B-cell populations and sub-populations in Sjögren’s syndrome

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Summary

Sjögren’s Syndrome (SS) is a chronic inflammatory disorder affecting exocrine glands, in particular the lacrimal and salivary glands. The disease can be primary (pSS) or secondary to other systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and others. The systemic autoimmune character of pSS is also apparent from the occurrence of (non-organ specific) autoantibodies in this disease. Histopathologically, glandular involvement is characterized by focal accumulation of lymphocytes, particularly around epithelial ducts, with, sometimes, germinal center-like structures. The infiltrates largely consist of T-cells, with a preponderance of CD4-positive T-cells. As a result, the pathology in SS was primarily attributed to T cells. However, a break with the fixation on the role of T cells in pSS came when therapeutic B-cell depletion strategies proved remarkably efficacious in this disease, thereby indicating a major role for B-cells in the immunopathogenesis of pSS. In this regard, a closer look at the composition of B-cells and B-cell sub-populations, both in the peripheral blood and in target tissues, is worthwhile. In this review, we discuss current data on B-cells in pSS. B-cell depletion offers a unique possibility to study the recurrence of (pathogenic) B-cells and their characteristics in pSS patients treated with rituximab. Data on B-cell sub-populations in the peripheral blood and B-cell repertoire in the target tissues following rituximab treatment are discussed as well. We also address their state of activation, repertoire, and relation to B-cell activating factor (BAFF).

SJÖGREN’S SYNDROME: THE LATE NEWS

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Sjögren’s syndrome (SS) is a rheumatic autoimmune disorder that primarily affects glandular tissues that produce moisturizing secretions such as the salivary and lacrimal glands. It is known as primary Sjögren’s syndrome (pSS) when it occurs on its own and as secondary SS when it occurs in tandem with other systemic autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis [1]. Extraglandular involvement is frequent, indicating that pSS is a systemic autoimmune disease. There is a strong female preponderance with a female to male ratio of 9 to 1, and a high prevalence of up to 3% in people above the age of 50 years [2].
For many years, the immune pathology in SS, as well as many other autoimmune diseases, was largely attributed to T cells as they were observed to infiltrate in large numbers within affected organs or glands. Experiments with autoimmune animal models also showed that T cells could transfer autoimmune diseases [3]. Diseases such as rheumatoid arthritis and insulin-dependent diabetes mellitus also showed strong statistical associations with certain MHC class II alleles, which was suggestive of a T cell-dependent process. However, a break with the fixation on the role of T cells in autoimmune disorders came when anti-T cell therapy failed to produce desirable clinical results in certain systemic autoimmune diseases [4].

B-cells on the other hand, were initially thought to be minor players that acted more as part of the effector arm of the autoimmune process, as was evident from the excessive production of (auto)antibodies in patients with autoimmune disorders. In pSS, the classical symptoms of hypergammaglobulinemia and increased production of autoantibodies such as anti-Ro/SSA and anti-La/SSB were evidence of B-cell hyperactivation. Moreover, a quarter of pSS patients also exhibit ectopic development of B-cell proliferations which resemble germinal centres (GC) in the target tissues and approximately 5–10% of them have the probability of progressing to MALT lymphoma, a B-cell malignancy [5,6]. These observations suggested a more primary role for B-cells in the immunopathogenesis of pSS. Consequently, B-cell depletion with the chimeric monoclonal antibody rituximab (RTX) was attempted in patients with pSS. The initial data was promising and showed restoration of glandular function in early pSS with positive effects as well on extraglandular manifestations and constitutive symptoms like fatigue [7]. In view of these findings, a closer look at the composition of B-cells and B-cell subpopulations, both in the peripheral blood and in target tissues, is worthwhile. In this review we will discuss current data on B-cells in pSS. B-cell depletion offers a unique possibility to study the recurrence of B-cells and their characteristics in pSS patients treated with RTX. Data on B-cell subpopulations in the peripheral blood and the B-cell repertoire in the target tissues following RTX treatment will be discussed as well. We will also address their state of activation and their response to the B-cell activating factor, BAFF.

