Association of endometriosis with Sjögren's syndrome: Genetic insights (Review)

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Abstract. Patients with a history of endometriosis have an increased risk of developing various autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis and celiac disease. There is a potential association between endometriosis and an increased susceptibility for Sjögren's syndrome (SS). SS is a common chronic, inflammatory, systemic, autoimmune, multifactorial disease of complex pathology, with genetic, epigenetic and environmental factors contributing to the development of this condition. It occurs in 0.5-1% of the population, is characterized by the presence of ocular dryness, lymphocytic infiltrations and contributes to neurological, gastrointestinal, vascular and dermatological manifestations. Endometriosis is an inflammatory, estrogen-dependent, multifactorial, heterogeneous gynecological disease, affecting ≤10% of reproductive-age women. It is characterized by the occurrence of endometrial tissue outside the uterine cavity, mainly in the pelvic cavity, and is associated with pelvic pain, dysmenorrhea, deep dyspareunia and either subfertility or infertility. It is still unclear whether SS appears as a secondary response to endometriosis, or it is developed due to any potential shared mechanisms of these conditions. The aim of the present review was to explore further the biological basis only of the co-occurrence of these disorders but not their association at clinical basis, focusing on the analysis of the partially shared genetic background between endometriosis and SS, and the clarification of the possible similarities in the underlying pathogenetic mechanisms and the relevant molecular pathways.

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Contents

1. Introduction

Sjögren's syndrome (SS) is a rare chronic and systemic autoimmune disorder, primarily characterized by lymphocytic infiltrations and autoimmune exocrinopathy and epithelitis as well as a female predominance (9:1 female-to-male predisposition ratio primarily in perimenopausal women) (1). The characteristic lymphocytic infiltration consists of activated T and B lymphocytes that affect exocrine glands and autoantibody production. SS occurs in 0.5-1% of the population, and the spectrum of the manifestations of the disorder may extend from organ-specific to systemic ones, including xerostomia, dry eyes, arthralgias/arthritis, rash, keratoconjunctivitis sicca, primary liver cirrhosis, lymphoma and lung involvement (2,3). The disorder is also characterized by hypergammaglobulinemia and autoantibody production, mainly against the ribonucleoproteins SS-A/Ro and SS-B/La characteristic of SS and identified in the serum of the patients (4). The increased levels

of various cytokines such as interferon (IFN)-γ, interleukin (IL)-6 and IL-10 found in patients with SS have suggested their notable role in the pathogenesis of the disease (5,6). SS has a complex pathogenesis, involving interacting genetic, epigenetic, hormonal and environmental factors. Furthermore, additional activators of the disease include specific viruses, such as Epstein-Barr virus, human T-lymphotropic virus, retroviruses and Coxsackie virus (7-9). No effective treatment for SS has been developed so far. Current medical treatments focus on the alleviation of the symptoms of the disease as well as the decrease of inflammatory events (10).

Endometriosis is an enigmatic, multifactorial disorder, representing one of the most common gynecological diseases affecting 3-10% of women in their reproductive years, and it can be a debilitating disease leading to poor quality of life (11). Despite the frequent occurrence, its etiology and pathogenesis are poorly understood and the exact cause is unknown (12-14). Multiple genetic and epigenetic factors, in combination with interacting environmental factors, including pollution agents and toxins, lead to the development of this condition (15). It is characterized by ectopic localization of endometrial cells and, therefore, the occurrence of endometrial tissue outside the uterine cavity on other organs (16,17). Endometriosis can appear as ovarian endometriotic cysts, peritoneal lesions, fibrosis and deeply infiltrative endometriosis (15). It is associated with chronic pelvic pain, dysmenorrhea, irregular menstrual bleeding, deep dyspareunia and urinary tract symptoms, while ~30% of patients with endometriosis also suffer from infertility (18-20). Considering that all endometriosis cases cannot be explained by a uniform theory, apart from the favorable and most accepted theory of Sampson (21) based on retrograde menstruation hypothesis, more pathways and cellular processes have been considered, including angiogenesis, chronic inflammation, increased oxidative stress and endothelial dysfunction (22,23). Clinical presentation varies widely, ranging from asymptomatic to severe, and no diagnostic biomarkers have been approved for routine clinical diagnosis of endometriosis (24). Notably, the type and severity of symptoms depend on the extent of the disease and the location of the involved organ(s).

Advances in the past years have shown that female patients with endometriosis are at higher risk of developing chronic diseases as systemic comorbidities, such as cancer (25), cardiovascular diseases (26,27), asthma (25), hypothyroidism (25) and psychiatric disorders (28). Most importantly, epidemiological studies demonstrated that patients with endometriosis were associated with an increased risk of developing a number of autoimmune diseases compared with unaffected controls due to notable changes in immune-related parameters. The autoimmune diseases included in this category include rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's disease, coeliac disease, ankylosing spondylitis and autoimmune thyroid disorder (29-33). However, it is unclear whether autoimmune diseases represent a risk factor of endometriosis, or these two types of diseases share similar pathogenetic mediators.

Previous and recent epidemiological studies have suggested that endometriosis can increase the susceptibility to SS in these females compared with unaffected controls (29,34-36). Although the pathogenesis of SS has not been elucidated, there has been strong evidence pointing out the important role of genetics in the development of this disease. Moreover, current research has demonstrated substantial deregulation of the immune system of female patients with endometriosis and epidemiological studies have presented evidence for a link between endometriosis and an increased risk of developing SS (29,34-36). The etiology of this co-occurrence remains poorly defined. It is possible that the immunological alterations and chronic inflammation characterizing endometriosis may lead to SS. These similarities between molecular and cellular pathways of endometriosis and SS may implicate a partially shared genetic background. Thus, in the current review, an overview of the shared genetic factors known thus far that are associated with an increased susceptibility for both disorders are presented, while the review did not focus on the plausible clinical basis and relevant aspects regarding the co-occurrence of both diseases.

2. Genetics of endometriosis and SS

Endometriosis is a highly complex disease with numerous genetic, epigenetic and environmental factors interacting with each other, thus contributing to its pathogenesis (15). The identification and functional analysis of the numerous genetic factors involved in the development of endometriosis have notably contributed to the better understanding of the biological processes and molecular mechanisms leading to the disease, as presented in detail in recent studies by our research group (27,30,32). In brief, the strong genetic predisposition of the disease was documented firstly in monozygotic twin-based and family studies (37,38), followed by linkage analysis, various candidate and gene association, genome wide association studies (GWAS), meta-analyses and next-generation sequencing studies (39-53). As a consequence, a number of disease-associated gene polymorphisms have been detected, which are involved in estrogen-induced cell growth (*WNT4* rs7521902), vascular function (*KDR* rs17773813), cell adhesion (*VEZT* rs10859871, *KAZN* rs10928050), growth and migration (*FN1* rs1250241), matrix remodeling and angiogenesis (*VEGF* rs699947, *LAMA5* rs2427284), cell cycle regulation (*FAS* rs1341643), transcription (*ID4* rs7739264, *MLLT10* rs1802669), differentiation (*GDAP1* rs554964149), proliferation (*MUC4* rs882605), oncogenesis (*TP53* rs1042522, *CHD5* rs9434741), inflammation (*COX-2* rs20417), sex steroid hormone activity and metabolism (*GREB1* rs13394619, *FSHB* rs74485684, *SYNE1* rs71575922, *CCDC170* rs1971256, *ESR1* rs2206949), immunity (*STAT4* rs7574865, *IL-1A* rs6542095, *IL-10* rs1800871, *IL-16* rs4072111) and oxidative stress (*HIF-1α* rs11549465) (41,42,46,47,52,53). Furthermore, accumulating evidence suggests that epigenetic aberrations seem to play an important role in the pathophysiology of endometriosis (54) and the development of some specific complications such as pain and infertility (11,55). The levels of DNA methylation, histone modifications and microRNA (miR/miRNA) expression reflect the main epigenetic information at the cellular level (56,57). These epigenetic changes may have potential applications in disease diagnosis, prognosis and therapeutic interventions (58). The importance of epigenetic modifications regarding numerous biological processes has been so

far demonstrated according to findings from aberrant methylation studies as well as epigenome-wide association studies (EWAS) (59,60).

