Genetic factors involved in the co-occurrence of endometriosis with ankylosing spondylitis (Review)

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Abstract. Previous research has revealed an association between endometriosis and various autoimmune diseases, while recent data suggest, for the first time, an association between endometriosis and the risk of developing ankylosing spondylitis (AS). AS, the prototype of spondyloarthritides diseases, is a systemic, chronic, immune-mediated inflammatory arthritis, which primarily affects the spine and sacroiliac joints, as well as the axial skeleton with or without extraspinal manifestations. AS is of polygenic inheritance and numerous immunologically relevant genes contribute to its development. Endometriosis is an enigmatic, relatively common, benign, estrogen-dependent, heterogeneous gynecological disease, influenced by multiple genetic, epigenetic and environmental factors. It is characterized by the growth of endometrial tissue occurring in sites other than the uterine cavity, most commonly in the pelvic cavity, including the ovaries and the uterosacral ligaments, affecting up to 10% of the female population of childbearing age, causing pain and infertility. The present review discusses whether a partially shared genetic background may explain the co-occurrence of these disorders, as well as potential similarities regarding the underlying pathogenetic mechanisms and specific molecular and cellular pathways.

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Contents

1. Introduction

Ankylosing spondylitis (AS) is a chronic, progressive, painful, systemic, immune-mediated, highly inherited multifactorial inflammatory arthritis that primarily affects the spine and sacroiliac joints, while, in some cases, it also affects the peripheral joints and extraarticular tissues (1). It is the major subtype of an inter-related group of rheumatic diseases sharing clinical, genetic and radiographic features, termed spondyloarthritides (SpA), which includes psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis, undifferentiated spondyloarthritis and juvenile-onset spondyloarthritis (2). AS is the most common form of inflammatory arthritis after rheumatoid arthritis (RA) in the developed world. Patients with AS suffer from pain and are characterized by stiffness and the loss of spinal mobility, which are explained by spinal inflammation and/or structural damage, by bone and joint erosion and, finally, ankylosis and fibrosis (3). AS is a disease that affects mainly young individuals, who generally develop the first symptoms at an age <30 years, and males are more often affected than females, with a ratio of roughly 2 to 1 (1). The prevalence of AS varies in different countries. Notably, in a Northern European region (Norway), the prevalence of AS is between 0.2 and 1.2%, and the incidence of the disease ranges from 0.5 to 14 per 100 000 individuals per year (4). The molecular pathogenesis of this complex disease involves genetic, immunological, microbial

and hormonal components (5). Of note, microbial infection plays a pivotal role as a triggering factor of the host innate immunity and AS development (1).

Endometriosis is an enigmatic, common, benign, estrogen-dependent gynecological disease with an unknown etiology and a poorly understood pathogenesis. It is characterized by the presence of endometrial tissue external to the uterine cavity, most commonly in the pelvic cavity, including the ovaries and the uterosacral ligaments, and is associated with chronic pelvic pain, dysmenorrhea, irregular menstrual bleeding, intestinal symptoms, recurrent urinary tract infections, dyspareunia and infertility, thus markedly affecting the quality of life of patients; however, a low percentage of patients with this condition may be asymptomatic (6,7). Endometriosis can appear as peritoneal lesions, ovarian endometriotic cysts and deeply infiltrative endometriosis (8). Endometriosis affects 6-10% of women of childbearing age, and it has been estimated that 176 million women worldwide are affected by endometriosis, with significant costs for both affected women and for society (9) (http://endometriosis.org). Genetic and epigenetic factors, as well as environmental ones, including pollution agents and toxins, contribute to the development of this disease (8,10). The pathogenetic mechanisms leading to its development remain unclear, although several theories have been suggested thus far regarding the development of endometriosis. Of note, all cases cannot be explained by one theory alone. Thus, apart from the most accepted Sampson's retrograde menstruation hypothesis, other processes related to angiogenesis, increased oxidative stress, endothelial dysfunction and chronic inflammation have been also enrolled in the development of this condition (11).

Women with endometriosis are at a high risk of developing several other chronic diseases, including cancer (12), endocrine disorders (hypothyroidism) (12), cardiovascular disorders (13,14) and, mainly, a number of autoimmune diseases including RA, multiple sclerosis, scleroderma, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, Sjögren's syndrome, coeliac disease and autoimmune thyroid disorder (15,16). Notably, recent findings have suggested that endometriosis can increase the susceptibility for AS in these women (17).

The present review discusses the genetic factors involved in the co-occurrence of AS and endometriosis in an attempt to deepen the knowledge concerning the shared underlying pathogenetic mechanisms and the relevant molecular and cellular pathways. A more in-depth understanding of these associations may allow physicians to develop novel therapeutic interventions for women with endometriosis, thus using this information in clinical practice.

2. Genetics of AS and endometriosis

The rapid development of technology, including genome-wide association studies (GWAS) and next-generation sequencing (NGS) approaches, has contributed to the identification of hundreds genetic associations between common DNA sequence variants and multifactorial diseases. Although single nucleotide polymorphisms (SNPs) are the preferred genetic markers for case-control association and GWA studies due to their abundance in the human genome, the exact functional consequences of most of these polymorphisms are still unclear. Therefore, various techniques have been developed over the past few years in an attempt to reveal the functional basis of genetic risks associated with human diseases.

