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SHORT REPORT

Alteration of innate lymphoid cell homeostasis mainly concerns salivary glands in primary Sjögren's syndrome

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ABSTRACT

Objective Innate lymphoid cells (ILCs) are a cell population implicated in the pathogenesis of various chronic inflammatory diseases, but little is known about their role in primary Sjögren's syndrome (pSS). The aim of this study was to assess the frequency of ILC subsets in peripheral blood (PB) and their quantity and location in minor salivary glands (MSGs) in pSS.

Methods The frequency of ILC subsets was analysed in the PB of patients with pSS and healthy controls (HCs) by flow cytometry. The amount and location of ILC subsets in MSGs were studied in patients with pSS and sicca controls by immunofluorescence assay.

Results In PB, the frequency of ILC subsets did not differ between patients with pSS and HCs. The circulating frequency of the ILC1 subset was increased in patients with pSS with positive anti-SSA antibodies and that of the ILC3 subset was reduced in patients with pSS with glandular swelling. In MSGs, the ILC3 number was higher in lymphocytic-infiltrated than non-infiltrated tissue in patients with pSS and normal glandular tissues in sicca controls. The ILC3 subset was preferentially located at the periphery of infiltrates and was more abundant in small infiltrates of recently diagnosed pSS.

Conclusion Altered ILC homeostasis mainly concerns salivary glands in pSS. Most ILCs in MSGs consist of the ILC3 subset, located at the periphery of lymphocytic infiltrates. The ILC3 subset is more abundant in smaller infiltrates and in recently diagnosed pSS. It might play a pathogenic role in the development of T and B lymphocyte infiltrates in the early stages of pSS.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterised by a chronic infiltration of exocrine glands by T and B lymphocytes.¹ Activated type I and II interferon pathways result in B cell hyperactivation and lymphocytic infiltrations of affected tissues, often organised as germinal centres. Little is known about the early stages leading to the autoimmune process in pSS.^{2,3} Some data suggest the involvement of innate immunity both in the disease initiation and maintenance

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Innate immunity is implicated in the pathogenesis of primary Sjögren's syndrome (pSS), especially in the early stages.
- ⇒ Innate lymphoid cells (ILCs) are involved in the pathogenesis of various chronic inflammatory diseases. The subset ILC3 contributes to the formation of lymphoid structures under physiological conditions and in some pathological situations.

WHAT THIS STUDY ADDS

- ⇒ Most ILCs in minor salivary glands are the ILC3 subset. The ILC3 subset is preferentially located at the periphery of the inflammatory infiltrates in minor salivary glands of patients with pSS. It is more abundant in the smaller infiltrates and in recently diagnosed pSS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The ILC3 subset may play a role in the development of T and B lymphocyte infiltrates in minor salivary glands in pSS.

of autoimmunity in pSS, but more studies are needed to dissect the role of innate immune cell actors.⁴ Among innate immune cells, natural killer cells and interleukin 22 (IL-22)-secreting NKp44⁺ cells have a role.^{5,6}

Innate lymphoid cells (ILCs) are a group of innate effector cells with a lymphoid morphology but lack rearranged antigen-specific receptors. They are characterised by the expression of the α -chain of the IL-7 receptor (CD127) and are divided into three groups, including ILC1, 2 and 3 subsets, on the basis of their transcription factors and cytokine production profiles.⁷ Although ILCs are normally involved in the maintenance of tissue homeostasis, they can also help generate tertiary ectopic lymphoid structures, as observed in some patients with pSS, and

potentiate inflammatory processes in different chronic inflammatory diseases.^{8,9}

The involvement of ILCs in the pathogenesis of pSS was mainly investigated in peripheral blood (PB),^{10,11} but the distribution of ILC1, 2 and 3 subsets in the minor salivary glands (MSGs) of patients with pSS has never been studied. The aim of this study was to analyse the frequency of ILC subsets in PB and their quantity and location in MSGs in pSS.

MATERIALS AND METHODS

PB and MSG collection

A total of 37 patients with pSS and 33 controls were included in this study (online supplemental table 1). Patients with pSS were included if they fulfilled the American-European Consensus Group criteria¹² without any immunosuppressive agents. PB samples were collected from 21 patients with pSS and 28 healthy controls (HCs). MSG samples were collected from 16 other patients with pSS and 5 sicca controls, those with no autoantibodies and a focus score <1.