SS is a complex autoimmune disease with a number of well-established susceptibility loci. Worldwide studies focused on the detection of SS-associated alleles of human leukocyte antigen (HLA) genes, which encode cell surface antigen presenting proteins. Before the era of GWAS, associations between HLA genes and SS were detected concerning *HLA-Dw3*, *HLA-B8*, *HLA-DRw3*, *HLA-DR3*, *DRw52* and *HLA-B8 20* (61), while more recent studies focused on *HLA* identified *DRw53* (62), *DR2* (63), *HLA-DRB1*01:01*, *HLA-B*35:01* (64), *HLA-DQA1*050* (65), *HLA-DRB1*0301* (66), *HLA-Cw7*, *HLA-DR3* and *HLA-DR11* (67). Other genetic studies of SS had been focused on familial aggregation (68). The first GWAS performed focusing on SS (69) detected six non-HLA loci, namely IFN regulatory factor 5 (*IRF5)-TNPO3*, *s*ignal transducer and activator of transcription-4 (*STAT4)*, *IL12A*, *FAM167A-BLK*, *CXCR5* and *TNIP1*, while previously reported HLA associations (61-67) were confirmed (69). Other GWAS established new associations with *GTF2IRD1-GTF2I* and tumour necrosis factor (*TNF)AIP3* (70) as well as *IRF5* (71). Other studies showed association of SS with *TNF-α* and *IL-10* (72), *OAS1* (73) and *IKZF1* (74). In the most recent GWAS conducted by Khatri *et al* (75) on patients of European ancestry, 10 novel genome-wide marked SS-associated loci were identified, including *CD247, NAB1, PTTG1-MIR146A, PRDM1-ATG5, TNFAIP3,* X Kell blood group complex subunit-related family member 6 *(XKR6), MAPT-CRHR1, RPTOR-CHMP6-BAIAP6,* tyrosine kinase 2 *(TYK2)* and *SYNGR1*, while a subsequent meta-analysis based on ImmunoChip-derived data revealed three additional SS-loci, *CD247*, *PRDM1-ATG5* and *TNFAIP3* (75). It is worth noting that the SS susceptibility loci identified by Khatri *et al* (75) are implicated in alterations in immune cell function, inflammatory signaling, and cell stress, survival and proliferation. Regarding the epigenetic studies in SS, it was reported that in type I IFN-regulated genes, which were upregulated in the blood and salivary glands (SGs) of patients with SS (76,77), DNA hypomethylation was observed (77). Previous studies assessed global DNA methylation levels and specific CpG sites in various candidate genes, such as *LTA* as well as type I IFN-induced genes, including *STAT1*, *IFI44L, MX1, IFI44L, PARP9* and *IFITM1* (68). Furthermore, numerous large-scale EWAS managed to identify genetic regions exhibiting a differential DNA methylation pattern between patients with SS and healthy controls, including *IRF5* promoter regions, *TNFSF7* promoter, *FOXP3*, *KRT19* and *DNMT1* genes as well as LINE-1 (68,69).

3. Influence of immune system and angiogenesis in endometriosis and SS

Immune dysregulation leading to chronic inflammatory response in the ectopic endometrium aggravates a number of abnormalities in the cell-mediated as well as the humoral immune systems of patients (30). Furthermore, other studies suggested the association of endometriosis with both antibody self-reactivity and chronic local inflammation (11,23,27,30), caused by a variety of inflammatory factors such as cytokines, macrophages and prostaglandins, thus characterizing this disorder as an autoimmune one (74). In this framework, extensive research has been conducted to understand the influence of autoimmunity in endometriosis, aiming to gain better insight of the pathogenetic mechanisms leading to this condition (30). The identification of antibodies against endometrial antigens and the subsequent detection of anti-nuclear and anti-phospholipid antibodies in the blood and the peritoneal fluid (PF) of patients in combination with elevated levels of inflammatory cytokines, such as IL-6, IL-8 and TNF-α, supported pre-existing data indicating a critical role of autoimmunity in endometriosis (78). This role was further strengthened by the loss of self-tolerance, leading to immune-mediated tissue destruction and multi-organ involvement, which represent immunological alterations also occurring in endometriosis (77). Furthermore, natural killer (NK) cells were found to be decreased in local NK-mediated cytotoxicity in the peripheral blood and PF of female patients with endometriosis (79), with this decrease being more pronounced in patients with endometriosis at stages II and IV as demonstrated by a notable reduction in NK activity (79). It has been suggested that inhibitory factors developing during the pathogenesis of endometriosis may suppress NK cell function (79). Abnormalities regarding the function and concentration of B- and T-lymphocytes as well as the total number of macrophages have also been observed in patients (77,80). Dysregulation of the immune system may prevent the ability to eliminate the endometrium of the pelvic cavity, while macrophages and NK cells (78) may be unable to destroy cells in ectopic sites (77). The hormonal alterations observed in endometriosis, such as higher levels of estradiol and progesterone (15,17), have been related to the inflammatory imbalance that is characteristic of this disorder, given that inflammation affects hormonal regulation (81). The strong association of endometriosis with inflammation has also been indicated by the elevated levels of the inflammatory cytokines IL-6, IL-10 and TNF-α (82) observed in the PF and peripheral blood of patients (83) (Fig 1).

As it was aforementioned, SS is a systemic, inflammatory, autoimmune disease characterized by exocrine dysfunction due to immunologically-mediated mechanisms (84). It follows the classical, multistep model of human autoimmune diseases. However, the immunological mechanisms that mediate the self-directed destruction of SG tissue are still not well understood. A periductal mononuclear cell infiltration has been found, leading to the collection of distinct cellular aggregates in SGs and lachrymal glands, and the subsequent chronic inflammation with signs in various organs including lungs, liver and kidneys (85). Moreover, it has been reported that the observed chronic inflammation is caused by an imbalance of cytokine production locally in the glands and systemically in the blood (86). The dysregulation of cytokines refers to alterations of both local and systemic expression of pro and anti-inflammatory cytokines released by infiltrating cells in inflamed tissues (87). A notable research finding refers to functional differences between the glandular and the peripheral blood lymphocytes, thus suggesting the existence of a distinct microenvironment in the gland compared with that in the peripheral blood, while the putative disruption of the T helper (Th) 1 and 2 cell balance cannot be underestimated (88). Notably, the aforementioned studies have also

