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REVIEW

The Antigen-Processing Pathway via Major Histocompatibility Complex I as a New Perspective in the Diagnosis and Treatment of Endometriosis

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Abstract
Endometriosis is a debilitating gynecological disease defined as the presence of endometrium-like epithelium and/or stroma outside the uterine cavity. The most commonly affected sites are the pelvic peritoneum, ovaries, uterosacral ligaments, and the rectovaginal septum. The aberrant tissue responds to hormonal stimulation, undergoing cyclical growth and shedding similar to appropriately located endometrial tissue in the uterus. Common symptoms of endometriosis are painful periods and ovulation, severe pelvic cramping, heavy bleeding, pain during sex, urination and bowel pain, bleeding, and pain between periods. Numerous theories have been proposed to explain the pathogenesis of endometriosis. Sampson's theory of retrograde menstruation is considered to be the most accepted. This theory assumes that endometriosis occurs due to the retrograde flow of endometrial cells through the fallopian tubes during menstruation. However, it has been shown that this process takes place in 90% of women, while endometriosis is diagnosed in only 10% of them. This means that there must be a mechanism that blocks the immune system from removing endometrial cells and interferes with its function, leading to implantation of the ectopic endometrium and the formation of lesions. In this review, we consider the contribution of components of the Major Histocompatibility Complex (MHC)-I-mediated antigen-processing pathway, such as the ERAP, TAP, LMP, LNPEP, and tapasin, to the susceptibility, onset, and severity of endometriosis. These elements can induce significant changes in MHC-I-bound peptidomes that may influence the response of immune cells to ectopic endometrial cells.

Keywords
Endometriosis • ERAP • TAP • LMP • LNPEP • Tapasin

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1. Endometriosis – Etiology, Classification, and Theories of Disease Development

Endometriosis is a debilitating gynecological disease defined as the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium of the uterine cavity usually with an associated inflammatory process (International Working Group of AAGL, ESGE, European Society of Human Reproduction and Embryology (ESHRE) and WES et al. 2021). The most-commonly affected sites are the pelvic peritoneum, ovaries, uterosacral ligaments, pouch of Douglas, and the rectovaginal septum. The aberrant tissue responds to hormonal stimulation, undergoing cyclical growth and shedding similar to appropriately located endometrial tissue. Endometriosis implants often contain fibrous tissue, blood, and cysts. Common symptoms of endometriosis are painful periods and ovulation, severe pelvic cramping, heavy bleeding, pain during sex, urination and bowel pain, bleeding and pain between periods, periods lasting 7+ days, digestive problems, and constant fatigue. Symptoms vary depending on the type of lesions and many endometrioses are asymptomatic, often diagnosed during infertility consultations (Burney and Giudice 2012; Dunselman et al. 2014; Johnson et al. 2017; Parasar et al. 2017; Allaire et al. 2023; Penrod et al. 2023). Most diagnosed cases of endometriosis can be divided into four main subtypes: first, superficial/peritoneal endometriosis (approx. 80% of the cases). Second, ovarian endometriosis (cysts or "endometrioma") may affect 2%–10% of women. Third, deep-infiltrating endometriosis is characterized by the invasion of the endometrioid glands into various pelvic organs, including the ligaments, rectum, vagina, and bladder. A characteristic feature is the infiltration of endometrial cells >5 mm below the surface of the peritoneum or connective tissue. Fourth, locations outside the pelvis, such as the abdominal organs, abdominal wall, diaphragm, pleura, and the nervous system (Signorile et al. 2023).

Endometriosis occurs in approximately 10%–15% of reproductive-aged women and is present in 20%–50% of women with infertility and 71%–87% of women with chronic pelvic pain (Strathy et al. 1982; Giudice and Kao 2004; Parasar et al. 2017; Carlyle et al. 2020; Allaire et al. 2023). Around 176 million women worldwide suffer from endometriosis; however, experts believe the number is significantly higher due to underreporting, misdiagnosis, and lack of a nonsurgical and noninvasive diagnostic method (Johnson and Hummelshoj 2013). Women wait for an average of 3–10 years for a

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diagnosis. Women have a 5–7 times higher risk of developing the disease if a close relative has the disease (Dunselman et al. 2014; Nnoaham et al. 2019).