**B-cell populations in primary Sjögren’s syndrome patients**

**In peripheral blood**

Many studies, including those from our group, have given evidence for disturbances in the distribution of peripheral blood B-cell subsets in pSS patients. In comparison to healthy controls, the peripheral blood from pSS patients exhibit a significant decrease in frequencies and numbers of CD27+ memory B-cells and an increase in those of both naïve and memory CD27– B-cells [8–12]. There are two possible explanations for the decrease in CD27+ memory B-cells in the peripheral blood of pSS patients. One could be the migration of CD27+ memory B-cells in patients into inflamed salivary glands due to the increased expression of the chemokines CXCL12 and CXCL13 in these glands [13]. The other possibility is that shedding of CD27 from the cell surface resulting in CD27– memory B-cells [10] may account for the reduced detection of circulating CD27+ memory B-cells in pSS patients. The latter possibility seems quite plausible since CD27− memory B-cells were also reported in healthy individuals. These B-cells were mostly of the IgG isotype and were somewhat less mutated than their CD27+ counterparts [14]. Strikingly, increased frequencies of CD27– memory B-cells that were class-switched were reported in the blood of SLE patients, and were positively correlated with higher disease activity and increased levels of disease-specific autoantibodies [15].

Our own group reported a significant negative correlation between frequencies and numbers of circulating CD27– B-cells and salivary gland function in pSS patients [16]. Given the fact that IgM−IgD+CD27− B-cells from healthy individuals were shown to bind to autoantigens, this raises the possibility that the subset of CD27− B-cells may be the precursors of autoantibody secreting plasma cells in autoimmune diseases [16,17]. Analyzing the presence of these subsets within affected glands of pSS patients may shed more light on the role of these B-cells in the autoimmune disease pathology. In addition to this, our group also reported a significant increase in the percentages and absolute numbers of circulating transitional B-cells, as well as a significant increase in the percentages (but not in the numbers) of naïve CD27−CD38low B-cells in pSS patients compared to healthy individuals [8].

Another study that explored the presence of long-lived plasma cells (PCs) in pSS, reported a significantly higher percentage of PCs in the peripheral blood of pSS patients with lymphocytic infiltration focus scores greater or equal to 2 in their salivary glands compared to those pSS patients with a focus score less or equal to 1 [18]. The authors also revealed a two-fold higher

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**Glossary**

- GC: germinal centre
- HSG: human salivary gland
- Ig: immunoglobulin
- IL: interleukin
- PC: plasma cell
- PKC: protein kinase C delta
- pSS: primary Sjögren’s syndrome
- RTX: rituximab
- SLE: systemic lupus erythematosus
- SS: Sjögren’s Syndrome
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The proportion of CD19—PCs compared to CD19+ PCs in pSS patients is lower than in normal controls [18]. Interestingly, the lack of CD19 and CD27 from the surface of PCs is reportedly associated with the susceptibility to malignancies [19,20]. Since reduced CD19 expression on long-lived PCs within the bone marrow is correlated with increased lifespan of these cells [21], these cells could be the precursors for long-lived PCs in pSS patients [18]. However, it remains to be elucidated whether these CD19+ long-lived PCs play a role in either persistent autoantibody production or the increased susceptibility to B-cell malignancies observed in pSS patients, or both.

In salivary glands

Studies on B-cell subsets present in the salivary glands of pSS patients are few and not very definitive. The lymphocytic infiltrates seen in the salivary glands of pSS patients are more akin to B-cells clusters or aggregates rather than typical germinal centers (GCs) owing to their lack of typical GC-markers such as CD10 and CD38 and the expression of activation-induced cytidine deaminase which is required in GC reactions for somatic hypermutation and class-switching [22]. These B-cells lacked expression of CD38, which is usually present on transitional T1-type B-cells that emigrate from the bone marrow into the circulation [23]. This indicated the presence of a more mature subset of transitional B-cells, termed T2 B-cells, which were CD19+IgD+CD38−IgM+CD21+CD23+ and present within pSS salivary glands [22,24]. However, another study on lower lip salivary gland (LSG) biopsies reported that in contrast to the widely dispersed presence of B-cells expressing CD38+, CD79α+ and CD5+ to a minor degree, and lacking CD20, CD21 and CD27 in LSGs from healthy controls, LSGs from pSS patients showed CD20+ B-cells and CD27+/CD38+ B-cells, with the CD20+ B-cells being concentrated in perivascular regions that did not overlap with focal infiltrates filled with the CD27+/CD38+ B-cell subset [25]. A more recent study also detected significant numbers of CD138+, non-proliferating, Bcl-2 expressing plasma cells in the salivary glands of pSS patients with high focus scores [26]. Our group [Hamza et al., in press, 2012] and others [27–29] showed increased clonal expansions of immunoglobulin-producing cells (B-cells and plasma cells) in the salivary glands of pSS patients compared to non-pSS control patients. In our study, some of these clones were composed of mixed IgA and IgG isotypes within the parotid salivary glands from pSS patients. This suggested the presence of localized class switching within the inflamed glands of pSS patients [30]. These observations suggest the existence of local B-cell hyperactivation and proliferation in the affected tissues.