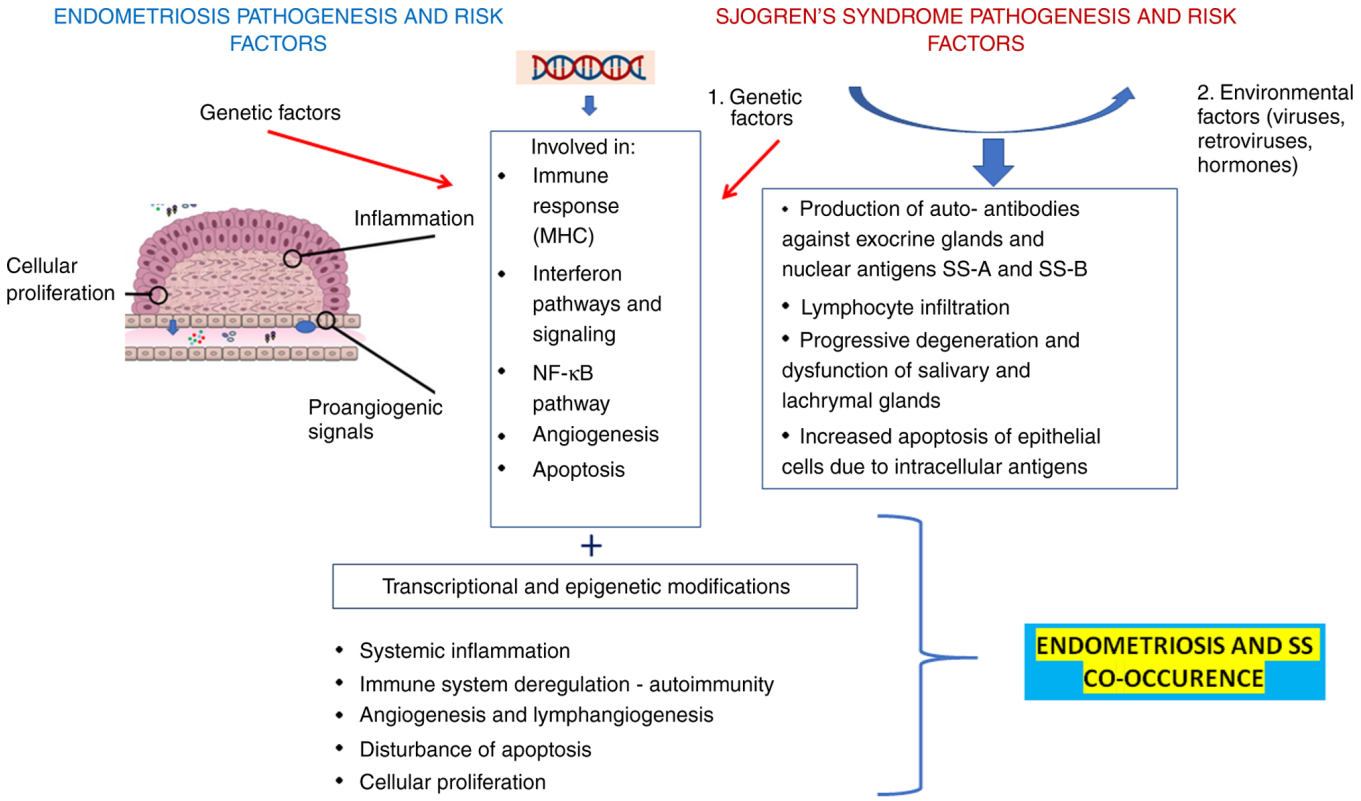

Figure 1. Proposed mechanisms for the interaction between endometriosis and SS. Major pathogenetic mechanisms include proinflammatory, proangiogenic, cell proliferation, aberrant apoptosis and immune functions. Genetic risk loci associated with both diseases are classified into major distinct mechanistic pathways. Shared genetic risk loci are associated with immune functions, interferon signaling, the NF-κB pathway, angiogenesis and apoptosis. All pathways, apart from the genetic factors, are influenced at a next step by transcriptional and epigenetic factors, thus formulating the cross-link between the shared genetic background, and endometriosis and SS. Figure partially adapted from Vazgiourakis *et al* (27). SS, Sjögren's syndrome.

suggested a differential role for the action of Th1 and Th2 cytokines in SS (85,86,88); The Th1 cytokines IL-10, IL-6 and TGF-β are critical for the induction of SS, but Th2 cytokines, such as IL-4 and IL-5, may be related to the disease progression (89). It is noteworthy that IL-6 functions as a key player regarding B-cell differentiation and the production of autoantibodies. IL-6 is found at higher levels in patients with SS compared with healthy controls, thus contributing to the characteristic inflammatory state of the disorder (90). Moreover, it was recently reported that the proinflammatory cytokine IL-17, produced mainly by Th17 cells, is upregulated in SS as shown in numerous studies, thus being involved in the development of SS and, in particular, associated with the degree of inflammation and clinical manifestations (91-93). TNF-α and TNF-α-receptors also appear to be dysregulated in peripheral blood and secreting cells from SGs from patients with SS (94,95). Mackay and Tangye (96) have emphasized the role of the B cell activating factor (BAFF), which is a protein member of the TNF family produced by monocytes, T and dendritic cells (DCs). This protein is upregulated in SS and is associated with autoantibody production and B-cell tolerance (97). Numerous pathways that are strongly associated with IFN signaling were found to be upregulated in patients with SS, especially in SGs and plasmacytoid DCs (98). TGF-β, a cytokine crucial in Th17 polarization (93), is linked to the growth of regulatory T cells which are upregulated in inflamed SGs of patients with SS (98). It is noteworthy that accumulating evidence document that a broad spectrum of impaired immune functions results in the pathogenesis of SS, including the cytotoxic cellular cytokines IL-1β, IL-12p40, IL-15 and TNF-α, the humoral cytokine IL-6, and the factors and death receptors TNF-RI and TNF-RII (99,100).

Although the etiology of endometriosis is highly complex and far from being fully elucidated, there is compelling evidence attributing a critical role in angiogenesis and lymphangiogenesis, which are involved in both the invasion to the extracellular matrix and ectopic implantation of endometrial tissue, and the development of endometriotic lesions (101). Angiogenesis confers to the maintenance of the endometriotic lesions by supplying them with functional blood vessels and, as a consequence, leading to the formation of a dense vascularization (102). The angiogenic properties of the endometrium and its strong potential to attract blood vessels from the surrounding tissue is well established (103). Moreover, various potent angiogenic factors such as TGF-α, TGF-β, basic fibroblast growth factor and angiopoietin (32) have been found to be altered in endometriosis, thus suggesting the involvement of angiogenesis in the ectopic implantation of the endometrial cells (104). A number of genetic polymorphisms of key components of the angiogenesis mechanism, including placental growth factor rs2268614, hypoxia inducible factor-1α (*HIF-1a*) rs11549465 and vascular endothelial growth factor (VEGF) receptor 1 (*VEGFR1*) rs9582036, were found to be associated with the development of endometriosis. Thus, it has been demonstrated that all these single nucleotide polymorphisms (SNPs) contribute to the variability in the plasma levels

Table I. An overview of the genetic polymorphisms associated with the development of both endometriosis and SS as confirmed by gene association studies and/or genome-wide association studies.

dbSNP ID	Endometriosis and SS-associated gene	Function	(Refs.)
rs7574865	*STAT4*	Intracellular signaling	(71,120)
rs7582694	*STAT4*	Intracellular signaling	(121,122)
rs10488631	*IRF5*	Transcription factor with diverse roles	(118,119)
rs2476601	*PTPN22*	T-cell activation	(123,151)
rs2304256	*TYK2*	Involved in interferon and cytokine signaling	(75,124)
N/A	*HLA-DQB1*0301*	Presents peptides derived from extracellular proteins	(129,130)
N/A	*HLA-DRB1*0101*	Presents peptides derived from extracellular proteins	(64,131)
rs1800629	*TNF-α*	Multifunctional pro-inflammatory cytokine	(125,126)
rs11549465	*HIF-1a*	Master transcriptional regulator of the adaptive response to hypoxia	(64,127)
rs11250098	*XKR6*	Involved in apoptotic process	(75,128)

SNP, single nucleotide polymorphism; SS, Sjögren's syndrome; STAT4, signal transducer and activator of transcription-4; IRF5, interferon regulatory factor 5; PTPN22, protein tyrosine phosphatase, non-receptor type 2; TYK2, tyrosine kinase 2; HLA, human leukocyte antigen; TNF-α, tumor necrosis factor-α; HIF-1α, hypoxia inducible factor-1α; XKR6, X Kell blood group complex subunit-related family member 6.

of the encoded proteins (105,106). In the same framework, data have shown that higher expression levels of VEGF and angiopoietin-1 led to dysregulated angiogenic activity of the utopic endometrium in patients with endometriosis (101,107). It is known that VEGF activates the migration of various inflammatory cells, including monocytes and lymphocytes, into the extracellular matrix (108). It is noteworthy that another study showed that predominantly in adolescent and young adult female patients with endometriosis, increased levels and marked activation of circulating proteins related to angiogenesis and cell migration were observed (109). The further identification of new factors associated with angiogenesis may be important for developing novel therapeutic approaches for endometriosis.