AS has a strong genetic predisposition and the investigation of genetic factors associated with AS susceptibility became more systematic following the discovery of the class I human leukocyte antigen B27, *HLA-B27* locus, which was suggested to be a major contributor to AS hereditability of ~30% (18). In particular, various subtypes of *HLA-B27*, such as *B*2702*, *B*2703* and *B*2710*, have been reported to increase the risk of developing AS, with these causative variants modifying the biochemical structure of the protein (19). Significant progress has been made in the discovery of genetic associations with AS by GWAS, as well as an Immunochip study over past decade (20). These studies performed to date have uncovered less than one-third of the overall genetic risk in AS (21), for the heritability of the disease, which is estimated as ~90% (22). Through these studies, >113 SNPs affecting the risk of developing AS have been identified thus far, including endoplasmic reticulum aminopeptidase (*ERAP*)-1 and *ERAP-2*, that are involved in antigen presentation, genes that are involved in the IL23/IL17 axis including interleukin (*IL*)-*23R*, Runt-related transcription factor 3, *JAK2*, *IL-1R1*, *IL-2R*, *IL-6R*, *IL-12B*, *IL-27*, caspase recruitment domain family member 9 (*CARD9*), signal transducer and activator of transcription (*STAT*)3 and tyrosine kinase 2 (*TYK2*), genes modulating the activation and differentiation of lymphocytes including zinc finger MIZ-type containing 1 (*ZMIZ1*), *IL-7*, T-box transcription factor 21 (*TBX21*) and *IL-7R*, and other genes such as*IL-1Ra*, *NOD2* (*CARD15*), cytochrome P450 (*CYP)2D6* and *TGF-1* (5,20,22-27). Of note, genetic studies regarding the clinical manifestations of AS, such as the extent of bony ankylosis or the presence of anterior uveitis have been very fruitful, given that some genes that were found to influence uveitis risk are not AS risk factors (28). The findings have uncovered novel pathways involved in the pathogenesis of the disease and have led to the introduction of novel therapeutic treatments for AS; however, much of the heritability of AS remains unknown and causal variants for most loci have yet to be defined.

Endometriosis is a complex disease, in which both genetic and environmental factors interact and contribute to risk, thus leading to the disease phenotype. The familial association of endometriosis suggests a genetic contribution to the disease. Thus, the relative risk for women who have immediate relatives with endometriosis was estimated at 2.3 in a study on Australian twins and their families (29), while the overall heritability has been estimated at ~50%, as shown from monozygotic twin studies (30). Gene association studies, GWAS and NGS techniques have played a primary role in depicting the genetic contributions to endometriosis development. The 'candidate gene' studies have firstly assisted investigators in identifying genetic variants associated with endometriosis over the past decades, taking into account hundreds of SNPs (31,32), while GWAS were adopted for endometriosis from 2007 onwards, aiming at identifying common genetic variants of moderate effects (31-35). Notably, the loci identified were categorized according to the function of their gene products involved in estrogen-induced cell growth, matrix remodeling, sex hormone activity, glucose homeostasis,

vascular function, cell adhesion, migration, growth and differentiation, inflammation and WNT/β-catenin signaling, hormone receptors and metabolism, transcription regulation, immunity and oxidative stress (36). However, considering that a number of studies have yielded controversial results (31,35), due mainly to the enrolment of small populations (37), many of these loci were confirmed by replication studies and further meta-analyses. As is typical for GWAS results, the majority of the loci reside in intergenic regions for which the functionality remains to be uncovered. Rahmioglu *et al* (34) conducted a meta-analysis that detected GWA significance for rs12700667 on 7p15.2, rs7521902 near *WNT4*, rs10859871 near *VEZT*, rs1537377 near *CDKN2B-AS1*, rs7739264 near *ID4* and rs13394619 in *GREB1*. Notably, all these SNPs, apart from the *VEZT* one, exhibited a stronger association with stage III/IV of endometriosis, which are characterized by ovarian (cystic) or deep infiltrating disease including extensive adhesions (34). In a further meta-analysis, Sapkota *et al* (38) identified five novel endometriosis risk loci exhibiting significance in GWA, namely fibronectin 1 (*FN1*), Coiled-coil domain containing 17 (*CCDC170*), estrogen receptor 1 (*ESR1*), spectrin repeat-containing nuclear envelope protein 1 (*SYNE1*) and follicle-stimulating hormone beta subunit (*FSHB*), with all of them being involved in sex steroid hormone pathways. In the largest GWAS and replication meta-analysis of endometriosis that has been performed to date, enrolling 60,674 cases and 701,926 controls of European and East Asian ancestry, 42 genome-wide significant loci were identified, including 31 novel ones, such as ADP ribosylation factor like GTPase 14 effector protein (*ARL14EP*), Bcl-2-modifying factor (*BMF*), homeobox A10 (*HOXA10*), long intergenic non-protein coding RNA 629 (*LINC00629*), alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase (*ABO*), bassoon presynaptic cytomatrix protein (*BSN*), PDZ and LIM domain 5 (*PDLIM5*), potassium channel tetramerization domain containing 9 (*KCTD9*), MLLT10 histone lysine methyltransferase DOT1L cofactor (*MLLT10*), actin like 9 (*ACTL9*) and inhibitor of DNA binding 4 (*ID4*) (39). The majority of SNPs exhibited larger effect sizes for stage III/IV disease, and when combined, they explained 5.61% of stage III/IV disease variance. Notably, the authors have previously used, for the first time in family studies, the whole exome sequencing technique, which allowed for the identification of UDP glucuronosyltransferase family 2 member B28 (*UGT2B28*) and ubiquitin specific peptidase 17 like family member 2 (*USP17L2*) as novel, endometriosis-associated genes, by analyzing a unique in the literature three-generation family from Crete (Greece) with seven members suffering from endometriosis (40).