In S5, the presence of anti-Ro (SS-A) and anti-La (SS-B) autoantibodies against RNA-protein complexes are an important diagnostic criterium [31]. Studies have shown that pSS patients with relatively high levels of anti-Ro/SSA and anti-La/SSB autoantibodies in their sera also presented with anti-Ro/SSA and anti-La/SSB producing cells in their labial glands, particularly along the periphery of germinal center-like structures and interstitial spaces within the labial glands [6,32]. Moreover, pSS patients who presented with germinal center-like microenvironments within their salivary glands, showed increased local production of anti-Ro/SSA and anti-La/SSB autoantibodies and apoptotic activity within these microenvironments, thereby indicating the significance of a highly localized interaction between the target glandular tissue and immune cells in pSS autoimmune pathology [6]. Some SS patients had detectable titres of anti-Ro and anti-La autoantibodies in plasma, yet no autoantibody-producing cells were found in their peripheral blood [33]. This suggests that (auto)antibody production probably occurs in tissues such as the bone marrow or in secondary lymphoid organs such as lymph nodes and tonsils. In diseases such as pSS, the sites of inflammation within salivary glands may also be used for this purpose. The (auto)antibody-specific memory B-cells may have an increased tendency to migrate to these inflamed sites due to the increased expression of chemoattractants such as CXCL12 and IL-6 (discussed later) within salivary glands of pSS patients [18] where the inflammatory microenvironment may contribute to their transformation to (auto)antibody-producing plasma cells.

Abnormalities of B-cell immunomodulation in primary Sjögren’s syndrome

It has been suggested that CXCL13 and CXCL12 overexpression in the inflamed glands of pSS patients could play an active role in the recruitment of B-cells as infiltrating cells [34]. Peripheral blood B-cells from patients with primary S5 show significantly higher gene expression of surface CXCR4 in contrast to healthy individuals and this was especially evident with respect to CD27−B-cells. However, transmigration assays based on the interaction between CXCR4 and its cognate ligand CXCL12 showed that the migratory potential of peripheral CXCR4+ CD27−B-cells from pSS patients was not different from that of healthy controls [13]. This may be due to the fact that significantly higher frequencies of CD27−naive B-cells from pSS patients expressed the mRNA for the inhibitory regulator of G protein signaling 13 (RGS13), which is known to inhibit the migrational response of CXCR4-transfected Chinese hamster ovary cells toward CXCL12 and CXCL13 in vitro [13,35]. Activated CD27+ B-cells from primary SSS patients showed significantly reduced migratory responses to the high expression of CXCL12 and CXCL13 in pSS glands when compared with those from healthy controls. However, analysis of peripheral blood revealed a moderately diminished frequency of CXCR5+ CD27+ memory B-cells in pSS patients compared to healthy controls. This was surprising because the CXCL13–CXCR5 pairing has been shown to be involved in the homing of B-cells into...
lymphoid follicles, as well as in the development of organized lymphoid follicles [13]. Given the low CXCR5 expression on CD27+ B-cells that are left in the pSS peripheral blood, the question arises as to which factors facilitate the migration of CXCR5+ CD27+ memory B-cells into the inflamed salivary glands of pSS patients and the formation of ectopic lymphoid tissue within them [36,37]. This is a significant point because CD27+ memory B-cells were shown to be reduced in the peripheral blood and accumulated in the inflamed salivary glands. The vast majority of these infiltrating CD27+ memory B-cells coexpressed CXCR5 and CXCR4, while the lower frequencies of peripheral CD27+ memory B-cells were accompanied by a reduction in CXCR4+ and CXCR5+ B-cells in pSS patients. Thus, coexpression of both CXCL12 and CXCL13 may attract the peripheral CXCR4+CXCR5+CD27+ memory B-cells into the inflamed glands, where they may reside and proliferate. This suggests that a process of selective migration leaves memory B-cells with lower migratory capacity remaining in the blood while those that can home into the inflamed glands may be retained within the glands through as yet undefined survival signals [13].