Marked discoveries regarding the molecular mechanisms leading to SS have highlighted the role of angiogenesis (110), a fundamental process in growth and development (111). Previous experiments have shown that the metalloproteinase TNF-α-converting enzyme, which participates in proangiogenic pathways leading to the formation of vessels (112,113), is involved in VEGF/VEGFR2-mediated angiogenesis in SS (114). Furthermore, it has been shown that infiltrating T-cells, in combination with human SG epithelial cells (SGECs), produce increased amounts of proangiogenic factors through the activation of the VEGF-A/VEGFR-2 system (115). Various findings have shown that a proangiogenic protein, the metalloproteinase TNF-α-converting enzyme (TACE) is overproduced in SS, thus emphasizing the role of the VEGF-A/TACE/VEGFR2/NF-κB axis dysfunction in the pathogenesis of SS (114). In the same framework, neuropilin, which represents a transmembrane co-receptor of the VEGF protein family members, was reported to promote angiogenesis in SS by activating NF-κB (116). Moreover, quantification and characterization of circulating angiogenic T (Tang) cells in minor SGs (MSGs) and in the peripheral blood of patients with SS showed that this type of cells may participate in endothelial dysfunction and glandular angiogenesis observed in SS (117). Importantly, Tang cells infiltrate MSGs and are directly associated with disease activity in patients with SS (117).

4. Shared susceptibility loci between endometriosis and SS and relative biological mechanisms

Shared genetic susceptibility loci. Previous findings have suggested an association between endometriosis and a higher risk of SS in various populations, including cases from the USA, Denmark and Taiwan (29,34-36), an observation that posed a reasonable question concerning the putative existence of shared genetic factors that are involved in the co-occurrence of these diseases. Notably, preexisting data that are presented in detail below, have demonstrated that various autoimmunity- and inflammation-associated genes play a crucial role in the development of both conditions and, therefore, it seems intriguing to further explore plausible shared mechanisms underlying endometriosis and SS. Endometriosis may be a risk factor for, or share a common cause with SS.

Thus, the results of the literature search carried out as part of the present review showed that the *IRF5* rs10488631 (118,119), *STAT4* rs7574865 (71,120-122), protein tyrosine phosphatase non-receptor type 2 (*PTPN22*) rs2476601 (30,123), *TYK2* rs2304256 (75,124), *TNF-α* rs1800629 (125,126), *HIF-1a* rs11549465 (64,127), *XKR6* rs11250098 SNPs (75,128) as well as the *HLA*-associated alleles *DQB1*0301* (65,129,130) and *DRB1*01:01* (64,131) are associated with both diseases (Table I).

Relative biological mechanisms

Polymorphisms in genes associated with IFN pathways and signaling. STAT4 is a key transcription factor expressed in activated peripheral blood monocytes, macrophages and DCs in humans (132), and it is involved in numerous processes, including transduction of IL-12, IL-23 and type 1 IFN-mediated signals into Th1 and Th17 differentiation, IFN-γ production and monocyte activation (133). STAT4 is encoded by the *STAT4*

gene, which is located at 2q32.2-q32.3, consists of 24 exons and spans a region of 120 kb (121). STAT4 is vital to signaling pathways in the immune response and autoimmune diseases; the requirement for a STAT4-dependent cytokine regulation has been well documented (134). The *STAT4* rs7574865 G/T SNP is a well-known SLE- and RA-associated polymorphism (134) that was found to be associated with an increased risk of SS (133) as well as endometriosis (120). A second *STAT4* SNP, rs7582694 (C/G), was reported to be associated with both SS and endometriosis (121,122). More specifically, the 'T' allele of the *STAT4* rs7574865 SNP was more common in patients with SS (133). This SNP has been demonstrated to be weakly associated with the mRNA levels of several IFN-induced genes when peripheral blood mononuclear cells (PBMCs) from patients with SS were analyzed (122). The SNP rs7574865 was shown to be associated with increased sensitivity to IFN-α signaling in patients with SLE (135). Although the functional role of rs7574865 SNP in SS is still unclear, it has been assumed that the rate of transcription is altered due to the resulting nucleotide change, leading an alteration of the binding of histones in this genomic area (133). Notably, a previous bioinformatics analysis showed that this SNP did not disrupt any activator or transcription factor binding site (136). Moreover, experiments performed by the same research group showed a distinct impairment in STAT4 production as well as in STAT4 phosphorylation in the presence of the 'T' allele (136). Regarding endometriosis, the frequency of the TT genotype of the rs7574865 SNP was increased in female patients with minimal or mild endometriosis compared with that in controls (120). Furthermore, it has been suggested that the rs7574865 SNP may affect either gene expression or mRNA splicing, thus playing an important role in the regulation of Th17 pathways, due to its involvement in the induction of Th1 and Th17 cytokine responses and IFN signaling (120). A relationship between Th1 response pattern and deep infiltrating endometriosis has also been suggested (137).

The *STAT4* rs7582694 C allele was associated with SS (122), but the levels of STAT4a (the full-length mRNA) and STAT4b (the truncated form) mRNAs in PBMCs did not appear to have any notable association with the rs7582694 genotypes. Of note, a strong association between the mRNA levels of *STAT4a* and type-1 IFN-induced genes was observed, suggesting that STAT4 may play a crucial role in both the production of type 1 and 2 IFN-mediated effects (122). Similarly to SS, a notable association between the 'C' allele and endometriosis was detected and the GC genotype was markedly overrepresented in patients with endometriosis compared with controls (121).

The *IRF5* gene, located on chromosome 7q32, encodes a transcription factor, of a range of 60-63 kDa (138), expressed in B-cells, macrophages as well as epithelial cells and DCs. It is involved in the regulation of the host defense and the transcriptional activation of various proinflammatory cytokines and type 1 IFN responsive genes (139). The IRF5 protein mediates toll-like receptor (TLR) signal transduction (140), while it has been suggested that it also acts as a molecular switch that controls macrophage cell-mediated inflammatory mechanisms (141). It has been shown that a polymorphism in the *IRF5* gene (downstream of *IRF5*), rs10488631 (T/C) SNP, is associated with an increased risk of developing both SS and endometriosis (40,119,142). Thus, it was found that the minor allele 'C' of rs10488631 is strongly associated with SS but further analysis based on bioinformatics did not manage to predict any clear functional role for this SNP (119). However, the genetic effect of *IRF5* is strong enough for SLE, followed by SS and RA, thus emphasizing the importance of the type I IFN system in the etiopathogenesis of SS, while the risk allele of *IRF5* SNP was reported to be independent of the autoantibody status of patients with SS (119,143,144). To date, the pathway with *IRF5* as well as the *STAT4* and *IL12A* genes involves increased IFN signaling and cytokine production, a finding that is consistent with the IFN gene signature observed in patients with SS (145,146). Of note, when our research group previously examined the levels of serum IFN-α in patients with SLE that had been stratified by the risk allele 'C' of rs10488631, an association of this allele with higher circulating type I IFN levels in these patients was observed (147). The Neanderthal-derived TACA haplotype, as determined by the rs2004640, rs3807306, rs10488631 and rs2280714 *IRF5* SNPs (148), which carries the rs10488631 allele 'C', was also associated with SLE susceptibility, further supporting a functional consequence of this polymorphism in disease development (147). Furthermore, Bianco *et al* (142) reported that the rs10488631 SNP is involved in the risk for the development of moderate/severe endometriosis.