3. Influence of autoimmunity, angiogenesis and inflammation in AS and endometriosis

It is well-known that endometriosis is a multifactorial condition involving, apart from hormonal and genetic, pro-inflammatory, pro-angiogenic and immunologic processes. All the multiple interconnected factors involved in these processes may explain the complex and heterogeneous manifestations of the disease. Although it is beyond the scope of the present review to discuss the aforementioned processes in detail, some aspects regarding their role in AS and endometriosis are presented below.

There is increasing evidence to indicate that women with endometriosis are more likely to have an additional autoimmune disease, probably due to underlying shared pathogenic pathways. Autoimmune diseases are characterized by the loss of self-tolerance, causing immune-mediated tissue destruction and multiorgan involvement. Considering that similar immunological alterations occur in endometriosis, thus increasing the number of macrophages and leading to various abnormalities in the function and concentrations of B- and T-lymphocytes (41), it has been suggested that endometriosis resembles an autoimmune disease. Endometriosis is often associated with the presence of a large variety of antibodies in the blood and peritoneal fluid of patients, including antinuclear, antiphospholipid, antithyroid, anti-survivin, anti-laminin-1, anti-carbonic anhydrase, anti-α-enolase and anti-endometrial autoantibodies (42,43). Of note, various theories have been put forth, suggesting that changes in the function and regulation of the immune system may prevent the ability to eliminate the endometrium of the pelvic cavity, while several types of immune cells appear to play roles in the destruction of cells in ectopic sites (41). Furthermore, it has been suggested that defects in immune surveillance in women with endometriosis may also lead to the development of autoimmune diseases (44). AS is an autoimmune disease and, as a consequence, it develops through complex interactions between genetic background and environmental factors, as described in detail in the previous section of the present review.

Endometriosis, which is characterized by systemic inflammation in the affected organs of the body, is caused by a variety of inflammatory factors, including cytokines, macrophages and prostaglandin. Of note, a strong support for a pivotal role of inflammation and its associated pathways dealing with the establishment of endometriosis derives from the detection and confirmation of the genetic background of the condition through GWAS and NGS techniques. It has been reported that women with endometriosis appear to have an altered inflammatory profile upon surgical lesion removal, thus suggesting that the ectopic lesions may drive systemic inflammation in endometriosis (45). Moreover, endometriotic lesions have been found to exhibit the production of estrogen themselves, thus stimulating mast cells to support the inflammatory process (46). In addition, the hormonal alterations that have been observed in endometriosis are related to the inflammatory imbalance that characterizes the disease, considering that inflammation affects hormonal regulation (47). The association of endometriosis with inflammation has also been strengthened by the initiation of several inflammatory responses by a network of pro-inflammatory proteins of the IL-1 cytokine family, while elevated levels of various inflammatory factors have been detected in the peritoneal fluid and peripheral blood of women with endometriosis (48). In particular, elevated levels of pro-inflammatory cytokines, including IL-6, IL-8 and TNF-α have been detected in women with endometriosis compared to those without this condition; however, it remains unknown whether endometriosis causes this altered peritoneal microenvironment or whether it can be considered as a consequence of the disease (49). Notably, the stimulation of peritoneal macrophages with LPS in patients with endometriosis has led to elevated levels of IL-6, IL-10 and TNF-α (50). Of note, the anti-inflammatory cytokine, IL-37,

has been enrolled in the development of endometriosis, given that it suppresses the proliferation, migration and invasion of cells of the ectopic endometrium from samples of ovarian endometrioma (51).

AS is a common inflammatory rheumatic disease that causes, among other clinical manifestations, characteristic inflammatory back pain and inflammation at other locations in the axial skeleton including spine (1). Accumulating evidence has indicated that inflammation plays a critical role in pathologic bone formation in patients with AS (52). Considering that AS represents a disease that is associated with chronic inflammation, it is characterized by the key role of dendritic cells, natural killer (NK) cells, macrophages and cells of adaptive immunity, with all these cells producing a variety of cytokines that lead to the development of the disease (39). Thus, elevated levels of pro-inflammatory cytokines, including IL-1B, IL-6, IL-8, IL-10, IL-17, IL-21 and IL-23 have been observed in patients with AS compared with normal subjects, whereas increased levels of interferon (IFN)-γ and TNF-α have been also reported in some patients as a result of aggressive inflammatory responses (5). Notably, the IL-23/IL-17 axis that causes the production and secretion of various inflammatory molecules in RA, also plays a prominent role in AS (53).