A recent study observed that CXCL12 and interleukin (IL)-6 survival factors were highly expressed in pSS salivary gland epithelium and within focal mononuclear infiltrating cells. Adipocytes present in the salivary glands were also proven to be an important source of CXCL12 [26]. Strikingly, plasma cells were detected in close proximity to CXCL12 and IL-6 expressing cells, suggesting that CXCL12 and IL-6 may be vital for plasma cell survival [26].

Another group of cytokines that play important roles in B-cell survival, differentiation and proliferation are the cytokine B-cell activating factor (BAFF) and the proliferation-inducing ligand (APRIL). Both BAFF and APRIL can bind to either of the receptors BCMA (B-cell maturation Ag) and TACI (transmembrane activator and calcium modulator and cyclophilin ligand activator), but only BAFF binds another receptor, BAFF-R or BR3 [38]. BAFF-transgenic mice develop a condition that has certain similarities with the human pSS condition [39]. In pSS patients, both BAFF and APRIL levels are increased [40]. In BAFF-transgenic mice, autoreactive marginal zone B-cell clonal populations that apparently proliferated in the spleen, were also found within salivary glands, indicating that cells deriving from the splenic marginal zone population may be the precursors for autoreactive cells in human pSS [16,39].

In pSS patients BAFF was shown to be produced not only by epithelial cells and T cells but also by B-cells [41]. An interesting observation though, was the fact that the BAFF receptor BR-3 was present on most B-cells within the salivary glands of pSS patients while TACI and, to a lesser degree, BCMA were observed on transitional B lymphocytes. This was suggestive of a form of autocrine feedback mechanism for B-cell activation and proliferation [41]. Furthermore, only the epithelial cell-bound BAFF extended the survival of normal B-cells while the secreted BAFF did not do so [41]. This is significant in view of the fact that studies on self-reactive B-cells in BAFF-transgenic mice have demonstrated that BAFF overexpression can promote the survival of autoreactive B-cells that are usually deleted during later stages of maturation and also facilitates their migration into niches from which they are normally excluded [42]. These observations also highlight the possible involvement of the glandular tissue (epithelial cells) within salivary glands in perpetuating the pSS disease process.

Elevated serum BAFF and APRIL levels in pSS patients were positively correlated to serum gammaglobulins, IgG, presence of anti-SSA or anti-SSB autoantibodies and focus score [39,43,44]. Moreover, BAFF expression within inflamed salivary glands was associated with the presence of germinal center-like structures [45], while elevated BAFF levels in the serum of pSS patients correlated with the increased number of peripheral CD27−CD38+IgD− B-cells [46].

As a result of all of these observations, anti-BAFF therapy is now being considered a serious option in the treatment of pSS. Belimumab, a monoclonal antibody to BAFF, has already shown significant benefits for patients with SLE [47], which is a disease that is comparable to pSS in its presentation of higher BAFF and APRIL levels in the sera of patients. To our knowledge, clinical trials targeting BAFF in pSS patients are still ongoing.

A pertinent development in the study of BAFF expression was the detection of multiple alternatively spliced transcripts for BAFF. An alternatively spliced mRNA, in which exon 3 is absent was shown in mice to negatively regulate BAFF by forming heterotrimers with the full-length form transcript. However, the translated form of this BAFF transcript has not been detected [48]. Another BAFF RNA variant which lacked a 114 base pair region within exon 4 of the BAFF gene was found to encode for a protein that could interact with DNA and perform as a transcription factor for the full-length BAFF transcript [24]. It remains to be seen if the differential expression of the former and/or the latter BAFF variant(s) in pSS patients compared to healthy controls may be a factor driving the excessive BAFF expression seen in pSS and other autoimmune diseases.

