Abnormal Histones Acetylation in Patients with Primary Sjögren's Syndrome

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Received: 7 September 2021 / Revised: 1 December 2021 / Accepted: 21 December 2021
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Abstract
Introduction Aberrant histone acetylation is increasingly thought to play important roles in the pathogenesis of autoimmune diseases. However, there are very few data on histone acetylation in primary Sjögren's syndrome (pSS). We aimed to investigate whether there was abnormal histone acetylation in patients with pSS.

Methods We investigated the expressions of histone acetyltransferase (HAT) genes (p300, CREBBP and PCAF) by real-time PCR in the peripheral blood mononuclear cells (PBMCs) of pSS patients. HAT activity and histone H3/H4 acetylation activity were measured by activity kit, and histone H3/H4 acetylation was verified by Western blot (WB). Spearman test was utilized to analyze the association between HAT activity levels and clinical parameters of pSS patients.

Results The mRNA expressions of p300, CREBBP and PCAF in PBMCs from pSS patients were decreased in comparison with healthy controls (P < 0.05). HAT activity and histone H3/H4 acetylation were reduced in PBMCs from pSS patients (P < 0.05). We found that HAT activity was negatively correlated with CRP (P = 0.040) and TNF-α (P = 0.012), and was positively correlated with C4 (P = 0.041).

Conclusions Histone hypoacetylation is observed in patients with pSS and is involved in the pathogenesis of pSS.

Key Points:
• The mRNA expressions of p300, CREBBP and PCAF in PBMCs from pSS patients were decreased in comparison with HCs.
• HAT activity and histone H3/H4 acetylation were reduced in PBMCs from pSS patients.
• HAT activity was correlated with disease characters.
• We show for the first time that the histone hypoacetylation may be involved in the pathogenesis of pSS.

Keywords Sjögren’s syndrome · Histone acetyltransferase · Epigenetic · Hypoacetylation

Abbreviations

| pSS | Primary Sjögren’s Syndrome |
| AIDs | Autoimmune diseases |
| HAT | Histone acetyltransferase |
| HDAC | Histone deacetylase |
| PCAF | P300/CBP associated factor |

CREBBP P300/CREB binding protein
ANA Antinuclear antibody
FS Focal sialadenitis
C3/4 Complement3/4
CRP C-reactive protein
RA Rheumatoid arthritis
SLE Systemic lupus erythematosus

Introduction

Primary Sjögren’s syndrome (pSS) is one of complex systemic autoimmune diseases (AIDs) affecting 0.3% to 0.7% of the general population with a 9/1 female predisposition [1, 2]. This disease manifests dry mouth and dry eyes, and 70–80% of patients appear protean extra-glandular symptoms [3, 4]. However, the pathogenesis of this disease is obscure. Growing evidences suggest that epigenetic dysregulations have been linked with pSS [5].
Epigenetic modifications, including DNA methylation, histone modification and micro-RNAs (miRNA), have been studied for many years in pSS, but the studies have focused on DNA methylation and miRNA. Altorok N et al. reported hypomethylated genes involved in type I interferon (IFN) pathway in naive CD4+CD45RA+ T cells in pSS patients [6]. Another study further identified prominent hypomethylation of IFN-regulated genes in tissues of pSS [7]. The global DNA hypomethylation in blood and salivary gland epithelial cells (SGEC) was associated with autoreactivity, lymphocyte infiltration and SSB expression [8, 9]. There were a lot of differences in miRNA expressions of T cells and B cells between pSS and healthy controls (HCs), such as miR-155, miR-146a, miR-378a and miR-30b-5p [10–14]. However, there are very little data on histone acetylation in pSS. A study found that TNF-α restrained aquaporin 5 (AQP5) expression in human salivary gland acinar cells through repression of histone H4 acetylation [15]. The results of this study indicate that histone acetylation may involve in SS salivary gland dysfunction.

The histones acetylation is mainly catalyzed by two opposite groups of enzymes: histone acetyltransferase (HAT) and histone deacetylase (HDAC) [16]. HAT involves the transfer of an acetyl group to the ε-amino group of lysine residues in histone and non-histones [17]. A variety of HAT proteins are clear, such as p300 and p300/CBP-associated factor (PCAF), p300/CREB-binding protein (CREBBP), and so on [18]. The main role of HDAC is regulating transcription by the removal of acetyl groups from lysine residues of histone tails. It is important to maintain a balance between HAT and HDAC.