The *PTPN22* gene maps to 1p13.3-13.1 and codes for lymphoid-specific phosphatase, which is also known as Lyp and represents an important downregulator of T-cell activation (149). Lyp protein is physically bound to the SH3 domain of the Csk protein, a kinase that is an important suppressor of kinases mediating T-cell activation (150). The missense, functional rs2476601 (C1858T) SNP has been associated with an increased risk for both endometriosis and SS (123,151). This polymorphism leads to the change of the amino acid at position 620 from arginine to tryptophan thus disrupting the physical interaction between Lyp and Csk proteins, given that it encodes a gain-of-function Lyp enzyme. As a consequence, the protein complex cannot be formed, and the suppression of T-cell activation is avoided (152). This SNP represents one of the best examples of a non-HLA common polymorphism that is involved in the development of various autoimmune diseases (153). Based on *in vitro* experiments, it has been shown that the 'T' allele of rs2476601 has a decreased binding efficiency to Csk compared with that of the major allele 'C', thus suggesting that T cells of subjects expressing the 'T' allele may have an overall increased reactivity of the immune system and are susceptible to autoimmune diseases (154). Of interest, it has been demonstrated that allele 'T' was more frequent in female patients with moderate/severe endometriosis than in patients with minimal/mild endometriosis (123). Consistently, the development and progression of this disease has been considered to be a result of genetic alterations and immune system deregulation (77). Moreover, the crucial role of the immune system in the onset and development of endometriosis has been pointed out given that in female patients with endometriosis, implantation of endometrial fragments in ectopic regions may be facilitated by alterations in T cell-mediated immunity (155).

TYK2, a locus that has been confirmed to be associated with various autoimmune diseases thus far (156,157), encodes a member of the Janus kinase (JAK) protein families (158),

involved in the STAT signaling pathway by mediating the signaling of both type I and type III IFN signaling pathways (159). The *TYK2* gene is located at 19p13.2 and the non-synonymous SNP rs2304256 (C/A) leads to a change of valine to phenylalanine at amino acid position 362 in exon 8, which was to be associated with endometriosis and SS (75,124). Thus, the frequencies of both allele 'A' and genotype AA were notably increased in female patients with endometriosis compared with controls (124). Importantly, it has been shown that the risk allele 'A' disrupts a putative exonic splicing enhancer binding motif that affects the pre-mRNA processing of TYK2. This pre-mRNA processing is crucial for the incorporation of exon 8 in the mRNA, considering the pivotal role of this exon in the binding of TYK2 to the cytokine receptor (160). In an attempt to elucidate further the functional significance of TYK2 in the development of endometriosis, an association between IL-13, which is a Th2 cytokine playing a central role to endometriosis (161), and TYK2 has been suggested (161). Thus, elevated mRNA and protein levels of IL-13 were detected in the PF of female patients with endometriosis (162) as well as in their ectopic endometrium (161). Moreover, TYK2 mediates the function of IL-13 in pathways that are associated with Th2 immune responses (163), while IL-13/TYK2 signaling in B cell proliferation and other biological processes have been shown in endometriosis (164). Therefore, any aberration in *TYK2* expression may result in escaping from the immune surveillance (165), thus pointing out its importance in the inflammatory responses characterizing endometriosis. Of note, a bioinformatics analysis suggested that the missense variant rs2304256 in *TYK2* is likely to be functional in SS pathogenesis (75).

Polymorphisms in genes involved in immune responses (MHC). *HLA* genes encode HLA proteins, which bind antigen peptides and then, present them to T cells. At a next step, the differentiation of T cells into cytotoxic or helper T cells takes place as a subsequent stage following specific recognition of the antigen-HLA molecules complexes (131). HLA proteins play a crucial role in order to restrict the recognition of antigenic peptides by T cells (166). *HLA* genes play key roles in the immune response and exhibit the highest degree of polymorphism, with most of them being involved in mechanisms that shape the T cell repertoire (166).

The *HLA-DQB1*0301* allele of the HLA class II gene *DQB1* has been associated with increased susceptibility for both endometriosis (129) and SS (65,130,167). In a sequencing analysis of *DQBI*0301* conducted in some patients with SS, data showed that the N-terminal domain was identical to the one found in a healthy population (168). This identity observed at the level of nucleotide sequences was also reported in the case of MS, another autoimmune disease (169). Thus, it is likely that susceptibility to SS cannot be attributed to the *DQBI*0301* HLA allele found in patients. Apart from data showing that leucine at the amino acid position 26 of the outermost domain of DQB1 chain plays a 'gene dosage' role of anti-Ro/La autoantibody response, no leucine was found at this position of the *DQBI*0301* allele in patients with SS (168). The association between endometriosis and the genes encoding the protein components of the HLA system has not yet been fully elucidated (129). However, a notably higher frequency of the *HLA-DQB1*0301* allele has been observed in patients with endometriosis, although the underlying mechanism of association has not been fully clarified thus far. This allele has also been associated with systemic sclerosis (170) and mycosis fungoides (171).

The *HLA-DRB1*0101* allele has been associated with an increased risk of endometriosis (131) and SS (64). In patients with SS, *HLA-DRB1*0101* was revealed as a risk factor for the development of this condition, while an association with an increased production of anti-Ro/SSA was also found (64). Moreover, an increased frequency of *HLA-DRB1*0101*, was observed in patients with endometriosis compared with controls (131). It has been suggested that defects in the activity of NK cells in the recognition and lysis of endometrial cells may be a crucial factor in the mechanism of endometriosis pathogenesis. Semino *et al* (172) revealed that the increased risk for lysis of endometrial cells by NK-like T cells has been associated with the expression of HLA class I molecules, including HLA-DRB1, on endometrial cells.

Polymorphisms in genes involved in the NF-κB pathway, angiogenesis and apoptosis. The *TNF-α* gene encodes the proinflammatory cytokine TNF-α, which plays an important role in the pathogenesis of a number of inflammatory and infectious diseases (173,174). This protein is produced mainly by monocytes, macrophages and activated leukocytes (175). The *TNF-α* gene has four exons, is mapped to 6p21 within the MHC between the *HLA-B* and *HLA-DR* loci (79). It has been found that, in patients with SS, TNF-α promotes the influx of mononuclear cells into SGs (176). The *TNF-α*-308 G/A rs1800629 SNP, located in the promoter region of *TNF-α*, has been associated with an increased susceptibility for endometriosis (125) and SS (126). Previous studies have suggested that the presence of the minor allele 'A' of rs1800629 in the promoter region results in an increase of the transcription levels of *TNF-α* compared with the major allele 'G', which subsequently increases the serum levels of the TNF-α protein (176,177). In endometriosis, inflammation is involved in the initiation as well as the development of ectopic endometrial tissue in the peritoneal cavity (178), and this process is mediated by various proinflammatory cytokines, including TNF-α (125). In this framework, TNF-α has been detected in the PF of patients with endometriosis (179), while elevated levels of TNF-α are associated with the implantation of ectopic endometrial tissue (180), establishing it as an important factor in the development of endometriosis. Altogether, the increased TNF-α levels observed in patients carrying the 'A' allele of rs1800629 may explain the role of this allele in endometriosis (125). Furthermore, a study focusing on patients with SS revealed an association between allele 'A' and elevated levels of TNF-α in the peripheral blood or tissue of patients (126,181).