Various studies have associated endometriosis with angiogenesis thus far, demonstrating the highly angiogenic properties of the human endometrium and its ability to attract blood vessels from the surrounding tissue (54). Indeed, immune-related and endometrial cells have been found to secrete high levels of various cytokines, as well as growth factors that promote invasion to the extracellular matrix, and the implantation and growth of the ectopic endometrium by inducing angiogenesis (55). Vascular growth factors, with VEGF representing one of the most potent angiogenic factors, are involved in angiogenesis, that has been reported to be altered under particular pathological conditions, including chronic inflammation and endometriosis, thus indicating the angiogenic potential of endometrial cells (56). Moreover, other factors reported to be involved in the angiogenesis of endometriotic lesions include TGF-α, TGF-β, basic fibroblast growth factor (bFGF) and angiopoietin (57). Of note, the eutopic endometrium in women with endometriosis is characterized by a dysregulated angiogenic activity, due mainly to higher expression levels of VEGF-A and angiopoietin-1 (58,59). Furthermore, endometriotic lesions at various locations have reported to exhibit lymphangiogenic properties, although the different types of lesions exhibited no differences in the numbers of vessels (60).

Angiogenesis, which is the process of the formation of new capillaries from pre-existing vessels, has been implicated in the pathogenesis of AS. It is regulated by pro-angiogenic factors and inhibitors of angiogenesis (61). Thus, endothelial cell stimulating angiogenesis factor, which is a specific mitogen for endothelial cells, has been found in tissue or in the serum of patients with AS (62). Furthermore, activating transcription factor 6 has been reported to function as a key regulator of angiogenesis by mediating FGF2 transcription in chondrocytes, thus resulting in the pathogenesis of AS. FGF2 is a well-investigated protein that is involved in both angiogenesis and tissue regeneration (63). VEGF, a pivotal factor of angiogenesis secreted by macrophages and other cell types, has been reported to play a crucial role in the pathogenesis of AS, given that its serum levels have been found to be significantly higher in patients with AS than in controls (64). Additionally, due to the crucial role of angiogenesis in synovial membrane vascularity and excessive bone formation, a contribution to the development of synovitis and enthesitis that characterize AS may be suggested (64).

4. Shared susceptibility loci between AS and endometriosis

The association between endometriosis and an increased risk of developing AS has posed an interesting question regarding the putative role of a shared genetic background on the co-occurrence of these diseases. Taking into consideration that various genes involved in inflammation, angiogenesis, endothelial dysfunction and immune deregulation (65) have been found to be associated with endometriosis or AS, the present review summarizes the existing knowledge dealing with the potential shared genetic background of these diseases through an extensive search of the current literature (Fig. 1).

The results of the literature research revealed that *IL-1A* rs2856836 and rs3783550 (66,67), *IL-10* rs1800871 (68,69), *IL-12B* rs17860508 (70,71), protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) rs2476601 (16,72), cyclooxygenase (*COX*)-2 and (*PTGS*)-2 rs20417 (73-75), *CYP17A1* rs743572 (76,77), *STAT4* rs7574865 (78,79), Toll like receptor 4 (*TLR4*) rs4986791 (76,80) and methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 (81-83) SNPs are associated with both diseases under investigation (Table I). The common genetic targets and their corresponding genes have been further analyzed towards estimating the candidate gene regulatory network and the major categories of the biological pathways using the GeneMANIA and the Reactome Knowledgebase platforms, respectively (Fig. 1A and B) (84,85).

Moreover, various microRNAs (miRs/miRNAs) have been reported to be associated with both diseases, including *miR-20-a* (22,86), *miR-21* (22,87), *miR-196-b* (22,88), *miR*-146-a (86,89,90), *miR-499a* (86,90) and *miR-214* (88,90).

5. Shared genetic polymorphisms and biological mechanisms

Polymorphisms in inflammation and autoimmune-related genes. The STAT proteins are members of a family of latent cytosolic transcription factors, which are activated in response to numerous cytokines, growth factors and hormones (91) (Fig. 1). STAT4, encoded by the *STAT4* gene located at 2q32.2-q32.3, represents a key transcription factor that is expressed in activated peripheral blood monocytes, dendritic cells and macrophages in humans (92), mediating IL-12 signaling that is critical for the development of protective immunity in intracellular infection. Moreover, STAT4, which is a member of the JAK/STAT pathway, appears to play a central role in IFN signaling, which is involved in regulatory networks related to the immunological processes that promote chronic inflammation and tissue destruction (93). The *STAT4* rs7574865 G/T polymorphism, located within the third intron of the gene, has previously been shown to be associated with an increased susceptibility for AS and endometriosis (78,79). The TT genotype of rs7574865 has been found to be significantly