Histones include H2A, H2B, H3 and H4, which are part of the nucleosome. Histones undergo post-translational modifications that alter their interaction with DNA and histones. The H3 and H4 histones have long tails protruding from nucleosome, which can be more easily covalently modified by acetylation, methylation and phosphorylation than H2A and H2B [19]. We investigated the alterations in global histone H3/H4 acetylation status and the expression of HAT in pSS. We assessed the aberrant histone H3/H4 acetylation in peripheral blood mononuclear cells (PBMCs) of pSS patients.

Methods

Patients and healthy donors

A total of 46 patients who fulfilled the 2016 ACR/EULAR classification criteria for pSS and 46 age- and sex-matched HCs were recruited from the outpatient clinic of the Department of Rheumatology [20]. All patients were primarily diagnosed as pSS (total score of ≥ 4 according to the classification criteria) without any treatment and excluded from other AIDs, such as RA and SLE. The HCs did not have any symptoms of SS, and the serum tests for antinuclear antibodies were negative. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University and performed by the Key Laboratory of Rheumatology and Immunology in Xiamen University. All patients signed the informed consent form. Table 1 summarizes the demographic and clinical characteristics of the patients with pSS and HCs.

Cell and serum preparation

PBMCs were isolated by standard density gradient centrifugation from sodium heparin vacutainer blood samples over Ficoll-Paque Plus (Axis-Shied PoC AS, Oslo, Norway). PBMCs were washed and resuspended in phosphate buffered saline (PBS). Red blood cells were removed by red blood cell lysis buffer. PBMCs in fetal bovine serum (Thermo Fisher) with 10% dimethyl sulfoxide (DMSO, Solarbio) were frozen and stored at -80 °C. Serum was separated from blood by centrifugation at 300 relative centrifugal force g (RCF) for 10 min and was stored at -80°C.

Reverse transcription-polymerase chain reaction (RT-PCR) and quantitative (qRT-PCR) analysis

Total RNA was extracted by TRIzol Reagent (Ambion by Life Technologies) from PBMCs and reverse-transcribed to cDNA according to the manufacturer’s instructions with reverse transcription reagent kits (Bio-Rad, Hercules, CA, USA). The expression of p300, PCAF, CREBBP and GAPDH was determined by qRT-PCR. The specific primer sequences are listed in Table 2. A 25 µl SYBR Green II PCR reaction mixture was used containing 12.5 µl of SYBR master mix (TaKaRa Shuzo), 1 µl of sense primer, 1 µl of antisense primer and 2 µl of cDNA. qRT-PCR was performed using MyiQ™ Real-Time PCR Detection Systems (Bio-Rad, Hercules, CA, USA), and relative gene expression was normalized to internal control as GAPDH. The gene expression values were calculated with the 2−ΔΔCt.

Cell lysate extraction

Isolation of nuclear was performed using the nuclear/cytoplasmic extraction kit according to the manufacturer’s directions (Thermo Scientific, Rockford, IL, USA). Protein concentration in nuclear was determined by the BCA protein assay kit (Thermo Scientific, Rockford, IL, USA). The nuclear protein was stored at -80 °C.
HAT activity assay

The HAT activity assay kit (Enzo Life Sciences, Koropi, Greece) was used to measure HAT activity in the nuclear extract according to the manufacturer’s instructions. 50 μg of nuclear extract was prepared in 40 μl water for each assay. The negative and positive control added 40 μl water and 10 μl NE (Cell Nuclear Extract) with 30 μl water instead of sample, respectively. Then 68 μl of assay mixture (50 μl 2X HAT Assay Buffer, 5 μl HAT Substrate I, 5 μl HAT Substrate II, 8 μl NADH Generating Enzyme) was added to each well. After incubating at 37 °C for 1–4 h, the HAT fluorescence signal was detected with 440 nm using a fluorescence microplate reader (BD, USA).

