg1 and NeST, is mapped adjacent to the interferon (IFN)-Υ-encoding gene in both human and mouse genomes [37]. It has been shown that IFNΥ-AS1 is involved in regulating IFNΥ expression and expressed selectively in Th1 cells. Important recent works suggest that IFNΥ-AS1 may have proinflammatory properties. It was indicated that lncRNA IFNΥ-AS1 contributes to the inflammatory responses in other autoimmune diseases myasthenia gravis and Hashimoto's thyroiditis [38, 39]. The cytokine IFNΥ has an important role in inflammation and cell death [40]. We hypothesized that based on the importance of IFNΥ in RA, IFNΥ-AS1 may also be involved in the disease. But our results showed no significant differences in the IFNΥ-AS1 level between RA and control subjects.

THRIL is the last lncRNA that was investigated in this study. Recently, a study by Li et al. [41] has revealed that THRIL forms an RNA-protein complex with heterogenous nuclear ribonucleoprotein L (hnRNPL) and regulates TNF-α expression in the innate immune system. Their data showed that THRIL knockdown leads to the dysregulation of many immune-associated genes. It was also reported that THRIL

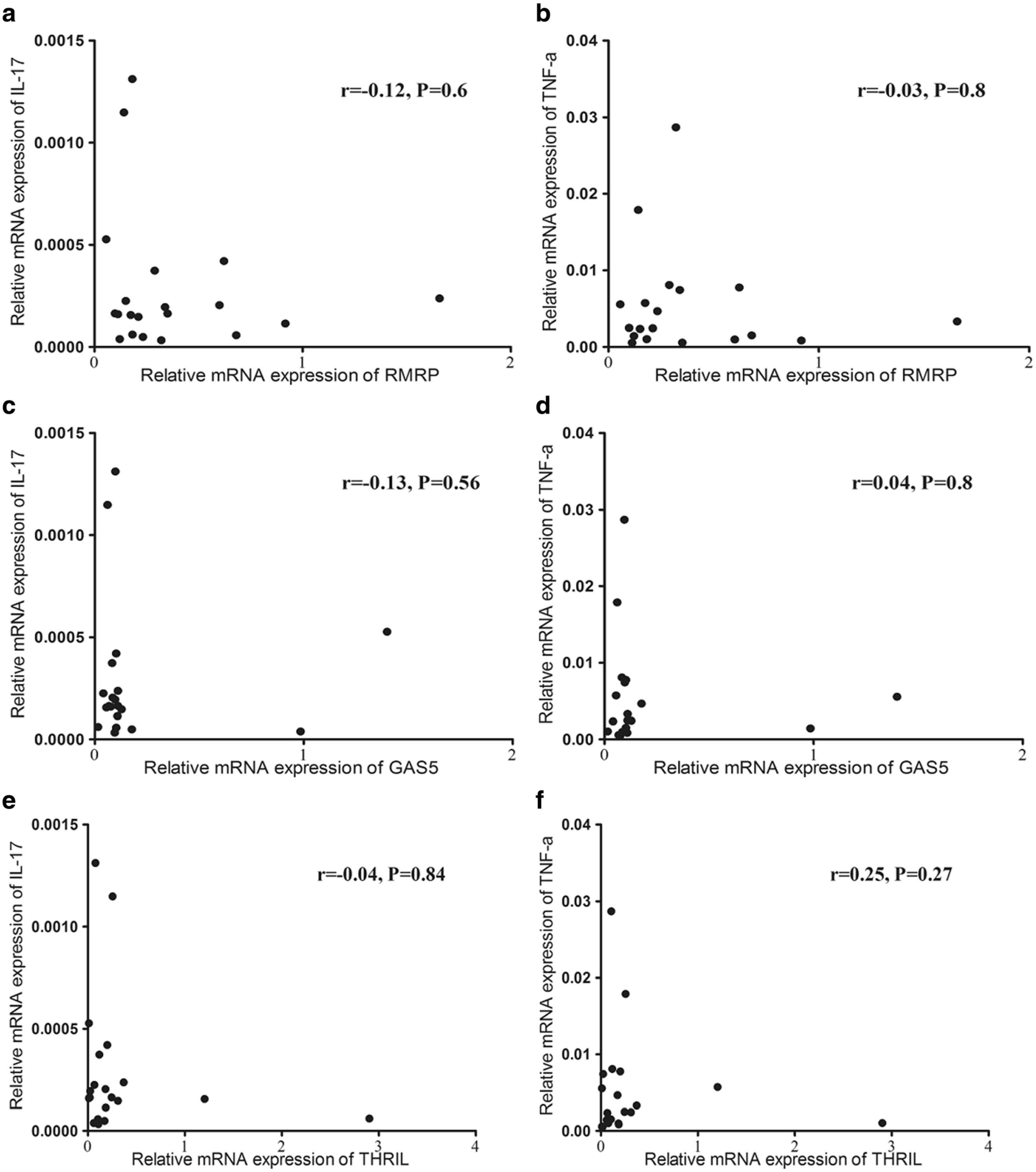

Fig. 3 The correlation between lncRNAs and TNF-α and IL-17 cytokine expression. The correlation was measured using the Spearman test (**a**–**f**). p values < 0.05 were considered significant

expression in PBMCs of Kawasaki patients was associated with the severity of symptoms [42]. The role of TNF-α in RA disease is obvious. Here our finding indicates a significant increase in T cells of RA individuals. But we observed no correlation between THRIL expression and TNF-α and clinical parameters of RA patients.