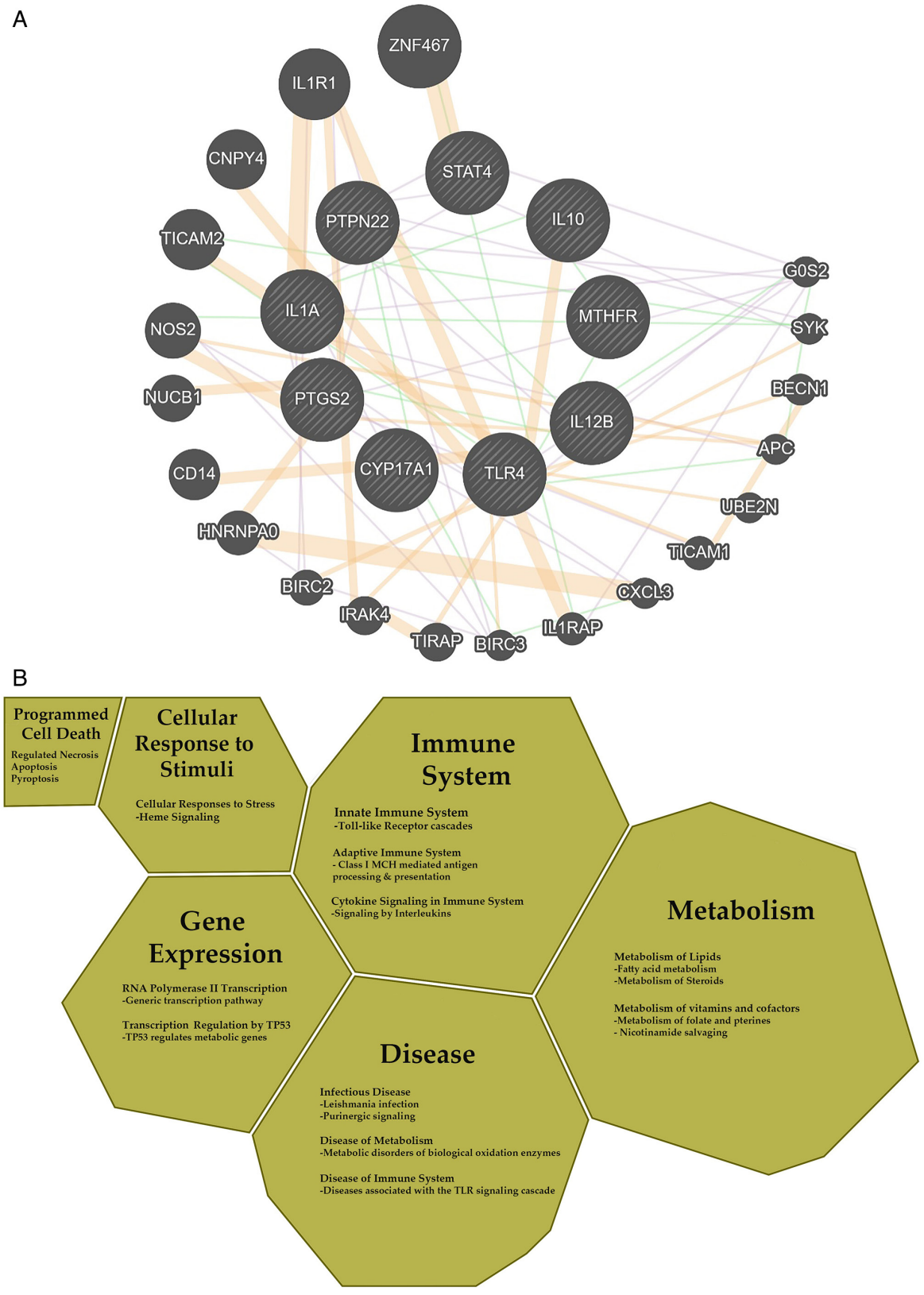

Figure 1. Analysis of the common genetic targets and their corresponding genes. (A) The gene regulatory network of the major genetic factors that play critical role in both diseases. (B) Major categories of the biological pathways as have been estimated from the common genetic targets and the corresponding genes.

more frequent in women with minimal or mild endometriosis than in the controls (79); however, the functional significance of this SNP as regards the pathogenesis of endometriosis has not yet been determined. It has been hypothesized that this SNP can affect the gene expression or mRNA splicing, thus inducing strong Th1 and Th17 cytokine responses and IFN signaling (79). Furthermore, the rs7574865 SNP has been shown to be significantly associated with an increased AS

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

dbSNP ID	Endometriosis- and AS-associated gene	Function	(Refs.)
rs2476601	*PTPN22*	Lymphoid-specific phosphatase; downregulator of T-cell activation	(16,72)
rs7574865	*STAT4*	Transcription factor involved in Th17 differentiation, monocyte activation and IFN-γ production	(78,79)
rs2856836 rs3783550	*IL-1A*	Pleiotropic cytokine involved in inflammatory processes and hematopoiesis	(66,67)
rs1800871	*IL-10*	Anti-inflammatory cytokine; inhibitor of Th1 differentiation	(68,69)
rs17860508	*IL-12B*	Cytokine acting on T- and natural killer cells	(70,71)
rs1801133	*MTHFR*	Key regulatory enzyme in folate and homocysteine metabolism	(81-83)
rs20417	*COX-2 PTGS2*	Key enzyme required for the conversion of arachidonic acid to prostaglandins	(73-75)
rs4986791	*TLR4*	Transmembrane protein, member of the toll-like receptor family	(76,80)
rs743572	*CYP17A1*	Monooxygenase, a member of the cytochrome P450 superfamily of enzymes	(76,77)

AS, ankylosing spondylitis.

susceptibility and radiographic severity, although its actual functional consequence in AS remains to be identified (78). However, in a bioinformatics analysis performed previously in the authors laboratory, the polymorphic site was not found to disrupt any transcription factor binding site, while preliminary experiments also conducted by the authors demonstrated an impairment in STAT4 production, as well as in STAT4 phosphorylation in the presence of the T allele (94). In particular, lower levels of the produced protein and a disruption in the phosphorylation procedure were observed, probably due to a defect in some stage of gene expression or protein production when T1D were analyzed (94).

