Review Article

Unique gene expression pattern of peripheral blood in patients with Sjögren's syndrome

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Sjögren's syndrome (SS) is a unique autoimmune disease that shows dry mouth (xerostomia) and dry eye (xerophthalmia). Some SS patients develop visceral involvement, including malignant lymphoma. However, the molecular markers for disease activity or disease progression of SS have not been established. Therefore, the gene expression pattern in SS peripheral blood was examined by DNA microarray analysis. The gene expression patterns of primary and secondary SS were similar, but different from that of rheumatoid arthritis. Interferon (IFN)-inducible genes were upregulated in primary and secondary SS. The interferon gene signature was more prominent in primary SS compared to secondary SS. Primary and secondary SS were distinguishable based on the gene expression pattern of peripheral blood. The most upregulated gene, IFNα-inducible protein 27, showed a significant positive correlation with serum IgG level in SS. IFN-inducible genes could be markers for disease activity. The expression of ribosomal protein S27 and S29 genes was upregulated in peripheral blood from SS patients with marginal zone B cell lymphoma. The levels of ribosomal protein S27 and S29 expression were decreased after chemotherapy against lymphoma. The ribosomal protein S27 and S29 genes could be molecular markers for lymphoma development in SS.

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration into salivary and lacrimal glands. Chronic inflammation leads to salivary and lacrimal gland destruction, and ultimately results in dry mouth (xerostomia) and dry eye (xerophthalmia). Although the precise mechanism of disease development is not known, the mechanisms underlying destruction of salivary glands have been partially clarified[1-7]. However, it is difficult to identify patients with disease progression or develop visceral involvement. For example, it is well

Table 1 Target genes analyzed by cDNA microarray

TNF-α cascade genes
Chemokine/Cytokine-associated genes
Growth Factor-associated genes
Kinase-associated genes
Osteo-associated genes
Cell surface protein-associated genes
MTX metabolism-associated genes
Matrix-associated genes
Cell cycle & transcriptional regulation-associated genes
Protease-associated genes
Oncogene/suppressor-associated genes

known that SS patients have a higher prevalence of malignant lymphoma, but there are no definite markers for lymphoma development in SS. It is also difficult to measure disease activity in SS. It is important to identify the molecular markers for disease progression or disease activity.

In systemic lupus erythematosus (SLE), genome-wide gene expression analysis was performed using peripheral blood, and upregulation of interferon (IFN)-inducible genes was reported[8-11]. Upregulation of IFN-inducible genes is correlated with more severe disease in SLE[8]. Moreover, the expression of several IFN-inducible genes was shown to be related to disease severity, and some representative gene expression levels could be significant biomarkers for evaluation of treatment for lupus nephritis[11].

There have been several reports of gene expression analysis in SS targeting the salivary glands[12,13]. It would be advantageous to use as easily accessible samples as possible to evaluate disease activity or progression in clinical practice. Here, we examined the gene expression profile in SS peripheral blood by cDNA microarray analysis. The expression levels of some genes were found to be related to particular clinical manifestations or laboratory data. Here, we propose several candidate molecular markers for SS disease activity or disease progression.

Interferon-inducible genes are upregulated in SS peripheral blood

First, gene expression in the peripheral blood of primary SS patients was examined by cDNA microarray analysis. We prepared a low-density DNA microarray for mRNA expression profiling in whole blood. Genes for this microarray were selected from the public database of SAGE results (http://133.11.248.12/; homepage of the Department of Molecular Preventive Medicine, School of Medicine, The University of Tokyo) from activated blood cells, such as T cells, dendritic cells, monocytes, and macrophages. Microarray analysis was performed using a DNA microarray system (Genomessage V2, GEO accession #GPL 5460, Japan Genome Solutions) with 778 genes (Table 1). Reference RNA was established from a mixture of whole blood RNA samples from healthy volunteers. Many IFN-inducible genes were found to be upregulated in the peripheral blood of primary SS patients compared to normal controls (manuscript in preparation). Ten of the top 20 upregulated genes were IFN-inducible genes in primary SS. The most highly upregulated gene was IFNα-inducible protein 27 (IFI27), the expression level of which was 56-fold higher than that in normal controls. On the other hand, downregulated genes were more variable. However, three interleukin 1β-related molecules were found among those that