Western blot analysis

PBMCs were washed with PBS and resuspended in RIPA buffer (Solarbio) including protease inhibitors (Roche). Cell lysates were centrifuged (12000 g revolutions per minute at 4 °C). 20ug of protein in each sample was subjected to a 15% SDS-PAGE gel and transferred into immobilon polyvinylidene difluoride membranes (Millipore, Bedford, MA, USA). After blocking with Tris-buffered saline containing 0.1% Tween 20 and 5% non-fat dry milk, the membranes were incubated with primary antibodies overnight at 4 °C. The following primary antibodies were used: anti-acetyl-histone H3 (rabbit polyclonal, 1:2000 dilution) purchased from Merck Millipore; anti-histone H4 antibody (rabbit monoclonal, 1:10,000 dilution) purchased from Abcam; and goat anti-rabbit secondary IgG antibodies purchased from Cell Signaling Technology. Protein detection was performed using the chemiluminescence reagent (Millipore, Billerica, MA, USA). Quantification of target proteins was normalized to β-actin. Proteins were quantified using Image Lab.

Global histone H3 and H4 acetylation assay

Acetylated histone H3 and H4 proteins were extracted according to the manufacturer’s protocol (Epigentek Group Inc). Histone H3 and H4 concentration was determined as described. We used the Global Histone H3 Acetylation Assay Kit and Global Histone H4 Acetylation Assay Kit (Abnova) to measure histone acetylation in histone extraction from PBMCs. The concentration of histones was adjusted to 200 ng/μl-400 ng/μl, and 5 μl (1–2 μg of histone) per well was used. Histone H4/H3 acetylation were detected with 450 nm using a microplate reader (BD, USA).

### Table 1
Demographic and clinical characteristics of the patients with pSS and HCs

|                      | pSS patients (n = 48) | HCs (n = 48) |
|----------------------|-----------------------|--------------|
| Age, mean (range) years | 53 (20–71)           | 51.9 (26–67) |
| No. of women/no. of men  | 41/5                | 39/7         |
| Anti-SSA (anti-Ro)-positive% | 91.3%              |              |
| Anti-SSB (anti-La)-positive% | 41.3%              |              |
| ANA-positive%          | 78.3%                |              |
| FS(foci/4mm²)%         | 60.9%                |              |
| C3 (g/L)              | 1.025(0.592–1.54)    |              |
| C4 (g/L)              | 0.194(0.072–0.464)   |              |
| IgG (g/L)             | 15.4(8.09–33.9)      |              |
| IgA (g/L)             | 2.72(0.905–6.97)     |              |
| IgM (g/L)             | 1.15(0.281–2.87)     |              |
| ESR (mm/h)            | 23.5(2–91)           |              |
| CRP (mg/L)            | 1.77 (0.1–63)        | 0.8 (0.2–1.9) |
| Disease duration, mean (range) months | 10.5 (1.3–17.8) |              |

ANA = Antinuclear antibody, LFS = Focal sialadenitis, C3/4 = Complement 3/4, Ig = Immunoglobulin, ESR = Erythrocyte sedimentation, CRP = C-reactive protein

### Table 2
Related Primer Sequences

| Gene   | Primer   | Sequences 5’ → 3’                  |
|--------|----------|-----------------------------------|
| P300   | forward  | CATCTACCAGACTTTGACC               |
| P300   | reverse  | CACTGTCACAACACTTGCT               |
| PCAF   | forward  | ATGAAATATGCAATTTGAC               |
| PCAF   | reverse  | CTCTCTCAAATCTGGTGA                |
| CREBBP | forward  | CTCGACACGACATGAC                  |
| CREBBP | reverse  | GAAGTGGCATTCCTGTG                 |
| GAPDH  | forward  | GATTCACCACATGGAAATT               |
| GAPDH  | reverse  | TCTCGCTCTGGAAAGATGTG              |

Gene Primer Sequences 5’ → 3’
Enzyme-linked immunosorbent assay (ELISA)

The concentration of TNF-α was measured using ELISA kit (Quantikine assay, R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions. The concentration of TNF-α was detected with 450 nm and 620 nm using an ELISA microplate reader (Molecular Devices, Sunnyvale, CA, USA).

Statistical analysis

Data were analyzed with Prism 6 software (GraphPad Software, San Diego, CA). The HAT mRNA expression, HAT activity, total histone H3 and H4 acetylation levels between pSS and HCs were compared by the Mann–Whitney test. Spearman test was utilized to analyze the association between HAT activity levels and clinical parameters of pSS patients. P values < 0.05 were considered significant.

Results

Decreased expression of HAT (p300, PCAF, and CREBBP) in PBMCs from patients with pSS

To assess whether histone acetylation played a role in pSS, we first detected the mRNA expression of HAT (p300, PCAF, and CREBBP) in PBMCs from patients with pSS and HCs by qRT-PCR. As shown in Fig. 1A, the average relative expression level of p300 was 3.0-fold higher for HCs than pSS patients (P < 0.0001). PCAF and CREBBP expressions were 2.0-fold higher for HCs than pSS patients (Fig. 1B and C, P < 0.0001).

