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Concise report

Hyperresponsive cytosolic DNA-sensing pathway in monocytes from primary Sjögren's syndrome

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Abstract

Objectives. Cytosolic DNA-sensing pathway stimulation prompts type I IFN (IFN-I) production, but its role in systemic IFN-I pathway activation in primary SS (pSS) is poorly studied. Here we investigate the responsiveness of pSS monocytes and plasmacytoid dendritic cells (pDCs) to stimulator of interferon genes (STING) activation in relation to systemic IFN-I pathway activation and compare this with SLE.

Methods. Expression of DNA-sensing receptors cGAS, IFI16, ZBP-1 and DDX41, signalling molecules *STING*, *TBK1* and *IRF3*, positive and negative STING regulators, and IFN-I-stimulated genes *MxA*, *IFI44*, *IFI44L*, *IFIT1* and *IFIT3* was analysed in whole blood, $CD14^+$ monocytes, pDCs, and salivary glands by RT-PCR, monocyte RNA sequencing data, flow cytometry and immunohistochemical staining. Peripheral blood mononuclear cells (PBMCs) from pSS, SLE and healthy controls (HCs) were stimulated with STING agonist 2′3′-cGAMP. STING phosphorylation (pSTING) and intracellular IFNα were evaluated using flow cytometry.

Results. STING activation induced a significantly higher proportion of IFNα-producing monocytes, but not pDCs, in both IFN-low and IFN-high pSS compared with HC PBMCs. Additionally, a trend towards more $pSTING^+$ monocytes was observed in pSS and SLE, most pronounced in IFN-high patients. Positive STING regulators *TRIM38*, *TRIM56*, *USP18* and *SENP7* were significantly higher expression in pSS than HC monocytes, while the dual-function STING regulator *RNF26* was downregulated in pSS monocytes. STING was expressed in mononuclear infiltrates and ductal epithelium in pSS salivary glands. STING stimulation induced pSTING and IFNα in pSS and SLE pDCs.

Conclusion. pSS monocytes and pDCs are hyperresponsive to stimulation of the STING pathway, which was not restricted to patients with IFN-I pathway activation.

Key words: Sjögren's syndrome, type I IFN, monocytes, DNA-sensing pathway, STING

BASIC SCIENCE

Rheumatology key messages

- pSS monocytes show hyperresponsive IFNα production and STING phosphorylation upon DNA-sensing pathway stimulation.
- Several regulators of DNA-sensing pathway activation are differentially expressed in pSS monocytes compared with HCs.
- DNA-sensing pathway stimulation induces active STING signalling and IFN-α production by pSS plasmacytoid dendritic cells.

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Introduction

The majority of primary SS (pSS) patients display persistent systemic type I IFN (IFN-I) pathway activation. Associations between clinical characteristics and IFN-I activation have been described in pSS [1]. Yet the cellular source of IFN-I and the initiating triggers are still enigmatic.

IFN-I can be rapidly induced upon binding of ligands to pattern recognition receptors, in particular nucleic acid-sensing receptors. Plasmacytoid dendritic cells (pDCs) are considered the classical IFN-I-producing cells, predominantly via the Toll-like receptor (TLR) 7/9 pathway [2]. IFN-I pathway activation in pSS frequently coincides with autoantibodies against nucleic acid-binding proteins [1]. RNA-containing immune complexes generated from pSS-derived autoantibodies are able to induce IFNα production by pDCs, presumably through TLR7 [3]. Nevertheless, the primary cellular source of IFN-I and the molecular pathways triggering IFN-I secretion are context dependent [2]. Along this line, a diverse range of cell types, including monocytes, express cytosolic sensors that detect dsDNA from both microbial and endogenous origins and can provoke the production of IFN-I [4].