The *HIF-1a* gene encodes the 'α' subunit of the transcription factor *HIF-1*, a heterodimer composed of an α and a β subunit. This protein functions as a master transcriptional regulator of the adaptive response to hypoxia (182), whereas additional data have suggested its involvement in innate immunity (183) and various cellular functions including cell proliferation, apoptosis, embryonic vascularization and angiogenesis (64,184).

Some genetic variants of the *HIF-1a* gene have been associated with development of various inflammatory and autoimmune diseases, including RA and SLE (185,186). It has been reported that the missense rs11549465 (C/T, Pro582Ser) SNP of the *HIF-1a* gene is associated with both endometriosis (127) and SS (64). This polymorphism, located in exon 12, leads to a substitution of proline with serine in the amino acid position 582 of the HIF-1α protein (64). The aforementioned amino acid position has been suggested to be important for the functionality of the protein, considering that the polymorphism is in the oxygen-dependent degradation/pVHL binding domain of HIF-1α (187). The 'T' allele of rs11549465 has been associated with increased susceptibility to minimal-mild endometriosis (127). Female patients with endometriosis who have the CT genotype of rs11549465 exhibited notably higher plasma levels of the HIF-1α in compared with patients with CC genotype (127). Regarding SS, it has been shown that HIF-1α enhances the development of Th17 cells by activating the transcription of RAR-related orphan receptor γ t (188), and this Th17 subpopulation was found to be increased in the SG tissue of patients with SS (91). Data have shown that HIF-1α upregulates the expression of *IFN-γ* in the synovial fibroblast of patients with RA (189) and, similarly, IFN-γ has been associated with severe types of SS that are characterized by high grade infiltration of macrophages, lymphocytes and DCs (190). Moreover, an additional *in vitro* study (191) emphasized the relevance of the rs11549465 variant in the transcription of several *HIF-1α* target genes involved in primary SS (pSS) pathology.

The *XKR6* gene is located on chromosome 8p23.1 (192), between the *FAM167A* and *BLK* genes (193). It encodes the XKR6 protein, which has been predicted to be an integral component of membranes, involved in the apoptotic process related to development and is expressed in red blood cells, colon, esophagus, small intestine, stomach and thyroid (194). The *XKR6* rs11250098 (A/G) SNP has been associated with both endometriosis and SS (75,128); for endometriosis, this SNP appears a GWA significance rate (128). The association of rs11250098 with increased SS susceptibility is unclear considering that there is not an obvious link to pathways implicated in the disease, probably because little is known about gene function (75). However, it has been suggested that rs11250098 is likely to impact enhancer activity that probably targets XKR6 and myotubularin-related protein 9 (75). Furthermore, another SNP in *XKR6* locus has been detected, considered to be a childhood-onset SLE-associated polymorphism, but no functional effects have been reported so far (193). The *XKR6* locus has been associated with inflammatory bowel disease as well (194), and based on its expression, it was suggested that it may be an immune-related protein (195). Since little is known about the function of XKR6, its actual role in endometriosis and SS pathogenesis remains uncertain, and additional studies are required to understand in depth its biological importance.

5. Role of miRNAs in the co-occurrence and pathophysiology of endometriosis and SS

miRNAs are naturally-occurring, small (~22 nucleotides in length), non-coding, post-transcriptional regulatory molecules, expressed in a tissue-specific and cell-type-specific manner, targeting numerous mRNAs (196,197). miRNAs represent an evolutionary system that regulates numerous biological processes such as embryonic development, cell cycle, migration and proliferation, differentiation, immune responses as well as apoptosis (198,199), while also being implicated in the development of various autoimmune diseases including SLE, RA, MS, AS, SS, experimental autoimmune encephalomyelitis, type 1 diabetes mellitus, inflammatory bowel disease, psoriasis, primary biliary cirrhosis and idiopathic thrombocytopenic purpura (199-201). To date, various studies have demonstrated an aberrant expression of miRNAs in affected tissues or blood serum samples of patients with endometriosis (56,57,202). Moreover, the critical role of miRNAs has been documented in SS with regards to the post-transcriptional mRNA expression on PBMCs and SGs (203). Thus, several studies have investigated the participation and contribution of miRNAs in endometriosis as well as SS etiopathogenesis (204,205). Notably, various miRNAs have been reported to have a similar expression profile in both diseases, including *miR16* (203,206-210), *miR18a-5p* (203,211,212), *miR19b-3p* (208,213-215), *miR26a-5p* (208,209,213), *miR30c-5p* (59,208,209), *miR122-3p* (214,216), *miR142* (217,218), *miR146a-5p* (217,219,220), *miR155-5p* (218,221), *miR181a* (222-225), *miR200b* (220,226), *miR223-3p* (203,213) and *miR378a-3p* (213,227) (Table II).

miR16 was found to be upregulated in the plasma of patients with endometriosis compared with controls (206) as well in the saliva of patients with SS (207). This miRNA is considered a potential diagnostic biomarker for endometriosis (228). Furthermore, it was shown that there is an association between *miR16* and autoantibodies against both Ro/SSA (SSA) and La/SSB (SSB) in labial SG tissues of patients with SS (205).

miR17-5p was reported to be downregulated in the serum and blood of female patients with endometriosis (162,208) as well as in the saliva of patients with SS (203,210). Investigation of the expression of this miRNA led to its use as a non-invasive diagnostic marker of endometriosis (162). The observed downregulation of *miR17-5p* results in the upregulation of the targets BCL2 and cell cycle repressor cyclin-dependent kinase inhibitor 1A repressing cell proliferation (229). Furthermore, the downregulation of *miR17-5p* is involved in neo-angiogenesis, through its association with HIF-1α (230) as well as VEGF-A (231). Notably, the miRNA under discussion exhibits a notable inverse association with thrombospondin 1 levels, a protein that modulates cell migration and adhesion (232).

miR18a-5p has been found to be upregulated in the serum of patients with stage III and IV endometriosis compared with control subjects (211), and in the SGs of patients with SS (203,212). It has been previously reported that this serum miRNA is considered a diagnostic marker of endometriosis (211).

miR19b-3p is downregulated in the blood of patients with endometriosis compared with controls (208) and in B-lymphocytes of patients with SS (213). This miRNA is a member of a miRNA cluster that plays a pivotal role in cell proliferation and apoptosis but is often deregulated in immune-associated diseases (233). Moreover, decrease in *miR19b-3p* levels was associated with accumulation of mature B cells that have been linked to autoimmune diseases including SS (210,234).