The lymphoid-specific phosphatase (LYP), which is encoded by the *PTPN22* gene, located on chromosome 1p13.3-13.1, is a potent downregulator of T-cell activation (95) (Fig. 1). The *PTPN22* rs2476601 (C1885T) SNP has been found to be associated with a number of autoimmune diseases, including SLE (96), RA (97), T1D (98) and JIA (99), as well as with AS (72) and endometriosis (71). This SNP, which corresponds to the functional A620W polymorphism, results in a variant that affects the protein-protein interaction with tyrosine kinase Csk and codes for a gain-of-function enzyme, which increases the inhibition of T-cell receptor signaling. As a consequence, the authors have previously demonstrated that it may have profound effects on the function of the immune system (16) and, therefore, it may influence the development of AS. Of note, subjects carrying the T-allele of rs2476601 are considered to have increased numbers of auto-reactive T-cells escaping negative selection, thus persisting in the circulation, and thus being prone to autoimmunity (100). Various studies on patients with endometriosis have revealed an aberrant function of cells involved in the immune system (15,101), thus suggesting a critical role of immunological factors in the development of the disease. Accordingly, it has been suggested that alterations in T-cell-mediated immunity may facilitate the implantation of endometrial fragments or cells in ectopic regions (102). As recently reported by the authors (16), patients with endometriosis exhibit elevated levels of inflammatory cytokines, decreased apoptosis and cell-mediated abnormalities, which are indicative of autoimmune diseases.

COX is the rate-limiting enzyme for the synthesis of prostaglandins and the names of its three isozymes are COX-1, COX-2 and COX-3 (103). COX-1 is COX-1 is constitutively expressed in the majority of cell types regulating vascular homeostasis. COX-2 enzyme is encoded by the *COX-2* gene, located at chromosome 1q25.2-25.3 and consists of 10 exons and nine introns (104). It is an inducible enzyme exhibiting either a low or no expression in the majority of tissues under normal physiological status (105); however, it can function upon proper induction. Thus, it can be induced and produced in inflammatory and injured sites, mediating the production of prostaglandin that causes local inflammation and pain (106). As a consequence, this enzyme may represent a key player in the inflammatory response (107). It has been previously reported that the functionally important rs20417 SNP of *COX-2* is associated with AS (74) and endometriosis (73). Previous studies had demonstrated that the G allele of the rs20417 SNP increases the expression of *COX-2* when compared to C (108), thus increasing the formation of prostaglandins (75). Notably, the excessive expression of *COX-2* has been found to be associated with the pathogenesis of endometriosis, since the mRNA levels of *COX-2* have been found to be 5-fold higher in ectopic issue when compared to the eutopic endometrium, thus leading to an abnormal production of prostaglandins (109). The -765G allele has been shown to be associated with an increased risk of developing endometriosis of stages II/III (75). Similarly, in another study, the G allele of this SNP was shown to be associated with an increased susceptibility of developing endometriosis of stages III and IV, with the eutopic endometrial tissue of patients presenting an elevated expression of *COX-2* compared to the controls (73). Of note, Liu *et al* (74) found that allele G of rs20417 was more frequent in patients AS, and was thus associated with an increased risk of developing AS.

TLRs form a family of transmembrane protein molecules, which are activated at the biochemical and structural level by pathogen molecular patterns. TLRs activate the cellular signaling pathways to induce immune-response genes, including inflammatory cytokines (110). TLRs have been extensively studied in endometriosis due to their role in the regulation of the activation of immune and inflammatory responses (111). TLR4 is an important pathogen recognition receptor that mainly recognizes the lipopolysaccharide (LPS) of Gram-negative bacteria, but also structures from fungal and mycobacterial pathogens (112). TLR4 is essential for the innate immune response and is composed of three domains. It is expressed in macrophages, endometrial and endometriotic epithelial cells, and alterations in its expression levels or function have been observed thus far in the endometrium (111). The rs4986791 (T399I, C/T transition) SNP of *TLR4* has been investigated in a number of studies focusing on inflammatory, infectious and autoimmune diseases. For example, it has been found that the T allele of rs4986791 is a risk factor for both endometriosis (80) and AS (76). The non-synonymous T399I variant is located on the extracellular domain of TLR4, which is critical for the LPS recognition and it has been reported that this polymorphism results in a mild LPS-hyporesponsive phenotype (113). Although previous crystallography analyses have demonstrated that the T399I change does not affect the TLR4 structure (114), recent approaches based on molecular dynamics have indicated that the polymorphism may abrogate the stability of the hexamer complex, thus leading to compromised TLR4 signaling (115). Of note, the genetic association of rs4986791 SNP with AS could indicate the involvement of the innate immune system in the progression of AS, considering that the upregulation of TLR4 has been reported in this disease (116).