The best-known classification system for endometriosis is the revised American Society for Reproductive Medicine (r-ASRM) classification (American Society for Reproductive Medicine 1997) based on the morphology of the peritoneal and pelvic implants such as red, white, and black lesions; the number, size, and location of endometrial implants, plaques, endometriomas, and adhesions. The stages of endometriosis according to the ASRM guidelines are I, II, III, and IV. They are determined based on point scores (40-point scale) and correspond to minimal (1–5 points), mild (6–15 points), moderate (16–40 points), and severe endometriosis (>40 points). The first and second stage is a mild form of the disease in which adhesions, if present, are only superficial. The third stage is cystic endometriosis, characterized by the presence of multiple implants or small lesions <2 cm and adhesions. The fourth stage is deep-infiltrating endometriosis, which is described as the appearance of large endometriosis and adhesions on the surface of the ovaries and fallopian tubes (American Society for Reproductive Medicine 1997). In addition to the r-ASRM classification, emerging systems include the Enzian classification for deep endometriosis, the endometriosis fertility index, and the American Association of Gynecological Laparoscopists classification (Johnson et al. 2017). In 2022, the latest ESHRE recommendations on endometriosis were released (Becker et al. 2022). It is a comprehensive document where we can find information ranging from diagnosis and pain management to infertility treatment. Detailed recommendations for the management of patients with endometriosis diagnosed accidentally (without pain and infertility), adolescents, and postmenopausal women with endometriosis are also presented. Information on endometriosis risk factors and associations with other diseases is provided, along with recommendations for prevention and monitoring. Until these recommendations appeared, laparoscopy was the main method of diagnosing endometriosis (often referred to as the gold standard). This procedure involves the excision of endometrial lesions. Currently, it is only recommended for patients with negative imaging results and/or for whom empirical treatment has been ineffective or inappropriate. The goals of treatment are primarily focused on restoring fertility and relieving pain, as well as preventing possible intestinal complications after laparoscopy. Hormone therapy and analgesics are used for the treatment of symptomatic endometriosis. However, the efficacy of these treatments is limited as endometriosis often recurs. Therefore, it is important to have a comprehensive and individualized approach to the patient and to find a noninvasive diagnostic marker of the disease.

The precise mechanisms underlying the origin and development of endometriosis remain mainly unknown. The mechanisms of attachment and growth and disease severity have been difficult to elucidate due to the complex nature of the disease; however, it is now well established that endometriosis is a chronic inflammatory condition and that the process of endometriotic-lesion development is analogous to the process of wound healing. The disease manifests by abrogated cellular and humoral immune responses including peritoneal infiltration with immune cells, the activation of macrophages, abnormal lymphocyte responses, and abrogated natural killer (NK) cell cytotoxicity as well as the excessive production of pro-inflammatory and regulatory cytokines (Jeung et al. 2016). Endometriosis is also associated with the polyclonal activation of B lymphocytes and the increased production of autoantibodies; however, the role of this phenomenon in the pathogenesis of the disease is still unknown. While the disruption of cytotoxic activity is responsible for the survival of endometrial cells in the peritoneal cavity, increased amounts of cytokines and growth factors promote implantation and growth of implants (Song et al. 2003). They enhance the activity of metalloproteinases, stimulate the adhesion of endometrial stromal cells to fibronectin, induce the proliferation of endometrial cells, initiate angiogenesis, and through chemotaxis ensure a constant inflow of mononuclear cells of the immune system into the peritoneal cavity. The peritoneal fluid of sick women shows increased levels of interleukin (IL)-1, IL-8, monocyte chemotactic protein 1, Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor, and many others. The inflammatory reaction occurring in the peritoneal cavity of women with endometriosis seems to be responsible for the main symptoms of this disease, i.e., pain (increased production of cytokines and prostaglandins) and infertility (adhesions and scars, which are the result of inflammatory processes that can mechanically damage the fallopian tubes; also the pelvic inflammatory disease, harming folliculogenesis, egg quality, fertilization, and embryo implantation) (Sidell et al. 2002).

Numerous theories have been proposed to explain the pathogenesis of endometriosis (Sourial et al. 2014; Rolla 2019). These include the theory of coelomic metaplasia, the stem cell theory, the embryogenic theory, and Sampson's theory of retrograde menstruation. All these theories are not fully confirmed. The coelomic metaplasia theory assumes that endometriosis has its origins in the metaplasia of specialized cells found in the mesothelial lining of the visceral and abdominal peritoneum (Gruenwald 1942). This transformation of peritoneal tissue/cells into endometrial tissue occurs under the influence of hormonal and/or immunological factors. The stem cell theory assumes that stem cells reside in the basal layer of the endometrium and migrate as a result of retrograde menstruation and can differentiate into endometrial cells in ectopic locations (Sourial et al. 2014). Brosens et al. (2013) postulated that the uterine bleeding in newborn

girls contains a large amount of endometrial progenitor cells. Some of these cells may accumulate and persist in the peritoneal cavity following retrograde flow and may reactivate in adolescence in response to ovarian hormones. In turn, the embryonic theory includes that cells that are the remnants of embryonic cells would transform into the endometrium (Czyzyk et al. 2017). Some studies also raise the role of other factors such as apoptosis suppression, oxidative stress, genetics and epigenetics, diet, and the environment (Sourial et al. 2014).