The primary cytosolic DNA-sensing receptor is cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS). Ligation of cGAS triggers IFN-I production by production of 2′3′-cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) and subsequent signalling via the downstream mediators stimulator of interferon genes (STING), TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3). Multiple additional putative DNA sensors have been described to induce IFNs [5]. Recent observations, including monocyte hyperresponsiveness to STING stimulation, have provided clues for a contribution of the DNA-sensing pathway to IFN-I pathway activation in SLE [6, 7]. In pSS, peripheral blood mononuclear cells (PBMCs) have been observed to contain elevated levels of short-fragmented dsDNA along with reduced expression and activity of DNase II [8]. In this study, we aimed to investigate the functional responsiveness of pSS monocytes and pDCs to DNA-sensing pathway activation and the association with systemic IFN-I activation and compare this with SLE.

Methods

PBMCs were isolated from patients with pSS ($n = 34$ IFN-high, $n = 27$ IFN-low) or SLE ($n = 8$) and HCs ($n = 32$) (Supplementary Table S1, available at *Rheumatology* online). Expression of DNA-sensing receptors and downstream mediators was analysed by RT-PCR and flow cytometry in $CD14^+$ monocytes and pDCs (Supplementary Fig. S1, available at *Rheumatology* online). STING in pSS salivary glands was visualized by immunohistochemical staining. PBMCs were stimulated with 2′3′-cGAMP (STING agonist), imiquimod (R837; TLR7 agonist) or CpG ODN2216 (TLR9 agonist). Phosphorylation of STING and intracellular IFNα were measured by flow cytometry (Supplementary Figs S2 and S3, available at *Rheumatology* online). Secretion of IFN-I was quantified in a cellular IFN-I reporter assay. Activation of the IFN-I pathway was determined from a composite expression IFN-I score of IFN-stimulated genes (ISGs) *MxA*, *IFI44*, *IFI44L*, *IFIT1* and *IFIT3* in whole blood. Details are provided in Supplementary data S1, available at *Rheumatology* online.

Results

High IFI16 expression in monocytes and pDCs is associated with systemic IFN-I activation in pSS

The expression levels of the most well-known (putative) DNA-sensing receptors cGAS, IFI16, ZBP-1 and DDX41 were explored in peripheral blood monocytes and pDCs. The primary cytosolic DNA-sensing receptor cGAS was expressed at equal levels in monocytes and pDCs from pSS patients and HCs (Supplementary Figs S4A and S5, available at *Rheumatology* online). Monocytes from IFN-high pSS patients expressed significantly higher IFI16 mRNA and protein levels compared with IFN-low pSS (Supplementary Figs S4B and S5, available at *Rheumatology* online). Despite upregulated *ZBP-1* mRNA expression in IFN-high pSS monocytes relative to HCs, no significant differences in protein expression were observed between pSS patients and HCs (Supplementary Figs S4C and S5, available at *Rheumatology* online). pDCs from IFN-high pSS showed significantly higher expression of IFI16 and DDX41 compared with IFN-low pSS (Supplementary Fig. S4D, available at *Rheumatology* online).

cGAMP induces phosphorylation of STING and IFNα production in monocytes and pDCs

Next the responsiveness of the STING pathway in PBMCs was investigated. Activation of the STING pathway with cGAMP, as well as specific TLR7 or TLR9 stimulation, induced IFNα in PBMCs (Supplementary Fig. S6A, available at *Rheumatology* online). The majority of IFNα-producing PBMCs upon STING stimulation were monocytes and pDCs in HCs, while the contribution of monocytes to IFNα-producing PBMCs is higher in pSS and SLE (Supplementary Fig. S6B, available at *Rheumatology* online). In line with this, the cGAMP-induced STING phosphorylation (pSTING) was most prominent in monocytes, peaking at 30-60 min (Supplementary Figs S3C and S7A, B, available at *Rheumatology* online). No difference was observed in the distribution of cell types among $pSTING^+$ PBMCs between HCs and patients with pSS or SLE (Supplementary Fig. S7B, available at *Rheumatology* online).