	Genes	Rheumatoid arthritis										Primary SS										Secondary SS				
1		1.51	1.92	0.54	0.87	1.22	0.97	0.92	1.92	0.56	3.52	3.94	2.82	2.59	2.17	2.70	2.23	3.36	3.28	2.12	2.24	1.75	2.03	2.39	2.21	2.07
2		1.81	1.54	0.46	0.58	0.89	0.99	0.71	2.39	1.10	2.57	4.10	2.98	5.60	4.92	2.70	2.22	4.07	3.23	2.98	5.23	1.14	1.65	1.18	1.61	2.04
3		1.74	1.19	0.49	0.91	1.22	0.86	0.78	1.60	0.90	3.15	5.43	3.24	3.40	2.94	4.02	2.21	4.93	4.36	3.00	2.27	1.37	2.12	1.21	2.23	1.80
4		1.67	1.81	0.46	0.61	0.94	0.80	0.59	1.40	0.68	1.88	5.64	3.53	2.36	2.60	2.59	2.09	5.16	2.85	2.36	2.29	1.84	2.22	2.22	1.92	2.60
5		1.79	2.64	0.49	0.41	0.73	0.52	0.52	1.11	0.35	1.65	5.42	3.00	2.92	2.85	3.29	2.55	4.46	3.90	2.25	3.41	0.95	1.49	1.33	1.83	1.68
6		2.10	1.16	1.41	1.15	1.39	1.28	0.75	1.02	0.74	2.48	29.02	9.21	26.14	13.08	75.74	1.91	49.83	28.70	20.89	101.49	1.63	2.24	0.83	2.38	3.03
7		1.40	3.10	0.67	0.70	0.95	0.63	0.68	2.28	0.48	1.70	7.30	3.38	5.53	2.10	2.24	1.74	3.43	5.26	3.49	2.10	1.60	1.93	3.35	1.46	1.80
8		1.83	3.96	0.52	0.71	1.13	0.92	0.74	3.33	0.45	4.26	5.67	3.08	3.11	2.39	3.18	2.13	2.93	3.52	1.62	1.48	1.71	1.81	3.24	2.20	2.78
9		1.24	1.18	0.91	0.76	1.13	1.04	1.55	1.48	1.49	1.11	2.32	2.26	2.34	2.06	1.71	2.30	2.01	1.94	2.32	2.56	1.28	2.16	1.22	1.44	1.20
10		2.47	2.15	0.57	0.66	1.20	0.55	0.98	1.29	0.54	3.23	4.34	2.97	2.00	1.95	3.52	2.58	4.06	3.29	2.59	1.86	1.32	2.04	1.29	2.05	2.52
11		2.23	3.01	1.38	1.61	2.23	1.19	1.11	1.51	1.17	1.67	3.07	1.79	2.02	1.45	2.24	1.46	2.28	2.42	2.65	2.30	1.60	1.84	1.49	1.71	1.70
12		1.89	3.63	0.63	0.83	1.20	0.99	0.78	2.95	0.52	3.68	4.50	2.43	2.55	1.83	2.84	1.77	2.43	3.48	1.62	1.43	1.67	1.69	2.95	1.91	2.34
13		1.48	0.62	0.63	1.19	1.00	1.02	0.97	1.14	1.73	0.89	1.72	1.65	2.08	2.23	1.98	2.22	2.26	1.73	2.30	2.61	1.22	1.84	0.86	1.93	1.32
14		0.97	1.48	0.59	0.54	0.92	0.67	0.57	1.54	0.46	1.59	3.03	2.11	2.02	1.91	2.75	1.63	2.20	2.79	1.49	1.62	1.04	1.19	1.53	1.39	1.74
15		2.25	1.10	1.29	1.81	1.09	1.16	0.54	1.20	0.83	1.21	1.10	1.08	2.46	1.68	4.61	2.89	1.91	2.62	1.08	2.85	1.51	1.58	0.75	0.77	1.21
16		1.23	0.60	0.54	1.04	0.81	0.93	0.73	0.99	1.16	0.79	1.32	1.45	2.51	1.66	2.21	2.32	1.93	2.24	1.11	2.14	1.00	1.41	1.60	1.57	1.64
17		0.76	0.94	0.64	1.06	1.16	0.95	1.23	1.13	0.72	1.54	2.35	1.70	2.09	1.27	1.67	1.42	2.41	2.30	1.24	1.03	0.97	0.97	2.03	1.35	1.36
18		0.41	0.31	0.55	0.51	0.33	0.61	0.52	1.34	1.16	0.36	3.12	1.52	1.59	3.44	1.26	1.93	1.42	1.09	3.43	2.07	1.32	2.24	0.28	1.10	1.65
19		1.93	0.64	0.27	0.49	0.37	0.35	0.76	1.53	2.02	0.38	1.12	0.44	0.91	0.72	2.11	1.24	1.03	2.17	1.24	4.46	0.49	2.72	0.15	0.80	0.80
20		1.88	0.67	0.26	0.50	0.36	0.33	0.70	1.48	2.00	0.39	1.12	0.44	0.86	0.64	2.13	1.41	1.15	2.01	1.24	4.18	0.48	2.71	0.15	0.78	0.86