Decreased nuclear HAT activity in patients with pSS

Based on the previous results, we speculated that HAT activity was abnormal in pSS. So, we further studied HAT activity in human pSS and HCs. As we expected, HAT activity was decreased in pSS patients (n = 11) compared to HCs (n = 10, P = 0.0037) (Fig. 2). Therefore, the decreased HAT activity may promote histone hypoacetylation.

Abnormal histone acetylation in pSS

To assess whether the reduction in HAT activity causes histones hypoacetylation, we further verified the acetylation levels of histone H3 and H4 by WB and histone H3 and H4 acetylation activity assay. As shown in Fig. 3A, global histone H3 and H4 acetylation was reduced in pSS compared to HCs. Quantification of histone H3 and H4 was normalized to β-actin, and the average relative expressions of acetylation histone H3 and H4 were 3.0-fold higher for HCs than pSS patients.

Fig. 1 The mRNA expression of p300, PCAF and CREBBP was significantly decreased in pSS patients compared to those of the HCs (P < 0.0001). A. The mRNA expression of p300 in the human pSS (n = 29) and HCs (n = 27). B. The mRNA expression of PCAF in the human pSS (n = 29) and HCs (n = 27). C. The mRNA expression of CREBBP in the human pSS (n = 27) and HCs (n = 28)
Global histone H3 and H4 acetylation activities were reduced in PBMCs of pSS patients compared with HCs ($P=0.0005$ for H3, $P=0.0033$ for H4; Fig. 3C). These data showed decreased histone H3 and H4 acetylation in the PBMCs of patients with pSS. 

**Fig. 3** Total histone H3 and H4 acetylation activities were reduced in PBMC of pSS patients compared to HCs. A. Expression of acetylation histone H3 and H4 was studied by WB. B. Relative expression of acetylation histone H3 and H4 protein in PBMCs normalized to β-actin ($P=0.0068$ for H3, $P=0.0089$ for H4). C. Total histone H3 and H4 acetylation activities were reduced in pSS patients compared to HCs ($P=0.0005$ for H3, $P=0.0033$ for H4).
**The correlation between HAT activity and pSS disease characters**

To further demonstrate the association between histone hypoacetylation and pSS, we analyzed the relationship between HAT activity and pSS disease characters. We found negatively correlations of the HAT activity with CRP (Fig. 4A, \( P = 0.040 \)) and TNF-\( \alpha \) (Fig. 4B, \( P = 0.012 \)) and a positive correlation between the HAT activity and C4 (Fig. 4D, \( P = 0.041 \)). No correlation between the HAT activity and C3 (Fig. 4C, \( P = 0.118 \)) was observed.

**Discussion**

Histones and their accompanying post-translational modifications are receiving increasing attention because they can affect chromatin structure, regulate gene expression and participate in other nuclear modification processes [21]. It has been found that there are imbalances in HAT and HDACs expression and abnormal histone acetylation in various AIDs such as rheumatoid arthritis (RA) [22, 23], systemic lupus erythematosus (SLE) [24] and multiple sclerosis [25]. But there are little studies on the histone acetylation in pSS. This study demonstrates the histone acetylation is aberrant in pSS.

In an earlier study, the researcher used stable isotope labeling combined with mass spectrometry to demonstrate histone H3 and H4 hypoacetylation in MRL-lpr/lpr mice compared to control MRL/MPJ mice. This study established a link between abnormal histone codes and the pathogenesis of SLE, demonstrating that HDAC inhibition (HDACi) trichostatin A (TSA) could reset the aberrant post-translational histone modifications in vivo [26]. Hu et al. reported that global histone H3 and H4 were less acetylated in active lupus CD4\(^+\) T cells than in the controls, and the degree of histone H3 acetylation was negatively correlated with disease activity SLEDAI in lupus patients [24]. Given that...

![Fig. 4](image-url) The correlations about HAT activity and pSS disease characters. A. HAT activity has a negative correlation with CRP (Fig. 4A, \( P = 0.040 \)). B. HAT activity has a negative correlation with TNF-\( \alpha \) (Fig. 4B, \( P = 0.012 \)). C. HAT activity has a positive correlation with C4 (Fig. 4C, \( P = 0.041 \)). D. Correlation between the HAT activity and C3 (Fig. 4D, \( P = 0.118 \)).
pSS and SLE are similar AIDs, we hypothesize that histone acetylation imbalance is involved in the pathogenesis of pSS.