Polymorphisms in cytokine genes. The *IL-1* gene cluster, a 360 kb region containing nine genes, is located on the chromosomal 2q13 locus, which represents a region harboring various inflammatory genes. Notably, various modifications in the expression of the members of this family have been shown to be associated with an increased susceptibility for human diseases (117). The *IL-1* cluster has also emerged as a robust susceptibility locus for AS (66). IL-1A is a pro-inflammatory cytokine that is involved in various immune responses, mainly produced by activated macrophages, which augments the activation of T- and B-lymphocytes and monocyte/macrophages, while it participates in the induction of fibroblast proliferation (118). Both *IL-1A* rs2856836 (T/C) and rs3783550 SNPs have been shown to be associated with susceptibility to endometriosis and AS (38,66,67,119). rs2856836 is located at the 3'untranslated region (UTR) of the gene; however, limited data are available regarding the effect of this SNP on the expression or function of the *IL-1A* gene (119). However, increased expression levels of *IL-1A* have been observed in the peritoneal fluid of women with endometriosis, thus probably stimulating the activity of the adhesion molecules and enhancing the implantation of fragments of menstrual endometrium on peritoneal surfaces (120). The second *IL-1A* SNP, rs3783550, which has been found to be associated with endometriosis, has been found to overlap with binding sites of three transcription factors, thus suggesting a possible regulatory or functional role of this SNP (121). Taken together, genetic variants of *IL-1A* may be involved in genetic susceptibility to endometriosis and, in parallel, may induce inflammation in AS through intracellular effects (122), thus being involved in the initiation of disease.

IL-10 is a key immunomodulatory cytokine, produced by Th2 cells and macrophages, with an ability to inhibit the activation and function of macrophages, monocytes and T-cells (123). The *IL-10* gene maps to chromosome 1q31-32 in humans, is composed of five exons and four introns, and various genetic variants that are located in the promoter region have been investigated thus far in relation to human diseases. However, the functional promoter rs1800871 (-819C/T) SNP of the *IL-10* gene has been found to be associated with AS (69) and endometriosis (68), considering that it can influence both the mRNA, as well as the protein levels of *IL-10* (124). As regards endometriosis, women with the TT genotype appear to have a 2-fold increased risk of developing endometriosis compared to those carrying the C allele. Of note, the T allele has been shown to be associated with lower IL-10 levels in comparison to the C allele in women suffering from endometriosis; this finding may reflect a mechanism that results in the upregulation of inflammation in the peritoneal cavity (68). As regards AS, the serum levels of IL-10 have been found to be significantly higher in patients with AS than in healthy controls (69). Again, the C allele of the rs1800871 SNP has been found to be associated with an increased risk of developing AS, with the CC genotype being associated with higher IL-10 levels produced by peripheral blood mononuclear cells in patients with AS as compared with the TT genotype (69).

IL-12 is involved in the differentiation of naive T-cells into Th1 cells, regulates the activity of antigen-presenting and NK cells (125) and induces IFN-γ production (126). IL-12 is a heterodimeric protein, consisting of two subunits, IL-12p35 and IL-12p40, encoded by the *IL-12A* and *IL-12B* genes, respectively, which are located on chromosome 5q31.1-33.1. Polymorphisms of the *IL-12B* gene have been found to modulate the secretion, as well as the activity of IL-12 (66,127). rs17860508 is a bi-allelic promoter polymorphism of *IL-12B*, a potential functional variant, and has been reported to be associated with the risk of developing AS and endometriosis (70,71). Notably, certain alleles may influence the release of specific cytokines, thus affecting the regulation of the immune response. The polymorphism under investigation, resulting from a 4-bp micro-insertion (CTCT) combined with an AA/GC transition, has been reported to be associated with alterations at the gene expression levels, as well as mRNA stability *in vitro* (128). Of note, Zhao *et al* (70) reported that cases carrying the GC allele had a significantly increased risk of developing ovarian endometriosis compared to individuals carrying the CTCTAA/CTCTAA genotype, while the level of *IL-12B* mRNA expression in the eutopic endometrial tissue of patients carrying the GC/GC genotype was significantly higher than in those with the CTCTAA/CTCTAA genotype. As regards the involvement of the rs17860508 polymorphism in the development of AS, data have indicated that it has an impact on the susceptibility for AS through a modulation of the IL-12p40 levels, thus conferring a variability in the immune response and contributing substantially to the disease phenotype (71).

Polymorphisms in metabolism-related genes. The *CYP17A1* gene is located at chromosome 10q24.32 and codes for the CYP17A1 protein, which is one of the key enzymes for glucocorticoid production and, most importantly, for steroidogenic pathway producing estrogen (129). The T allele of *CYP17A1* rs743572 SNP, which is located in the 5-UTR of the gene, 34 bp upstream from the translation start site, has been found to be a risk factor for AS and endometriosis (75,76). Endometriosis is an estrogen-dependent disease and abnormal expression levels of estrogen and consequent disruptions in estrogen metabolism may be closely associated with the development of endometriosis (130). Mutations in the *CYP17A1* gene have been shown to be associated with gene expression, as well as with hormone levels; Cong *et al* (76) reported that the rs743572 TT genotype, as well as the T allele significantly enhanced susceptibility to endometriosis. Notably, cases carrying the TT genotype had the shortest menstrual cycle and highest frequencies of intrauterine device use, although the SNP under investigation had no significant influence on the severity and specific characteristics of endometriosis (76).

The 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene is located in chromosome 1p36.3, encoding a key rate-limiting, regulatory enzyme in folate and homocysteine metabolism, which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (131). The *MTHFR* rs1801133 (Ala222Val) SNP, which is located in exon 4, has been found to be significantly associated with both AS and endometriosis (81-83). It has been previously suggested that polymorphisms in the *MTHFR* gene may result in alterations in gene expression levels and protein function, thus leading to an abnormal metabolism of 5,10-methylenetetrahydrofolate (82,83). Thus, the C677T missense mutation, which has been characterized as a thermally unstable one, probably influences the thermostability and activity of MHTFR protein, while it has been also reported that the rs1801133 T allele results in elevated plasma homocysteine levels, which, in combination with endothelial injury and vascular inflammation, may result in the development of cardiovascular disease, a well-known comorbidity of endometriosis (13,132).