Figure 1 Gene expression pattern in peripheral blood from patients with primary (n=10) and secondary (n=5) Sjögren's syndrome, and with rheumatoid arthritis (n=10) (top 20 genes in primary SS)

Gray: IFN-inducible genes; pink: upregulated genes compared to normal controls; blue: downregulated genes compared to normal controls. Numbers in each column represent the ratio of each gene expression level against normal control.

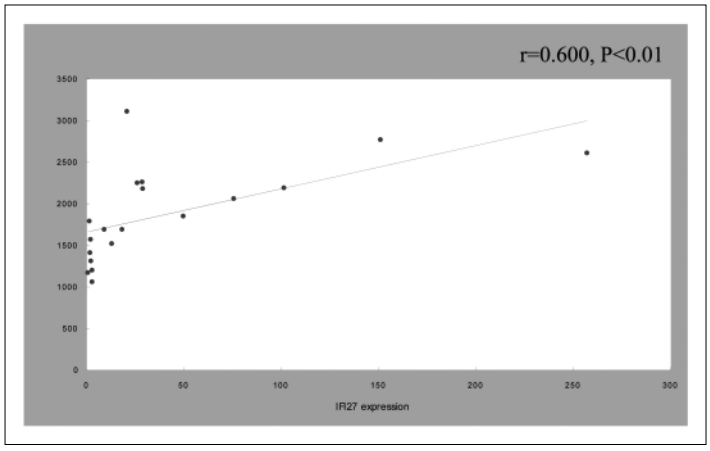

Figure 2 Correlation of IFI27 level with serum IgG level

The IFI27 expression showed a significant positive correlation with serum IgG level (r=0.600, p<0.01)

Table 2 IFI27 expression according to the presence or absence of SS clinical features

There were no significant correlations between IFI27 and clinical parameters. However, the IFI27 level in anti-SS-A antibody-negative patients was greater compared to anti-SS-A antibody-positive patients although the difference did not reach statistical significance.

	Present		Absent		
Feature	No of patients	IFI27	No of patients	IFI27	P
dry eye	12	30.0±31.3	7	62.2±101.8	0.670
parotid swelling	6	60.5±97.9	13	33.3±47.1	0.890
arthritis	9	21.9±32.0	10	59.8±83.3	0.840
Raynaud	4	8.78±13.5	15	50.7±71.4	0.400
eruption	4	72.5±123.7	15	33.7±43.8	1.000
allergy	7	83.6±90.8	12	17.5±28.2	0.270
depression	5	32.9±40.5	14	45.1±19.7	0.550
anti-SS-A Ab	16	33.3±42.4	3	87.7±146.7	0.083
anti-SS-B Ab	7	95.6±85.0	12	10.5±14.2	0.120

were downregulated in SS (data not shown).

Next, we performed cDNA microarray analysis using peripheral blood from 5 secondary SS patients (4 with systemic sclerosis, 1 with SLE). The gene expression pattern of secondary SS patients was similar to that of primary SS patients. Among the top 20 upregulated genes in secondary SS, 16 genes were also included in the top 20 genes in primary SS (manuscript in preparation). Likewise, the pattern of downregulated genes in secondary SS was similar to that of primary SS. However, there were some genes that were differentially expressed between primary and secondary SS. Some of the IFN-inducible genes were significantly more upregulated in primary SS compared to secondary SS.