In this study, at first, we detected the mRNA expression of HAT (p300, PCAF and CREBBP) by qPCR. The results showed that the mRNA expressions of HAT (p300, PCAF and CREBBP) were reduced in pSS patients compared to HCs. In order to further clarify the histone acetylation, we next detected the HAT activity. The data showed that the activity of HAT in patients with pSS was lower than that in HCs. At the same time, Western blot and activity assay were used to detect the acetylation of histone H3/H4 in PBMCs. We certificated global histone H3/H4 hypoacetylation in pSS compared with HCs, which were consistent with the HAT activity. We also investigated the correlation between HAT activity and disease characters (CRP, C3/C4, TNF-α). In addition, we observed negative correlations of the HAT activity with TNF-α and CRP and a positive correlation between the HAT activity and C4. Taken together, these results suggest that the aberrant histone acetylation might play an important role in the pathogenesis of pSS.

Previous experiment demonstrated aberrant global hypoacetylation in the histone H3/ H4 with SLE. p300, PCAF and CREBBP, capable of acetylating histone in vitro and possibly in vivo, were decreased at expression levels [27]. Our results also showed that the mRNA expressions of p300, PCAF and CREBBP were significantly decreased, and histone H3/H4 was less acetylated in pSS than HCs. The reduction expression of p300, PCAF and CREBBP may explain the significant reduction in total histone H3 and H4 acetylation observed in PBMCs in pSS. CREBBP and p300 are key regulators of RNA polymerase II-mediated transcription and also are used to disrupt activator and repressor complexes, and their expression alterations are linked to human diseases [28–30].

Our study found that HAT activity was correlated with CRP, C4 and TNF-α, indicating that HAT activity was associated with disease activity of pSS patients and may be involved in the inflammatory cytokine expression. We considered the decreased HAT activity in pSS as a factor contributing to the pathogenesis of pSS. HAT activity can be a new entry point for treatment of pSS.

Current studies have tested drugs that modulate epigenetic responses in a variety of rheumatic diseases in vitro and in animal models [31]. Histone deacetylase inhibitors (HDACi) have become a potential anti-inflammatory agent that regulates the function of immune cells. The application of HDACi leads to a wide ranged acetylation of histones and thus reduces the expression level of those inflammatory cytokines, such as IL-2, interferon (IFN)-γ and IL-6 [31, 32]. PLGA-based SAHA (suberoylanilide hydroxamic acid) micropheres, a specific HDACi released in the lachrymal gland, can reduce the expression of proinflammatory cytokines and increase the expression of FoxP3 in the lachrymal glands in DED mice [33]. It indicates that HDACi might be a potential drug in the pSS therapy.

Conclusions

In our study, histone hypoacetylation is observed in patients with pSS and may be involved in the pathogenesis of pSS. The global histone H3 and H4 hypoacetylation is the result of the decreased HAT activity and HAT (CREBBP, p300 and PCAF) expression in pSS. These findings will assist us to elucidate the epigenetic pathogenesis of pSS and provide a new direction for monitoring and treating pSS. We need to ascertain what triggers the abnormal histone codes in patients with pSS, as these may represent a novel target for therapeutic intervention in pSS.

Acknowledgements

We are grateful to the Department of Rheumatology and Immunology of the First Affiliated Hospital of Xiamen University for their work on this research. We thank the healthy controls and patients who participated in the study.

Author contributions

Yan Li and Xiuying Lv designed, performed and analyzed the experiments and data. Mi Zhou, Ying Wang and Yan He performed the laboratory work. Yan Li and Jingxiu Xuan contributed to paper writing. Guixiu Shi planned experiments and wrote the paper.

Funding

This work was supported by the NSFC (Natural Science Foundation of China) grant 81302565 and the Xiamen Medical and Health Project (Project No.35022Z20189009) to Yan Li. NSFC grant U1605223 to Dr Guixiu Shi and the First Affiliated Hospital of Xiamen University Projects for Translational Medicine, China Funding (No. XFY2020002) to Xiuying Lv.

Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval

Patient consent was obtained. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University in accordance with the World Medical Association Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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