Increased proportions of cGAMP-inducible IFNα-producing monocytes in pSS

The proportion of cGAMP-induced IFNα-producing monocytes was higher in pSS than HC PBMCs, while the median fluorescence intensity of IFNα$^+$ monocytes was comparable (Fig. 1A and B). A similar trend was observed in PBMCs from SLE patients (Fig. 1A and B). Mirroring these data, cGAMP upregulated IFNβ mRNA expression and the secretion of IFN-I by PBMCs, which were increased in pSS patients compared with HCs (Supplementary Fig. S8A and B, available at *Rheumatology* online). The cGAMP-induced response showed no association with HCQ treatment or the patient's IFN score (Supplementary Fig. S9, available at *Rheumatology* online).

Trend towards more pSTING+ monocytes in cGAMP-stimulated PBMCs from pSS and SLE

The frequency of pSTING$^+$ monocytes in response to cGAMP stimulation showed considerable donor-to-donor variability. Although not reaching statistical significance, the proportion of monocytes positive for pSTING tended to be higher in SLE than HC PBMC cultures at 15 and 45 min and to a lesser extent in pSS after 15 min of cGAMP stimulation (Fig. 1C). The cGAMP-induced pSTING$^+$ monocytes tended to be more abundant in IFN-high pSS than IFN-low pSS (Fig. 1D), while the median fluorescence intensity of pSTING$^+$ monocytes was comparable between both groups (Fig. 1E). Compared with HCs, a small but significantly lower *TMEM173*/*STING* transcript abundance was observed in monocytes from pSS patients (Fig. 1F). Downstream signalling mediators *TBK1* and *IRF3* were expressed at equal levels in pSS and HC monocytes (Fig. 1F and Supplementary Fig. S5, available at *Rheumatology* online). Although not statistically significant ($P = 0.08$), protein expression of stromal interaction molecule 1 (STIM1), a negative regulator of STING signalling, appeared slightly reduced in pSS monocytes compared with HC monocytes (Fig. 1G). STING was abundantly expressed in infiltrating mononuclear cells and ductal epithelial cells in labial salivary glands of pSS patients (Fig. 1H).

Monocytes from pSS differentially express positive regulators of DNA-sensing pathway

A complex regulatory network involving post-translational modifications ensures balanced control of STING signalling. Monocytic expression of genes known to regulate the STING pathway was analysed using a publicly available RNAseq dataset of pSS monocytes (GSE173670) (Supplementary Tables S2 and S3, available at *Rheumatology* online). The explored negative regulators of STING did not differ between pSS patients and HCs (Supplementary Fig. S5, available at *Rheumatology* online). Expression of positive regulators *TRIM38*, *TRIM56*, *USP18* and *SENP7*, each modulating post-translational modifications, was higher in pSS monocytes compared with HCs. In contrast, RNF26, which promotes STING activity early on but suppresses in late response [9], was expressed at lower levels in pSS monocytes.