Table II. miRNA expression profiling in endometriosis and patients with SS.

miRNA	Source of miRNA	Expression	(Refs.)
miR16	Plasma, saliva	Upregulated	(206,207)
miR17-5p	Serum, blood, saliva	Downregulated	(208,210)
miR18a-5p	Serum, SGs	Upregulated	(211,212)
miR19b-3p	Blood, B-lymphocytes	Downregulated	(208,213)
miR21-3p	Endometrium, PBMCs	Upregulated	(214,215)
miR26a-5p	Blood, B-lymphocytes	Downregulated	(208,213)
miR30c-5p	Serum, saliva	Downregulated	(59,208)
miR122-3p	Serum, PF, PBMCs	Upregulated	(214,216)
miR142	Endometrium, saliva, SGs	Upregulated	(217,218)
miR146a-5p	Endometrium, PBMCs	Upregulated	(217,220)
miR155-5p	Plasma, PBMCs	Downregulated	(218,221)
miR181a	Blood, SGs, SGECs, PBMCs	Upregulated	(222,223)
miR200b	Endometrium, PBMCs	Upregulated	(220,226)
miR223-3p	Endometrium, PBMCs, saliva	Upregulated	(203,214)
miR378a-3p	Plasma, B-lymphocytes	Downregulated	(213,227)

In the 'source of miRNA' column, the upper line refers to endometriosis and the lower one to patients with SS. PF, peritoneal fluid; PBMCs, peripheral blood mononuclear cells; SGs, salivary glands; SGECs, cultured salivary glands epithelial cells; miR/miRNA, microRNA.

miR21-3p was found to be upregulated in ectopic endometrium of female patients with severe endometriosis compared with control subjects (214) as well as in patients with SS (215). This miRNA was previously shown to be associated with endometrial receptivity as well (235), while it has been reported to be regulated by oxidative stress (236). Thus, this miRNA participates in the oxidative stress- and immune-related AKT pathway, by targeting the inhibitory molecule PTEN (237), while it also targets PDCD4, E2F1 and TGFBRII (238).

miR26a-5p was found to be downregulated in the blood of patients with endometriosis compare with controls (208), and in B-lymphocytes of patients with SS (213).

miR30c-5p was shown to be downregulated in the serum of patients with endometriosis compared with controls (208,209), and in the saliva of patients with SS (59,203). Furthermore, downregulation of this miRNA by targeting PAI-1 was shown to increase the invasion, migration and proliferation of human embryonic stem cells, thus pointing out the role of *miR30c-5p* in endometriosis (215). Functional experiments showed that the expression of *miR30b-5p* in B cells from patients with SS was inversely associated with the expression of the *BAFF* gene (209). Furthermore, this miRNA was found to play a role as a negative regulator of *BAFF* in both systemic sclerosis and RA fibroblasts (239). *miR30b-5p* was also found to be notably deregulated in the B cells of patients with SS (209). Thus, *miR30b-5p* was found to be 3.5 times more downregulated in B cells of seropositive (anti-SSA$^+$) patients with pSS compared with control subjects, than B cells from seronegative (anti-SSA) patients with SS (209).

miR122-3p is upregulated in the serum and PF of patients with endometriosis compared with controls (213,240); similarly, the same miRNA was found to be upregulated in PBMCs from patients with SS (215). The diagnostic power of this miRNA has been assessed in endometriosis, and it was shown that serum *miR122-3p* had a sensitivity of 95.6 and a specificity of 91.4 for the diagnosis of the status of the disease (216). Thus, this miRNA can be considered as a putative serum biomarker for endometriosis (216).

miR142 was found to be upregulated in the utopic endometrium of patients with endometriosis compared with controls (228), while it was also found to be upregulated in the saliva and SGs of patients with SS (218). This miRNA regulates autophagy mediated by KLF9 and, therefore, may suppress endometriosis (35).

miR146a is upregulated in the utopic endometrium of patients with endometriosis compared with controls (217), and is also upregulated in the PBMCs of patients with SS (218,220). It represents an excellent example of a master regulator as it contributes to numerous aspects of immunity, including the control of cytokine overproduction, the suppression of regulatory T (Treg) cells and the control of TLR signaling in recurrent bacterial infection (241-243). This miRNA can also modulate cell death processes and, therefore, it can act as an antiapoptotic factor in T cells (244). Moreover, *miR146a* is activated by NF-kB that plays a crucial role in controlling the TLR/IFN pathway (245). In this framework, the elevated expression of *miR146a* found in PBMCs from patients with SS (220) is of high importance given that it regulates the inflammatory response (negative regulator) by controlling properly the expression of *IRAK1* and *TRAF6* genes (246). Furthermore, elevated miR146a levels have been associated with an increased percentage of Th17 cells in patients with SS compared with healthy subjects (247). All aforementioned data suggest that abnormal regulation of *miR146a* is involved in early disease pathogenesis and progression.

miR155-5p was found to be downregulated in the plasma of patients with endometriosis compared with control

subjects (221) and in PBMCs of patients with SS compared with controls (219). This miRNA is considered a key modulator regarding both the innate and adaptive immune response, activated by NF-kB, which is known to control the TLR/IFN pathway (245), while it further regulates the proliferation and function of B and T cells (248). *miR155-5p* is also involved in the regulation of immune cells, particularly in SS (220).

miR181a is upregulated in the blood of patients with endometriosis compared with controls (222) as well as in the SGECs and PBMCs of patients with SS (223-225). The levels of *miR181a* in PBMCs of patients with SS have been associated with exocrine gland dysfunction and antigen sensitivity (225), while additional data have shown that *miR181a* targets the muscarinic receptor 3 gene, which harbors genetic variants that are markedly associated with SS (249,250). The increased levels of *miR181a* have been associated with the degree of inflammation observed the patients with SS (209).

miR200b is upregulated in the ectopic endometrium of patients with endometriosis compared with the utopic endometrium of controls (226). This miRNA is also upregulated in SS (220). Regarding endometriosis, it has been suggested that the regulation of *miR200b* may modulate the proliferation and differentiation of stem cells (251). *miR-200b* targets the *ZEB1*, *ZEB2* and *KLF4* genes, thus affecting the proliferation and invasiveness of endometriotic cells (251). Furthermore, it participates in the regulation of various target genes involved in epithelial-mesenchymal transition and angiogenesis (252), thus contributing to the pathogenesis of endometriosis (253).

miR223-3p is upregulated in the ectopic endometrium of patients with endometriosis compared with the utopic endometrium of control subjects (214). Similarly, it is upregulated in PBMCs and saliva of patients with SS (203,254). The *miR223* gene is located within the q12 locus of the X chromosome and its product was also found at high levels in vascular smooth muscle cells (255). It has been assumed to play a role in endometriosis considering its well documented involvement in cell proliferation, migration as well as in vascular remodeling and apoptosis (256). The role of *miR223-3p* in SS is still unclear. However, it was also found to be upregulated in $CD4^+$ naïve T lymphocytes from patients with RA patients, suggesting a possible role of this miRNA in disease pathogenesis (257). This miRNA has been characterized as an inflammation-related one but it has also been linked to oxidative stress regulation (258). A study focused on a neuronal model treated with H_2O_2, overexpression of *miR223* reduced malondialdehyde and reactive oxygen species levels, a finding that could be explained by the effect of this miRNA that targets *FOXO3a* and leads to the inhibition of thioredoxin interacting protein (258).

miR378a-3p is downregulated in the plasma of patients with endometriosis compared with controls (227), and in B-lymphocytes of patients with SS (213).