ILC identification

ILCs and their subsets were identified using markers selected from the literature.^{13–15}

Flow cytometry

PB mononuclear cells were isolated according to the Ficoll gradient procedure. Flow cytometry was performed on 3 million PB mononuclear cells stained with the antibodies detailed in online supplemental table 2. ILCs were identified as CD45⁺, lineage (CD1a, CD3, CD4, CD14, CD16, CD19, CD34, CD303, FcεRI)⁻ and CD127⁺. Within the ILC gate, the ILC1 subset was identified as c-kit⁺ and CRTH2⁻, the ILC2 subset as CRTH2⁺, and the ILC3 subset as c-kit⁺ and CRTH2⁻ (figure 1A).¹⁵

Immunofluorescence assay

Paraffin-embedded MSG samples were cut into 5 μm sections, then dewaxed and rehydrated. Antigen retrieval involved heating the sections for 15 min at 750 W in a citrate solution. Permeabilisation involved using 0.1% Triton in phosphate-buffered saline (PBS). We used 5% horse serum in PBS to block non-specific staining. Sections were incubated with primary antibodies and secondary antibodies detailed in online supplemental table 3 and

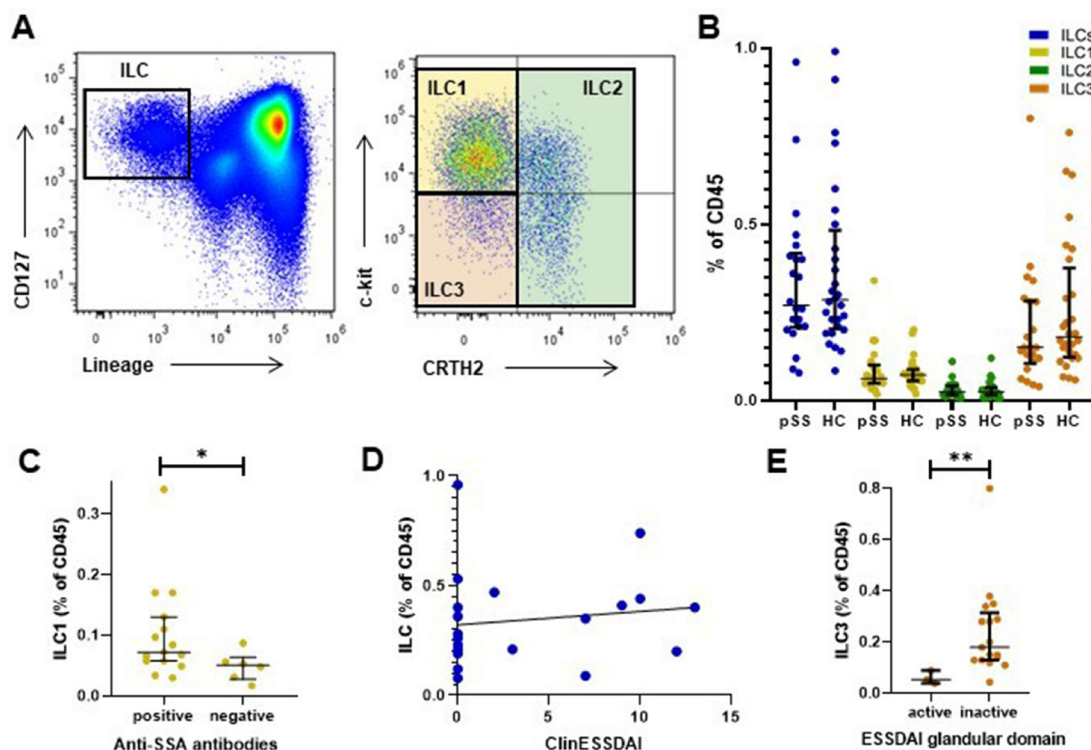


Figure 1 Peripheral blood analysis: frequency of total innate lymphoid cells (ILCs) and ILC1, 2 and 3 subsets and association with disease activity or clinical and biological manifestations in primary Sjögren's syndrome (pSS) and healthy controls (HCs). (A) Identification of ILC subsets in peripheral blood by flow cytometry: after gating on singlets and CD45⁺ cells, ILCs were identified as CD127⁺ and lineage (CD1a, CD3, CD4, CD14, CD16, CD19, CD34, CD303, FcεRI)⁻ (top panel), and the ILC1 subset was identified as CRTH2⁻ c-kit⁺, the ILC2 subset as CRTH2⁺ c-kit⁺ and the ILC3 subset as CRTH2⁻ c-kit⁺ (bottom panel). (B) Proportions of total ILCs and ILC subsets among CD45⁺ cells in patients with pSS (N=21) and HCs (N=28). (C) ILC1 frequency in patients with pSS with or without positive anti-SSA antibodies (N=21). (D) Correlation between total ILC frequency and disease activity measured by clinical EULAR Sjogren's Syndrome Disease activity Index (ClinESSDAI) in patients with pSS (N=21). (E) ILC3 frequency in patients with pSS with or without glandular manifestations defined as active ESSDAI glandular domain (N=21). Data are median±IQR. *P<0.05; **p<0.01.