Finally, we compared the gene signatures of primary and secondary SS with that of rheumatoid arthritis (RA). The results indicated that primary and secondary SS had a unique gene signature compared to RA (Figure 1).

IFI27 expression level showed a correlation with some clinical parameters

To investigate the significance of the upregulation of IFN-inducible genes in SS, the relationships of clinical and laboratory parameters with the most highly upregulated gene, IFI27, were examined. As shown in Figure 2, IFI27 expression showed a significant positive correlation with serum IgG level (r=0.600, p<0.01). There were no significant correlations between IFI27 and any other parameters, except that IFI27 level in anti-SS-A antibody-negative patients was greater than that in anti-SS-A antibody-positive patients although the difference was not statistically significant (Table 2). IFI27 is one of the IFN-induc-

Table 3 Top 20 upregulated genes in two SS patients complicated by marginal zone B cell lymphoma

Eight of the 20 top upregulated genes in SS with lymphoma were ribosomal protein genes (gray).

No	Gene Bank#	Gene Name	1	2
1	X67325	interferon, alpha-inducible protein 27 (IFI27; ISG12)	5.13	17.76
2	U09953	ribosomal protein L9 (RPL9)	6.35	2.14
3	U57847	ribosomal protein S27 (RPS27); (metallopanstimulin 1)	5.11	3.36
4	AF026844	ribosomal protein L41	4.23	2.75
5	M84711	fte-1 (v-fos transformation effector protein), ribosomal protein S3a	5.29	1.63
6	X57959	ribosomal protein L7 (RPL7)	4.10	1.84
7	AB021288	beta 2 microglobulin (B2M)	2.82	2.78
8	U14973	ribosomal protein S29 (RPS29)	3.70	1.85
9	BC015739	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3) (GZMA)	3.57	1.87
10	M13755	IFN-induced 17/15-KDa protein (G1P2)	2.77	2.15
11	M15661	ribosomal protein L36a (RPL36AL)	2.63	1.88
12	U12465	ribosomal protein L35 (RPL35)	2.78	1.65
13	M20259	thymosin β -10 (TMSB10)	2.22	2.17
14	X15822	COX VIIa-L liver-specific cytochrome c oxidase (COX7A2)	2.92	1.47
15	NM_006417	IFN-a/b-inducible p44 (p44) (IFI44)	2.39	1.95
16	D00068	2,5-oligo-adenylate synthetase (2,5-AS) 40/46kDa (OAS1)	2.45	1.88
17	X06233	calcium-binding protein in macrophages (MRP-14) macrophage migration inhibitory factor (MIF)-related protein; S100 calcium binding protein A9 (calgranulin B) (S100A9)	2.95	1.31
18	U94586	NADH:ubiquinone oxidoreductase MLRQ subunit	2.72	1.53
19	X02875	2-5A synthetase E (1.8 kb RNA)	1.76	2.48
20	D50663	t-complex-associated-testis-expressed 1-like 1(TCTEL1) (dynein)	2.46	1.61

Table 4 Genes expression levels of which were significantly changed after chemotherapy including rituximab in an SS patient with marginal zone B cell lymphoma

Five of the top 10 genes that showed a decrease in expression level were ribosomal protein genes (gray). Among the ribosomal protein genes, the levels of ribosomal protein S29 and S27 gene expression were decreased to the greatest extent after chemotherapy (44% and 54% of the values before chemotherapy, respectively).

No	Gene Bank#	Gene Name	Before	After	Ratio
1	M63438	Ig-γ chain; Ig rearranged gamma chain, V-J-C region	0.27	0.04	0.14
2	Y14736	immunoglobulin kappa (light chain) variable 1D8	0.28	0.04	0.16
3	U14973	ribosomal protein S29 (RPS29)	3.70	1.64	0.44
4	S63368	TNF receptor 2 (p75); tumor necrosis factor receptor superfamily, member 1B (TNFRSF1B)	0.75	0.39	0.53
5	U57847	ribosomal protein S27 (RPS27); (metallopanstimulin 1)	5.11	2.76	0.54
6	U37230	ribosomal protein L23a (RPL23A)	1.13	0.62	0.55
7	X98296	ubiquitin hydrolase (ubiquitin specific protease 9)	1.13	0.63	0.55
8	U14969	ribosomal protein L28 (RPL28)	1.28	0.71	0.56
9	S79522	ubiquitin carboxyl extension protein; Uba80 for ubiquitin	1.68	0.94	0.56
10	D23661	ribosomal protein L37 (RPL37)	1.21	0.68	0.56

ible genes, reported to be upregulated in psoriatic skin[14] and in the peripheral blood of SLE patients[15].