The role of miRNAs. The VEGFA-related *miR-20-a*, which has been reported to be involved in the regulation of angiogenesis, has been found to be expressed in decreased levels in the ovarian endometrioma compared to the eutopic endometrium (133). Furthermore, it has been found that the peritoneal fluid from women with endometriosis reduces the expression of *miR-20-a* in primary stromal cell cultures from patients (134). Moreover, Zhao *et al* (70) revealed that *miR-20-a* expression was upregulated in patients with AS.

It has previously reported in the literature that *miR-21* is associated with endometrial receptivity, which is possibly associated with endometriosis (87), while it has also been found to be upregulated in women with endometriosis (135). As regards AS, given than bone loss is a feature of AS, this miRNA that has been implicated in the activation of osteoclasts was investigated; a higher expression of *miR-21* was observed in patients with AS when compared with the controls, with a parallel repression of its target programmed cell death 4 (*PDCD4*) gene (136).

miR146-a has been shown to be significantly associated with increased incidence rates of endometriosis, with the G allele being a risk factor for the disease (137). In particular, *miR-146a* expression has been found to be upregulated in ectopic vs. eutopic endometrial tissues (138). Furthermore, *miR-146a* expression has been found to be upregulated in patients with AS, and to induce the expression of *TNF-α*, *IL-6* and *IL-1B* (139), while the frequency of the G allele and GG genotype of the rs2910164 SNP of *miR-146a* was shown to be significantly higher in patients with AS compared to healthy controls (87,89). Previous research has demonstrated the potential role of *miR-196b* in the pathogenesis of endometriosis, by targeting proliferation, angiogenesis and apoptosis (140). The endometriosis-associated *miR-214* has been found to regulate major signaling pathways of critical genes participating in inflammatory and cell proliferation pathways, including angiogenesis, and may thus be implicated in the development of endometriosis (70,141).

6. Conclusions and future perspectives

Based on the data presented in the present review, a clear identification of a link between endometriosis and AS would necessitate a radical shift in public health management. However, although a relatively long list of genes identified to be involved in the development either of endometriosis or AS is available, thus far there appears little overlap between genetic factors affecting susceptibility to both diseases. One remaining challenge in immunogenetic research in endometriosis, as well as AS involves the determination of the functional mechanisms underpinning the identified genetic associations. Although GWAS have already identified >100 SNPs associated with an increased susceptibility for developing AS, there is currently a possible explanation for only a small number of these genetic associations, thus minimizing their potential for translation into therapeutic options. Thus, apart from the efforts to analyze the biochemical pathways leading to endometriosis, it remains an emerging public health issue of reproductive-age women and its pathogenesis remains elusive. Of note, endometriosis has been shown to be associated with various autoimmune diseases, including AS, thus suggesting that this condition may be considered a risk factor for AS, which requires specific counseling and medical management. Considering that AS is an autoimmune disease with a poorly-defined etiology (142), further elucidation of the underlying pathophysiology may lead to the development of novel therapeutics.

The treatment of AS has undergone substantial changes over the past decades, thus leading to the establishment and application of novel targeted therapies. The development of efficient drugs targeting the IL-23/IL-17 axis represents a successful paradigm of the value of genetics in the scientific field of drug design (143). Moreover, the targeting of TNF-α that is expressed in high levels in patients with AS (144) is another beneficial therapeutic option for a large percentage of affected patients, while alternative promising therapeutic options include JAK inhibitors that interrupt the JAK/STAT transduction of IL-23/IL-17 and some other cytokine signals (145,146). Notably, it should be kept in mind that the causal genes, which

are regulated by the disease-associated SNPs, are optimal targets for drug design, considering the plausible importance of some well-analyzed downstream molecular pathways (143). However, in spite of all this progress being made in patient management, a significant proportion of patients remain difficult to treat due to the heterogeneous character of the disease at the clinical and/or the molecular level. In this framework, polygenic risk scores involving the testing of all known susceptibility variants may prove useful in order to derive a personalized risk score for the disease or an estimation for disease severity.

Immune and inflammatory dysfunctions have always represented challenging therapeutic targets for endometriosis and AS. Considering the lack of different studies focusing on the co-occurrence of endometriosis with AS, further detailed studies need to be conducted in an attempt to fully elucidate the underlying pathophysiological mechanisms. Of note, it has been suggested that clinicians should pay attention to the occurrence of AS in patients with endometriosis and possible underlying endometriosis in female patients with AS. As a consequence, a suitable medication must be provided to these women.

In conclusion, the ultimate task may be the use of all genetic information collected in order to better understand the mechanisms leading to development of endometriosis and AS, in order to design new mechanism-driven therapeutics, and to may in the diagnosis and management of patients. The genetic profiling should also play a role in the clinician's selection of therapy as part of a precision medicine strategy towards the management of these diseases.

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MIZ, EE and GNG. designed the study and drafted the manuscript. GNG, MIZ, DV, LP and DAS searched the literature for related studies to be included in the review. GNG, EE, DV, LP and MIZ analyzed and organized the data from the literature for inclusion in the review. DAS, DV and LP critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

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