6. Conclusions and future perspectives

The present review is a first attempt at searching the literature and analyzing the genetic and epigenetic factors that are involved in the co-occurrence of endometriosis and SS, aiming to shed a light in some shared mechanisms involved in both conditions while also pointing to the delineation of the relevant biochemical and molecular pathways. In the present review, the clinical basis underlying the co-occurrence of both diseases was not investigated. As presented already in the current review, the influence of autoimmunity, inflammation, tissue remodeling and angiogenesis in the underlying biochemical, cellular and pathophysiological mechanisms leading to the reported association between endometriosis and SS has been documented. Although it was beyond the scope of the present review to discuss all these processes in detail, some aspects regarding their role in the development of SS and endometriosis were clearly shown in previous sections. The role of autoimmunity in endometriosis has been hypothesized and/or established considering that a series of anti-nuclear, anti-phospholipid and anti-endometrial antibodies are present in this condition, in combination with elevated levels of inflammatory cytokines and various immune cell-mediated abnormalities (74,78). Aiming to unravel the aforementioned mechanisms, different explanations can be given, including the putative role of chronic inflammation and immune dysregulation appearing in endometriosis when it co-occurs with SS. The development of ectopic endometrial cells and lesions may provoke an increased immune response, which may be combined with pathological causes leading to SS. Furthermore, the hypothesis that endometriosis should be considered an autoimmune disease has been strengthened by the beneficial effects of danazol and GnRH agonists as part of endometriosis treatment, likely due to their immunomodulatory action (259) as well as the increased number of peritoneal macrophages, high T and B lymphocyte counts (260) and the increased levels of circulating anti-endometrial antibodies (261). However, the putative mechanisms leading to endometriosis in female patients with SS remain largely uncertain, given that studies from different countries examining this relationship have not yet reached a consensus. Together, the possible role of SS in the etiology of endometriosis or the occurrence of SS as a secondary response to endometriosis needs further exploration from a genetic and biological aspect (36).

It is known that understanding the genetic basis of complex diseases may provide a unique window into human disease pathogenesis, which will facilitate the development of improved diagnostic and therapeutic strategies and enable personalized medicine. However, apart from the substantial contribution of various GWAS to the identification of a number of SNPs associated with an increased risk of endometriosis or SS development, only a small number of these associations have been analyzed in depth from a functional aspect, thus minimizing the potential of these SNPs to be considered as putative therapeutic targets. Therefore, despite the efforts to analyze the biochemical pathways leading to endometriosis, it remains an emerging public health problem of reproductive-age women and the pathogenesis remains elusive. It has been reported that the prevalence rate of endometriosis in women with chronic pelvic pain is >33%, and in patients with SS the prevalence rate is 6.3% (262). In the same study (262), it was reported that patients with endometriosis were more likely to also have SS compared with controls (262). The risk of endometriosis has been strongly linked to ethnicity but the main differences between population groups have not been well defined (263). A nine-fold increase in the risk of developing endometriosis among females from the East Asian

population was found compared with European or American female populations (263). It is noteworthy that various studies are currently trying to delineate how disease risk variation is linked to ethnicity, and to identify minor differences in SNP variation and differences in autoimmune disease risk variants reported across different continental populations (263). The worldwide range of prevalence of SS is 0.05-4.8% with an overall 9:1 female-to-male ratio, which appears highest in Asian females (36). However, a limitation of this type of studies is the lack of information on the patient's socioeconomic status, personal health behaviors or toxic habits, with all of them representing confounding factors of the association between endometriosis and SS (36).

Taking into account that endometriosis has been associated with various autoimmune diseases, this condition may be considered a risk factor for SS, which requires specific counseling and medical management. Immune and inflammatory dysfunctions are considered challenging therapeutic targets for endometriosis and SS. The ultimate task of this type of study is the development of either novel therapeutic alternative by using the in depth understanding of the role of the associated shared genetic factors or the use of some miRNAs, a class of agents considered possible immunomodulators, considering that miRNAs exhibiting a deregulation in both endometriosis and SS have been identified. Thus, translation of recent discoveries based on miRNAs may allow the development of novel therapeutics for endometriosis and SS in the near future, considering that it has been shown that this type of drugs provide specificity and reduced toxicity compared with other therapeutic agents (264,265). The human miRNAome has been recently analyzed to define a saliva-based diagnostic miRNA signature for patients with endometriosis, based on their expression profile, and the results of this study may contribute to the early diagnosis of this condition (266).

The treatment of complex diseases has undergone substantial change over the last few years and novel, promising therapies have been developed. As presented in the current review, two SNPs of the *STAT4* gene, a member of the JAK/STAT pathway playing a pivotal role in IFN signaling related to immunological processes promoting chronic inflammation, are associated with both endometriosis and SS. As a consequence, a promising therapeutic option may be JAK inhibitors that interrupt the transduction of the aforementioned JAK/STAT pathway (267,268). Accumulated results suggest that the JAK inhibitor tofacitinib, a signal transducer associated with inflammation, can be used as an anti-inflammatory agent in patients with SS (269). The JAK/STAT pathway, especially STAT3 phosphorylation, is upregulated in the utopic endometrium of female patients with endometriosis (270), and it has been reported that inhibition of JAK/STAT signaling using tofacitinib may be a viable method for the treatment of endometriosis as well (271). One of the genes that are activated by STAT3 is *HIF1α*, which is associated with both diseases (64,127).

The SNP rs1800629 of the *TNF-α* gene is associated with both endometriosis and SS (Table I). The targeting of the inflammatory cytokine TNF-α expressed at high levels in the peripheral blood or tissue of patients with SS (126,181) may represent another beneficial therapeutic option for a large percentage of affected patients. In this context, it has already been shown that TNF-α also stimulates proliferation of endometriotic stromal cells, thus playing the role of an essential factor for the pathogenesis of endometriosis (272). This cytokine was found at high levels in female patients with endometriosis (273). Etanercept, a TNF-α blocker that can neutralize the activity of TNF and is currently used to alleviate the symptoms of autoimmune diseases clinically (274), has been shown to block the ability of the PF in endometriosis to enhance the proliferation of utopic or ectopic endometrial cells (275). However, the efficacy of etanercept in the treatment of SS has not been addressed. When it was used for a prolonged treatment of patients with SS, it did not appear to reduce the main symptoms of the patients, being beneficial in a small subgroup of patients with severe fatigue only (276), while Sankar *et al* (277) did not find any evidence suggesting that treatment with etanercept is clinically efficient in patients with SS (277). Consistently, Moutsopoulos *et al* (278) also presented data indicating that etanercept is an ineffective therapeutic agent in SS, thus suggesting that TNF-α may not be a pivotal cytokine in the pathogenesis of SS (278). In addition, infliximab, another anti-TNF-α agent, failed to demonstrate any beneficial effect in SS (279) and endometriosis (280).

Clinicians should always keep in mind that patients with endometriosis may also have additional autoimmune diseases, including SS, while the possible co-occurrence of endometriosis in patients with SS should not be underestimated. Thus, female patients with endometriosis, apart from their reference for follow-up with the gynecologist have to be alerted if they have any symptoms characterizing SS, such as xerophthalmia, xerostomia, fatigue, vaginal dryness, myalgia or arthralgia, and report it immediately to the rheumatologist. It has been reported that female patients with endometriosis have a higher risk of developing SS within the first 5 years (36). Thus, a suitable medication must be provided to these female patients by clinicians. In this framework, Bardi *et al* (281) presented the new concept of 'holism' for endometriosis, which leads physicians to evaluate this disorder in a complex and global way, considering its increased risk to co-occur with various autoimmune diseases. This combined, global approach is expected to result in beneficial patient management, taking into account the heterogeneous character of these diseases. In conclusion, information that can be derived by analyzing the intersection between autoimmunity, inflammation and angiogenesis, and the identified shared genetic factors may be of high value in understanding the underlying biochemical and cellular mechanisms of the association between endometriosis and SS, thus contributing to the development of novel therapeutic alternatives for both disorders.

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MIZ, BCT and GNG designed the current study and drafted the manuscript. GNG, TBN, BCT, GFG and MIZ searched the literature. MIZ, GNG and DAS analyzed and organized the data. DAS, GFG and TBN critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

MIZ, BCT, GFG, TBN and GNG (all authors other than DAS) declare that they have no competing interests. DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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