The above findings suggest that IFN-inducible genes, such as IFI27, could be useful as molecular markers for disease activity related to the pathogenesis of SS.

Differentially expressed genes in SS patients complicated by malignant lymphoma

The gene expression pattern in the peripheral blood from SS patients with malignant lymphoma was analyzed because SS

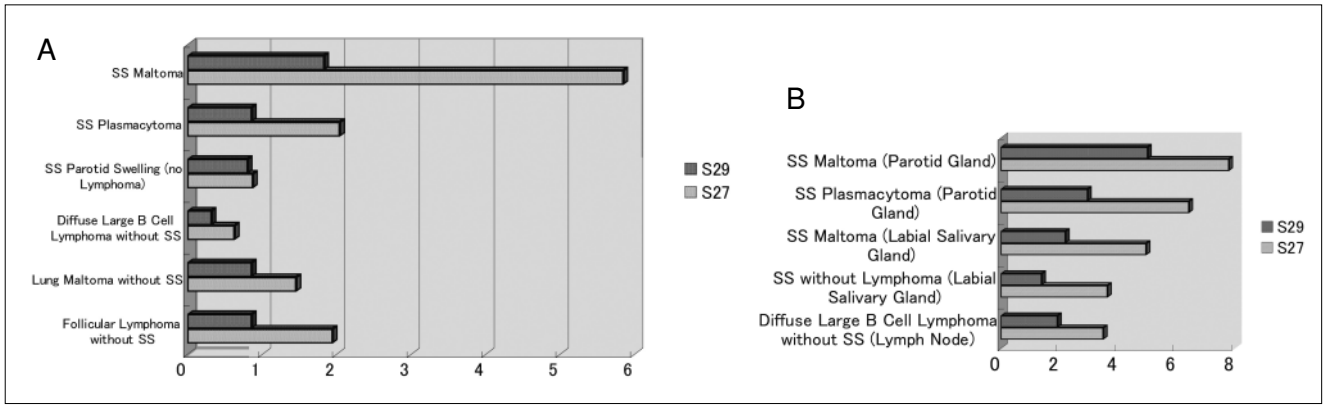

Figure 3 Real-time PCR analysis of ribosomal protein S27 and S29 mRNA expression in (A) peripheral blood and (B) salivary glands and lymph nodes

Peripheral blood samples from an SS patient with marginal zone B cell lymphoma (maltoma), an SS patient with plasmacytoma, and an SS patient without lymphoid malignancy were examined for the expression of ribosomal protein S29 and S27 by real-time PCR. The ribosomal protein S29 and S27 genes were most upregulated in peripheral blood from an SS patient with marginal zone B cell lymphoma. Peripheral blood samples from a patient with diffuse large B cell lymphoma, from a patient with lung maltoma, and from a patient with follicular lymphoma were used as disease controls.

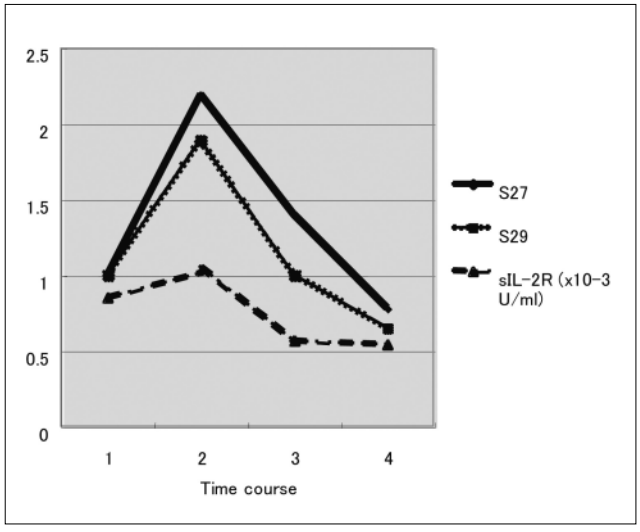

Figure 4 Time course analysis of mRNA of ribosomal protein S27 and S29 in peripheral blood from an SS patient with marginal zone B cell lymphoma (maltoma)