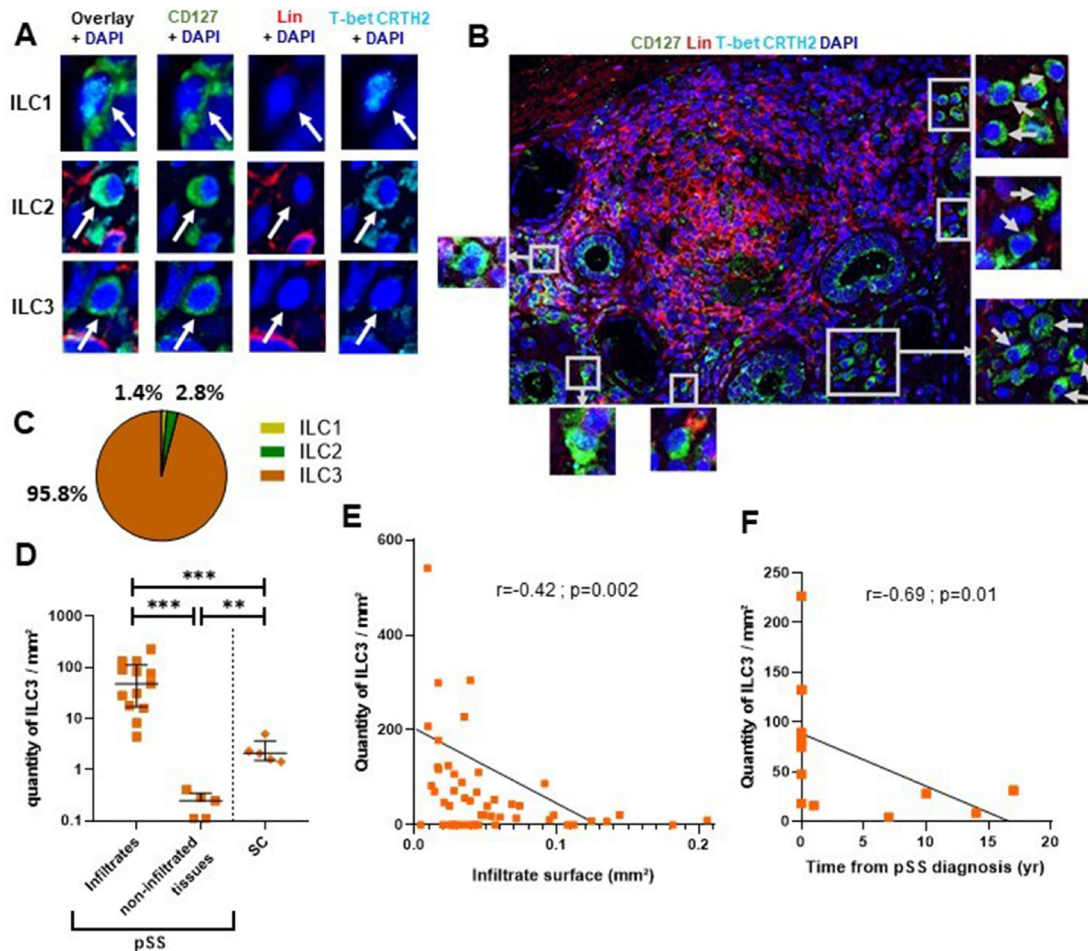


Figure 2 Minor salivary gland (MSG) analysis: quantity, proportion and distribution of ILC1, 2 and 3 subsets. (A) Strategy of identification of ILC subsets in MSGs by immunofluorescence multicolour staining: ILCs were identified as CD127+ and lineage (Lin) and the ILC1 subset was identified as T-bet⁺ and CRTH2⁻, the ILC2 subset as T-bet⁻ and CRTH2⁺, and the ILC3 subset as T-bet⁻ CRTH2⁻. The Lin contains antibodies against CD3, CD14 and CD19. (B) Example of identification of ILC3 (surrounded and designed with arrow) in an inflammatory infiltrate in MSGs of a patient with pSS. (C) Mean proportion of ILC subsets among total ILCs in patients with pSS (N=13). (D) Quantity of ILC3 subset per surface area of glandular tissue inflammatory infiltrates (N=13) and non-infiltrated tissues (N=5) in pSS and sicca control (SC) MSGs (N=5). (E) Correlation between the quantity of ILC3 subset in each inflammatory infiltrate of MSGs of a patient with pSS and the infiltrate surface (N=54). (F) Correlation between the quantity of ILC3 subset in infiltrates of MSGs of a patient with pSS and time from pSS diagnosis (N=13). Data are median±IQR unless specified. **P<0.01; ***p<0.001; DAPI, 4',6-diamidino-2-phenylindole; ILC, innate lymphoid cell; pSS, primary Sjögren's syndrome; yr, years.

counterstained with 4',6-diamidino-2-phenylindole (DAPI). MSG sections were scanned by using the Axio observer Z1 imaging system in confocal mode with a 40× objective. ILCs were defined as lineage (CD3, CD14, CD19)⁻ and CD127⁺. The expression of T-bet (nuclear) and CRTH2 (cytoplasmic) was used to distinguish ILC1 (T-bet⁺), ILC2 (CRTH2⁺) and ILC3 (T-bet⁻ and CRTH2⁻) subsets (figure 2A).^{15,16} The frequency of ILCs was described with the quantity of cells used to analyse surface ratios. Surfaces of MSG tissue or infiltrates were obtained by manual contouring with ImageJ V.1.8.0 (National Institutes of Health, Bethesda, USA).

Statistical analysis

Quantitative data are described with median (IQR) and qualitative data with frequencies (percentages). Categorical variables were compared by X² test or Fisher's exact

test and quantitative variables by Mann-Whitney U test. Statistical significance was established at p<0.05. All analyses were performed with GraphPad V.8.