A recent study using co-culture experiments of human salivary gland (HSG) cell line cells and tonsilar B lymphocytes, showed that direct HSG cell-B-cell contacts were able to induce apoptosis in epithelial cells [49]. This B-cell-mediated apoptosis required the translocation of protein kinase C delta (PKC δ) into the nucleus of epithelial cells, which then resulted in histone H2B phosphorylation on serine 14 and poly (ADP-ribose) polymerase cleavage [49]. This is particularly noteworthy since the treatment of B-cells with BAFF is reported to prevent nuclear accumulation of PKC δ and enhance B-cell survival [50].
Selection of the autoimmune immunoglobulin repertoire in primary Sjögren’s syndrome

Previous studies have shown that the immunoglobulin variable light chain repertoire within peripheral blood B-cells exhibits a disordered selection in pSS patients compared to controls. The VL-\(\lambda\) genes 2A2, 2B2, 2C and 7A together accounted for 56% of all functional VL joints [51], whereas in another study of peripheral blood from a single pSS patient, 43% of the VL-\(\kappa\) repertoire was represented by the V\(\kappa\) genes L12, O12/02 and B3 [52]. A study on a parotid gland biopsy from the same patient revealed an increased usage of the rheumatoid factor and lymphoma-associated V\(\kappa\)/A27 gene (29%) compared with blood-derived B-cells (8%) [53]. Moreover, an increased frequency of B-cells expressing the V\(\kappa\)/A27–J\(\kappa\)/2 rearrangement was observed within the parotid glands of this pSS patient. It remains to be seen whether this apparent bias in V\(\kappa\) gene usage is also seen in larger series of pSS patients. However, with regards to the immunoglobulin variable heavy chain gene usage, we [Hamza et al., submitted], [30] found no evidence for a biased usage of a particular Vh gene in pSS patients compared to non-pSS controls.

With regards to isotype usage, we noted significant differences in IgA and IgG subclass usage in the salivary glands of pSS patients compared to non-pSS controls. In parotid glands from pSS patients, among IgA transcripts, the expression of IgA1 was significantly higher than IgA2 (figure 1), whereas among IgG transcripts, IgG1 was the dominant IgG subclass [Hamza et al., submitted]. In non-pSS controls on the other hand, the dominant IgA and IgG subclasses were IgA2 and IgG2, respectively. It is uncertain whether increased IgA1 expression could contribute to pSS disease pathology. However, the role of IgG1 could be significant since IgG1 is thought to be more effective at phagocytosis and complement-fxation than IgG2 [54]. Hence, the relative predominance of IgG1-expressing cells which possibly bind (auto)antigens within the diseased salivary glands of pSS patients, may attract a powerful complement-mediated detrimental immune response locally, leading to the pathology observed in the salivary glands of pSS patients [Hamza et al., submitted].

B-cell depletion therapy in primary Sjögren’s syndrome

B-cell depletion therapy using the anti-CD20 monoclonal antibody RTX resulted in clinical relief from disease symptoms in treated pSS patients and is characterized by a near complete depletion of B-cells from the blood [8,55]. Although a significant therapeutic effect was observed with respect to various disease parameters such as saliva production, visual analog scale (VAS) scores for dryness (particularly in patients with recent disease onset), fatigue and extraglandular manifestations [56–60], the clinical relief experienced by these patients was temporary and the recurrence of disease symptoms coincided with the return of B-cells within the peripheral circulation [8,55].

Following RTX treatment, repopulation of the peripheral compartments was characterized by the appearance of CD19+ B-cells at 24 weeks which were phenotypically akin to CD27– CD38 in transitional B-cells (figure 2) and whose numbers normalized partially or fully at 36–48 weeks after RTX [8,61]. This indicates the influx of newly-generated B-cells from the bone marrow into the peripheral circulation of treated pSS patients. Among the memory B-cell populations in the peripheral blood of pSS patients treated with RTX, approximately 70% of them belonged to an isotype-switched subset described by the markers CD19+ CD27+ IgM– IgD–. However, in our studies on concomitant parotid gland biopsies from the same pSS patients, we observed that the near complete depletion of B-cells from the peripheral circulation noted at 12–16 weeks after RTX, was not mirrored by the parotid salivary glands and B-cells were still present there [30,59] (figure 3). This is in contrast to previously reported observations where a complete absence of B-cells was noted in the labial salivary glands biopsies of pSS patients for up to one year after RTX [61]. The repopulation of B-cells within these labial glands was mostly represented by memory and transitional B-cells.