The levels of ribosomal protein S29 and S27 gene expression were significantly upregulated before chemotherapy, and decreased after therapy. The levels of ribosomal protein S29 and S27 gene expression paralleled those of a well-known lymphoma activity marker, soluble interleukin-2 receptor (sIL-2R). Time points: 1, 6 months before chemotherapy; 2, just before chemotherapy; 3, just after chemotherapy; 4, 3 months after chemotherapy.

patients have significantly higher rates of developing lymphoma, which is typically mucosa-associated lymphoid tissue-type lymphoma (marginal zone B cell lymphoma). Two SS patients with marginal zone B cell lymphoma were examined by DNA microarray analysis. In peripheral blood from these two patients, many IFN-inducible genes were upregulated just as seen in SS patients without lymphoma. However, many other genes were differentially expressed in SS with lymphoma compared to SS without lymphoma. Interestingly, 8 of the 20 most highly upregulated genes in SS with lymphoma were ribosomal protein genes (Table 3).

Rituximab-CHOP chemotherapy was performed in an SS patient with marginal zone B cell lymphoma. To identify candidate genes related to lymphomagenesis in SS, cDNA microarray analysis using peripheral blood before and after chemotherapy was performed. Five of the top 10 genes that showed a significant decrease in expression level were ribosomal protein genes (Table 4). The ribosomal proteins S29 and S27 showed the most significant decreases in expression level after chemotherapy (44% and 54% of those before chemotherapy, respectively). The ribosomal proteins S29 and S27 were reported to be associated with proliferating cells and tumor tissues[16-19].

Confirmation of significance of ribosomal protein S29 and S27 genes in the lymphomagenesis of SS patients

To further analyze the significance of upregulated ribosomal protein gene expression in peripheral blood from SS patients with lymphoma, real-time PCR analysis of gene expression levels using peripheral blood or lymphoma tissues was performed. First, peripheral blood samples from an SS patient with marginal zone B cell lymphoma, an SS patient with plasmacytoma, and an SS patient without lymphoid malignancy were examined for the expression of ribosomal protein S29 and S27 by real-time PCR. As shown in Figure 3A, the ribosomal protein S29 and S27 genes were most upregulated in peripheral blood from the SS patient with marginal zone B cell lymphoma.

Next, lymphoma tissues were subjected to analysis of ribosomal protein gene expression by real-time PCR. Again, the ribosomal protein S29 and S27 genes were upregulated to the greatest extent in lymphoma tissue from the SS patient with marginal zone B cell lymphoma developed in the parotid gland (Figure 3B).

Finally, time course analysis of the levels of ribosomal protein S29 and S27 gene expression was performed using peripheral blood by real-time PCR in another SS patient with marginal zone B cell lymphoma who received rituximab-CHOP therapy. The levels of ribosomal protein S29 and S27 gene expression were significantly upregulated before chemotherapy, and decreased after therapy (Figure 4). Moreover, the levels of ribosomal protein S29 and S27 gene expression paralleled those of a well-known lymphoma activity marker, soluble interleukin-2 receptor (sIL-2R). These findings suggest that the ribosomal protein S29 and S27 genes could be molecular markers for lymphoma development in SS.

Conclusions

Upregulation of IFN-inducible genes was one of the characteristics of the gene signature of peripheral blood in SS. Interestingly, the gene upregulated to the greatest extent in SS peripheral blood, IFI27, showed a significant positive correlation with serum IgG level. This finding suggested that abnormal expression of IFN-inducible genes is associated with immunological abnormalities in SS. In SLE, a phase I trial of an anti-IFNα monoclonal antibody resulted in neutralization of overexpression of IFN-inducible genes in peripheral bood[20]. The findings reported here indicated that SS is an autoimmune disease in which anti-IFN therapy would be effective. Another important finding is the upregulation of ribosomal protein genes in peripheral blood from SS patients with marginal zone B cell lymphoma. By following up the expression of ribosomal protein genes, it would be possible to detect lymphomas in SS patients at a very early stage. Gene expression analysis of the above molecules may provide a unique tool for identification of subsets of SS patients who should be treated vigorously or be followed up carefully for visceral involvement, including lymphoma.

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