RESULTS

ILC subset frequencies in PB do not differ between patients with pSS and HCs

We included 21 patients with pSS and 28 HCs for the PB analysis. Many patients with pSS were women (95.2%), and their median age was 56 years (IQR: 42.5–68) (online supplemental table 1). In total, 71.4% patients had positive anti-SSA antibodies and 33.3% had moderate or high systemic disease activity (clinical EULAR Sjogren's Syndrome Disease activity Index [ClinESSDAI] >4).

The frequency of total circulating ILC and ILC subsets did not differ between patients with pSS and

HCs (figure 1B). The ILC1 frequency was significantly increased in patients with pSS with anti-SSA antibodies ($p=0.03$, figure 1C). In patients with pSS, the frequency of total ILCs in PB was not correlated with systemic disease activity measured by the ClinESSDAI (figure 1D). The ILC3 frequency was significantly decreased in patients with pSS with glandular involvement defined as positive glandular domain of ClinESSDAI, corresponding, in the present study, to salivary gland swelling ($p=0.01$, figure 1E). No other significant difference or association was found between the frequency of total circulating ILC or ILC subsets and pSS clinical or biological parameters (online supplemental file 1).

ILC3 subset represents most of the ILCs in MSGs

We included 16 patients with pSS for the MSG analysis. Most were women (81.2%) and their median age was 54 years (IQR: 39.8–58.8) (online supplemental table 1). In total, 56.2% ($n=9$) of patients with pSS had positive anti-SSA antibodies and 46.7% ($n=7$ of 15) had moderate or high systemic disease activity (ClinESSDAI >4). The median focus score was 1.15 (IQR: 1–2.75).

Most of the ILCs identified in MSGs of patients with pSS were the ILC3 subset (95.8%) (figure 2C). In patients with pSS, the ILC3 subset was more frequent in MSG tissue with lymphocyte infiltration than in non-infiltrated tissue ($p=0.0002$) and MSGs of sicca controls ($p=0.0005$; figure 2D) and was more frequent in non-infiltrated tissue of patients with pSS than in sicca controls ($p=0.008$, figure 2D). The two groups did not differ in frequency of ILC1 and ILC2 subsets in MSGs (not shown).