pDCs from pSS and SLE pSTING upon cGAMP stimulation

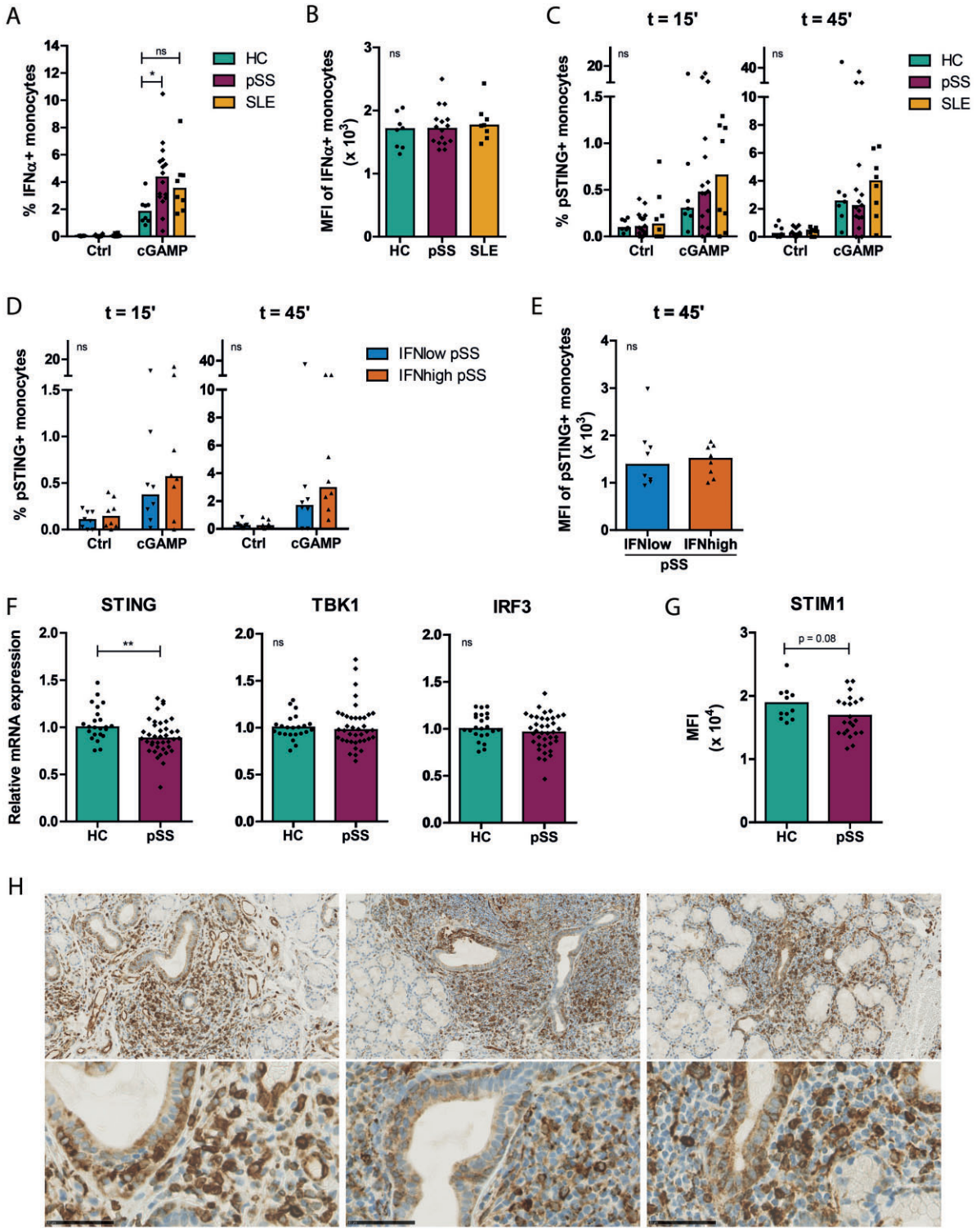
pDCs are uniquely equipped to generate robust IFN-I responses, particularly upon engagement of TLR7/9. Yet STING activation in pDCs can also induce IFN-I production (Supplementary Fig. S6B, available at *Rheumatology* online) [10]. Therefore the responsiveness of each of these IFN-I-inducing pathways in pDCs was further explored. As expected, TLR9 stimulation strongly stimulated IFNα production by pDCs (Supplementary Fig. S10A, available at *Rheumatology* online). HCQ is known to inhibit endosomal TLR signalling. In line with this, the proportions of TLR7/9-induced IFNα-producing pDCs were significantly lower in PBMCs from HCQ-treated pSS (Supplementary Fig. S10B, available at *Rheumatology* online). In HCQ-untreated pSS, the frequency and median fluorescence intensity of IFNα$^+$ pDCs were comparable to those of HCs upon TLR9 stimulation (Supplementary Fig. S10C and D, available at *Rheumatology* online). In contrast, IFNα-producing pDCs were increased in TLR7-stimulated PBMCs from IFN-high pSS (Supplementary Fig. S10C and E, available at *Rheumatology* online). Opposed to monocytes, the frequency of IFNα$^+$ pDCs in cGAMP-stimulated PBMC cultures did not differ between HCs and pSS or SLE patients (Fig. 2A). While cGAMP did not induce pSTING in pDCs from HCs, pSTING was clearly induced in pDCs from pSS and SLE patients, most notably after 45 min of stimulation (Fig. 2B and Supplementary Fig. S11, available at *Rheumatology* online). The frequency of pSTING$^+$ pDCs was significantly increased in SLE compared with HCs at 45 min of cGAMP stimulation and a trend for a higher frequency was also observed in pSS (Fig. 2B). No association was observed between the patient's IFN score and *in vitro* cGAMP-induced pSTING in pDCs (data not shown).