We have previously reported the persistence of certain clonal populations of immunoglobulin (Ig)-producing cells within the parotid glands of pSS patients even after B-cell depletion.
with RTX [30]. One obvious reason for the survival of these Ig-producing cells could be the lack of CD20 expression on plasma cells, as is widely believed. However, there are reports of CD20+ plasma cells being present in tonsils even after RTX [62]. We also showed that Ig-producing clonal populations persisting after RTX were more mutated in the variable region of the immunoglobulin heavy chain (IGHV) genes than their clonally-related counterparts present before RTX [30]. This is an

**Figure 2**

**B cell reconstitution after rituximab in primary Sjögren’s syndrome patients is dominated by transitional B cells**

Frequencies and absolute numbers of transitional (CD27–CD38high) B cells in healthy controls (HC), shown with open circles and pSS patients before and after rituximab treatment, shown with black circles. Placebo-treated patients are indicated by black squares. P-values were calculated using the nonparametric Mann-Whitney U test for comparison between groups and the Wilcoxon matched pairs test for intraindividual comparison of values at different time points.

Source: Reproduced with permission from reference [8].
indication that B-cells surviving after RTX may have undergone proliferation.

All of the above observations point to a model of disease relapse after RTX therapy that may be seeded by persisting Ig-producing cells. The surviving B-cells may be situated in restricted niches that enable them to evade depletion and proliferate with time. The existence of such niches with restrictive access to RTX was previously reported in murine systems, where B-cells in certain tissue sites such as the splenic marginal zone, germinal center and peritoneal cavities exhibit significant resistance to anti-CD20 depletion [63,64]. These RTX-resistant B-cell niches were also observed in the GCs of lymph nodes from non-human primates [65] and in tonsils [66] and other lymphoid organs in humans [67].

The transient clinical relief from SS symptoms after RTX is probably due to the depletion of large numbers of B-cells and some CD20+ Ig-producing cells [62], which may lead to a reduction in effector B-cell functions, such as antigen presentation and cytokine production. Although no significant decrease in serum Ig levels was observed after RTX [58], lower levels of certain (auto)antibodies may contribute to clinical relief. At the same time, the underlying autoimmune mechanisms are probably maintained by long-lived plasma cells as has been indicated in studies in SLE where patients who expressed autoantibodies secreted by long-lived plasma cells, had a higher chance of experiencing early flares or disease relapse after B-cell depletion therapy than patients who did not express these autoantibodies [68–71].

Serum BAFF levels have been measured in pSS patients before and after RTX therapy [72]. Following RTX therapy, serum BAFF levels increase significantly during periods of B-cell depletion and BAFF levels return to baseline when B-cell numbers return to normal values. The augmented BAFF levels following B-cell depletion may contribute to the return of self-reactive B-cells, as excessive BAFF has been shown to rescue self-reactive B-cells from apoptosis [73]. In our studies, we showed that although RTX treatment does result in the almost complete depletion of peripheral B-cell populations, its effect on the B-cell populations within diseased salivary glands is not so dramatic. Moreover, compared to baseline, we found no significant changes with respect to the relative usage of the immunoglobulin heavy chain gene repertoire or IgA and IgG isotype subclass usage in pSS patients after RTX treatment [Hamza et al.; submitted]. Hence, the B-cells that survive after RTX may ultimately contribute to the disease relapse observed in pSS patients who have undergone RTX therapy [30]. This is a sound rationale for the development of therapeutic strategies that combine RTX with an anti-BAFF agent to prolong the therapeutic efficacy of RTX [74]. Alternatively, designing therapies that target persisting Ig-producing cells (or plasma cells) could also synergistically increase the efficacy of B-cell depletion therapy [68].

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References

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