ILC3 subset locates at the periphery of lymphocytic T and B infiltrates and is associated with smaller infiltrates and recent diagnosis

Most of the ILC3 subset was detected in infiltrates in MSGs of patients with pSS. Within the infiltrates, the ILC3 subset was mostly located at the periphery (figure 2B) and was increased in the smaller infiltrates ($r=-0.42$; $p=0.002$, figure 2E). The size of lymphocytic infiltrates was inversely correlated with disease duration after diagnosis ($r=0.60$; $p<0.0001$) (not shown). The quantity of the ILC3 subset was inversely correlated with time since pSS diagnosis ($r=-0.69$; $p=0.01$; figure 2F). The quantity of total ILC or ILC subsets in MSG infiltrates was not associated with anti-SSA antibodies, salivary flow or systemic disease activity measured by ClinESSDAI (ILC3 data shown in online supplemental figure 2).

DISCUSSION

The present study demonstrates that most ILCs in MSGs consist of the ILC3 subset and suggests their involvement in the early pathogenic stages of pSS.

In PB, the present results are consistent with two previous studies^{10 11} showing no change in ILC subset frequency in pSS versus controls. One of the studies¹¹ found an increase in the inflammatory ILC2 subset, potential precursors of the ILC3 subset,¹⁷ in pSS. Of note,

the circulating ILC3 subset was decreased in patients with MSG swelling in the present study. This decrease might suggest the migration of the circulating ILC3 subset in salivary glands in some patients with pSS but must be confirmed by the concomitant analysis of ILCs in PB and MSGs of the same patients. As previously observed, here we found an association between autoantibodies and the ILC1 subset. In contrast to a previous study with a low number of patients who had high systemic disease activity,¹⁰ here we found no association between the circulating ILC1 subset and the ClinESSDAI.

Because ILCs are mostly tissue-resident and tissue-effector cells, we then analysed their role in MSGs, one of the main target organs in pSS. Most of the glandular ILCs in MSGs were the ILC3 subset, as in other mucosal tissues.¹⁸ In patients with pSS, the frequency of the ILC3 subset was found increased in lymphocytic infiltrates and decreased in non-infiltrated tissues as compared with controls. A previous study showed a higher frequency of IL-22-secreting NKp44⁺, which might correspond to the ILC3 subset, in salivary glands from patients with pSS than controls.⁵ The ILC3 subset was located at the periphery of infiltrates, similar to natural killer cells in pSS.¹⁹ Moreover, the subset was more abundant in recently diagnosed patients. The ILC3 subset might play a role in the early migration of T and B lymphocytes in salivary glands. They were found involved in the migration and activation of lymphoid cells.^{20 21} In animal models of pSS, innate immune cells are the first to infiltrate salivary glands.^{22 23} In the DMXAA-induced model of pSS in female C57BL/6 (B6) mice, salivary ILC1 population increased significantly within 3 days after induction.²⁴ Indeed, in this study, the lymphocytic gland infiltration could be assessed at the early initiation of the pathogenic process (as it is an induced disease) in contrast to human pathology. It could be speculated that ILC1 might precede ILC3 in salivary glands but this remains to be demonstrated in patients.

ILC3 might also play a role in the persistent activation of T and B lymphocytes and in lymphoid organisation in salivary glands as reported in other chronic inflammatory diseases.^{25 26} Lymphoid tissue inducer cells are a subset of the ILC3 subset, depending on IL-7.^{9 27} IL-7 plays a pathogenic role in pSS,¹⁷ and targeting IL-7 receptor, currently evaluated in pSS, might also target ILC.

CONCLUSION

Abnormal ILC frequency affects mostly the targeted organs in pSS, the salivary glands, with a specific polarisation to the ILC3 subset and a preferential distribution at the periphery of inflammatory infiltrates. Our results suggest that the ILC3 subset might play a role in the development of infiltrates in the early stages of pSS.

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Contributors Study conception and design—LK, RF and J-EG. Data collection—LK, RF, CS and PLVQ. Interpretation of results—all authors. Preparation—all authors. All authors reviewed the results and approved the final version of the manuscript.

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Patient consent for publication Obtained.

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