Discussion

Activation of the cytosolic DNA-sensing pathway induces IFN-I production, but the role of this pathway in systemic IFN-I pathway activation in pSS is poorly studied. Here we demonstrated a hyperresponsiveness of pSS monocytes to STING stimulation, illustrated by an increased number of IFNα-producing monocytes. In accordance with literature [7], similar findings were observed in SLE monocytes.

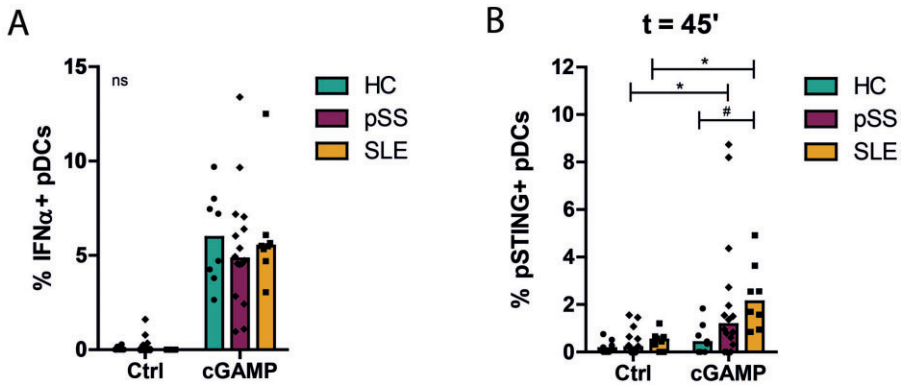
Several positive regulators of STING pathway activity mediating post-translational modifications were upregulated in pSS monocytes relative to HCs. On the other hand, STIM1, which negatively regulates STING by retaining it at the endoplasmic reticulum, was slightly reduced in pSS monocytes. Targeting STIM1 by an influenza-A-derived peptide has been reported to inhibit IFN-I production in an *in vitro* culture of SLE PBMCs

Fig. 1 Increased proportions of cGAMP-inducible IFNα-producing monocytes in pSS



(A) Frequency and **(B)** MFI of IFNα$^+$ monocytes in PBMCs stimulated with 25 μg/ml 2′3′-cGAMP for 6 h. **(C, D)** Frequency and **(E)** MFI of pSTING$^+$ monocytes in 2′3′-cGAMP-stimulated PBMCs from HCs, SLE and pSS, **(D, E)** stratified by IFN-I score. **(F)** Relative mRNA expression of *STING*, *TBK1* and *IRF3* in CD14$^+$ monocytes. Symbols represent individual samples, bars indicate medians. **(G)** STIM1 MFI in CD14$^+$ monocytes. **(H)** STING expression in pSS labial salivary glands ($n = 3$; scale bar = 50 μm). *$P < 0.05$, **$P < 0.01$. ns, not significant; MFI, median fluorescence intensity.

FIG. 2 pDCs from pSS and SLE phosphorylate STING upon cGAMP stimulation



(A) Frequency of IFNα$^+$ pDCs and **(B)** frequency of pSTING$^+$ pDCs of total pDCs in 25 μg/ml 2′3′-cGAMP-stimulated PBMC cultures from patients with pSS, SLE or HCs. Symbols represent individual samples and bars indicate medians. *$P < 0.05$. ns, not significant.

[11]. Thus, altered balances between positive and negative regulators could potentially alter the sensitivity of the STING pathway in pSS monocytes.