The current study, for the first time, indicates the expression of GAS5, RMRP, and THRIL lncRNAs in T cells of RA

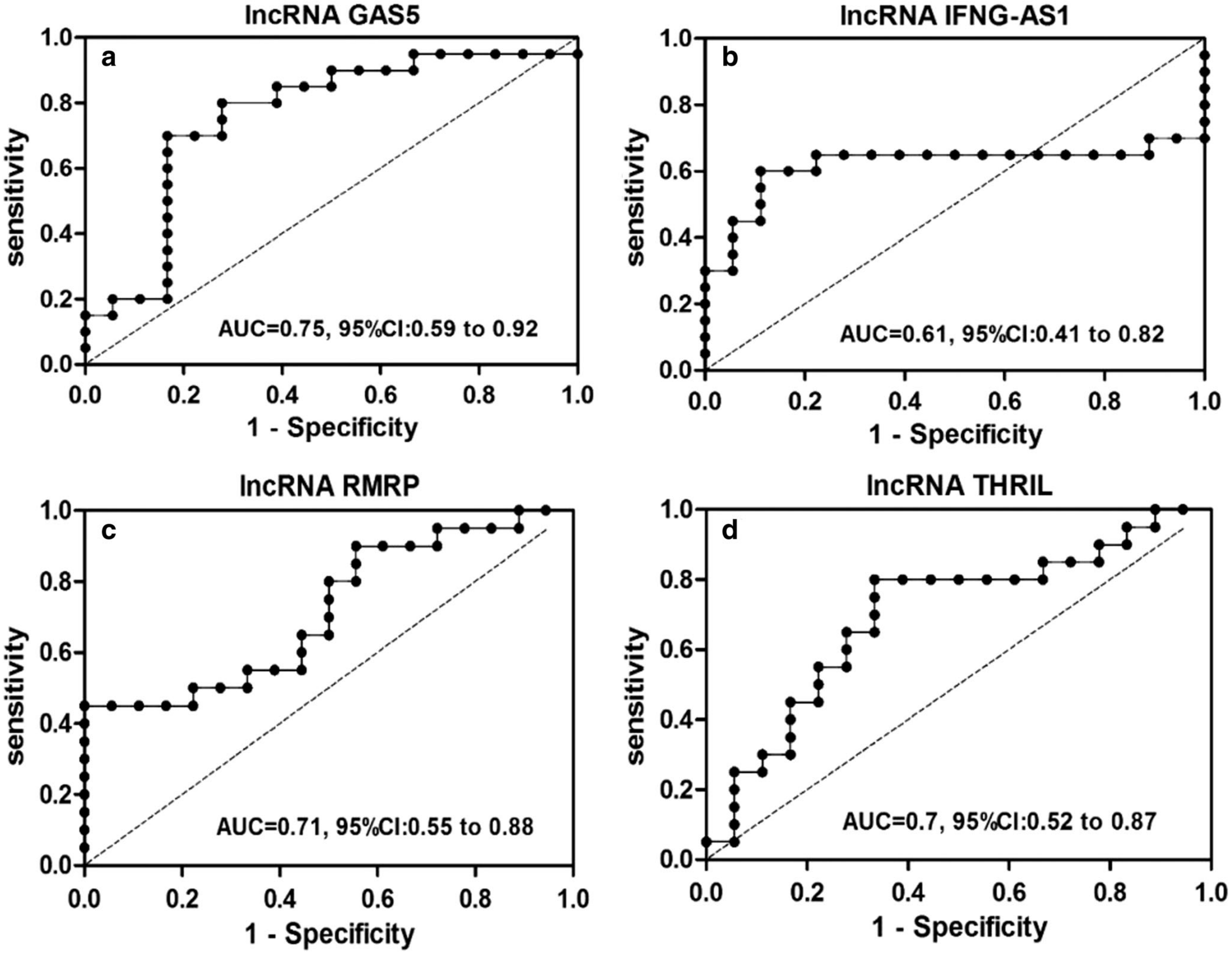

Fig. 4 The ROC curve of GAS5, IFNG-AS1, RMRP, and THRIL expression levels in T cells for RA diagnosis. The ROC curve showed that GAS5 (AUC 0.75, 95% CI 0.59–0.92, $p = 0.006$), RMRP (AUC 0.71, 95% CI 0.55–0.88, $p = 0.02$), and THRIL (AUC 0.7, 95% CI 0.52–0.87, $p = 0.03$) had good diagnostic efficacy

patient. Also, it shows a positive correlation between RMRP expression and disease duration in RA. Further studies are required to ask whether lncRNAs examined in the current study are involved in the pathogenesis of RA.

Compliance with ethical standards

Disclosure None.

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