Compared with HCs, monocytes from pSS patients displayed hyperresponsive IFNα production after STING stimulation. Yet this did not associate with *in vivo* systemic IFN-I pathway activation. The expression of *SLC46A2*, the presumed primary cGAMP importer in CD14$^+$ monocytes [12], was unaltered in pSS monocytes (Supplementary Fig. S5, available at *Rheumatology* online). The mechanism underlying the elevated cGAMP-stimulated IFN-α production in IFN-low pSS remains to be elucidated, but might potentially be based on IFN-independent inflammatory pathways, epigenetic imprinting or STING regulators. Notably, STIM1 was equally downregulated in IFN-low and IFN-high pSS compared with HCs. Lower expression of STIM1 protein has previously been described in pSS salivary gland epithelium and linked to inhibition of STIM1 translation by an Epstein-Barr virus-derived miRNA [13]. Although evidence is currently lacking for a similar mechanism in monocytes, it might be an interesting hypothesis to explore given unchanged STIM1 mRNA levels in pSS monocytes.

Although STING phosphorylation tended to be increased in IFN-high pSS, cGAMP-induced IFNα production did not differ between IFN-high and IFN-low pSS. This apparent discrepancy between the degree of STING phosphorylation (indicator of active STING signalling) and the final amount of IFN-I could have been influenced by various factors, acting at different levels of the pathway. Autocrine and paracrine signalling are important in coordinating cellular responses. Not surprisingly, inhibition of the IFN-α/β receptor (IFNAR) affected the number of IFN-α-producing monocytes (data not shown). In this context, it is interesting to note that the positive STING regulator ubiquitin specific peptidase 18, which had significantly higher expression in IFN-high pSS *vs* IFN-low pSS, also has inhibitory activity on IFNAR signalling by interacting with IFNAR2 and signal transducer and activator of transcription 2 [14]. Therefore differential regulation of autocrine/paracrine IFNAR signalling in IFN-high and IFN-low pSS might impact the final IFN-α response. Alternatively, methodological factors such as assay sensitivity and measurement of intracellular IFNα, which is only one of the IFN-Is, could have influenced these results.

The unique expression pattern of TLR7/9 and the transcription factors IRF7/IRF3 in pDCs drives robust IFN-I responses after endosomal TLR stimulation [15]. Despite this specialized function, pDCs contain a functional cGAS-STING pathway able to induce IFN-I [10]. Here we showed that DNA-sensing pathway stimulation induced active STING signalling and IFNα production by pDCs from pSS and SLE patients. STING activation in pDCs has been demonstrated to inhibit TLR9 signalling [16]. In contrast to previous observations [17], we did not observe reduced TLR9-stimulated IFNα production in pSS pDCs. On the other hand, TLR7-stimulated IFNα production was increased in pDCs from IFN-high pSS compared with IFN-low pSS, consistent with previous data [17]. While acknowledging methodological differences and the limited number of patients included in our study, our findings contrast with the refractory state of pDCs described in SLE [18]. This suggests that functional differences exist between pDCs from SLE and pSS.

HCQ treatment of patients greatly affected the *in vitro* responsiveness of PBMCs to TLR7/9 stimulation, but not STING activation. Although HCQ downregulates blood IFN scores in pSS [19], patients using HCQ in clinical practice often still display elevated IFN scores [1]. These data support involvement of IFN-I-inducing pathways beyond TLR7/9 in pSS, such as the cytosolic DNA-sensing pathway. Importantly, PBMCs from pSS patients have been reported to contain excessive cytosolic dsDNA [8]. This mislocalized dsDNA might be originating from leakage from the endosomal compartments caused by reduced DNase II activity and could potentially activate the cGAS–STING pathway and increase IFN-I production [20]. STING

pathway activation has the potential to elicit pSS-like disease in mice [21]. Our study highlights the relevance of this observation for human pSS showing both functional alterations in STING pathway sensitivity in circulating immune cells as well as readily detectable STING expression in the mononuclear cell infiltrates and ductal epithelial cells in pSS salivary glands. In conclusion, monocytes and pDCs from patients with pSS are hyperresponsive to stimulation of the STING pathway. This phenomenon was not restricted to patients with IFN-I pathway activation and was unaffected by HCQ treatment.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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