Sampson's theory of retrograde menstruation is considered to be the most accepted and at the same time is the oldest (Sampson 1927). This theory assumes that endometriosis occurs due to the retrograde flow of endometrial cells through the fallopian tubes during menstruation. However, it has been shown that this process takes place in 90% of women, while endometriosis is diagnosed in only 10% of them. This implies that there must be a mechanism that blocks the immune system from removing the endometrial cells and therefore interferes with its function, thus leading to the implantation of the ectopic endometrium and the formation of lesions. However, this theory has been questioned in the past because it could not explain the occurrence of endometriosis in prepubescent girls, newborns, and men.

In this review, we consider the role of the endoplasmic reticulum (ER) aminopeptidases (ERAPs), transporters associated with antigen processing (TAPs), TAP-binding protein-related (TAPBPR), immunoproteasome low molecular weight proteins (LMPs), leucyl and cystinyl aminopeptidase (LNPEP), and tapasin in the susceptibility, onset, and severity of endometriosis. These components participate in the antigen-processing pathway via the Major Histocompatibility Complex I (MHC-I) (in humans known as HLA class I—human leukocyte antigen class I) and can induce significant changes in MHC-I-bound peptidomes that may, in turn, influence the response of immune cells to ectopic endometrial cells. Changed or incorrect peptidomes can affect the interaction of NK cells and that of T lymphocytes with ectopic endometrial cells because on their surfaces, there are receptors with an activating or inhibitory function, e.g., killer immunoglobulin-like receptors (KIRs), leukocyte immunoglobulin-like receptors (LILRBs), natural cytotoxicity receptors, or killer cell lectin-like receptors (Ścieżyńska et al. 2019). The appropriate interaction determines whether the immune system cells will remove the ectopic endometrial cell or not. Therefore, the expression of HLA class I on endometrial cells is also important. Kawashima et al. (2009) and Maeda et al. (2012) reported that HLA-G expression was identified in eutopic endometrium only in the menstrual phase but not in the proliferative or secretory phase. Moreover, HLA-G-expressing cells were also detected in the peritoneal fluid during the menstrual period. During retrograde menstruation, HLA-G-expressing endometrial tissue may enter the peritoneal cavity and may be eliminated by an immune system. Our research also indicates the influence of HLA-C, HLA-G, KIR2DS5, and LILRB1/2 genetic polymorphisms in the susceptibility to endometriosis. Moreover, we indicated genetic differences between women depending on the location of lesions and the severity of the disease (Nowak et al. 2015; Bylińska et al. 2018). Table 1 presents studies showing the role of HLA class I in endometriosis.

2. The Antigen-Processing Pathway via MHC-I

Initially, the *de novo* synthesized MHC-I heavy chain associates with the binding immunoglobulin protein (BIP) and calnexin and then binds to β2-microglobulin (β2m). Then, calnexin is replaced by its soluble counterpart, calreticulin. Subsequently, this complex is linked by the disulfide isomerase ERp57. Tapasin bridges this MHC-I complex to TAP leading to the multicomponent peptide-loading complex (PLC). Therefore, tapasin serves as a critical checkpoint in the generation of the MHC-I immunopeptidome (Thomas and Tampé 2017). Antigenic peptides are generated first as long precursors by the cytosolic proteasome. These precursors are transported into the ER by transporters TAP1 and TAP2, where they are then N-terminally trimmed by heterodimeric aminopeptidases ERAP1 and ERAP2 (Lankat-Buttgereit and Tampé 2002; Evnouchidou et al. 2014; López de Castro 2018; Evnouchidou and van Endert 2019). Kinetically stable peptide/MHC-I complexes can leave the PLC and finally are transferred via the Golgi network to the cell surface, where their antigenic cargo is inspected by cytotoxic T-lymphocytes (Scholz and Tampé 2005; Trowitzsch and Tampé 2020) and NK cells (Lee 2017; Compagnone et al. 2019). Figure 1 illustrates the MHC class I antigen-processing pathway.

2.1. ERAP1 and ERAP2

These enzymes critically shape the MHC-I immunopeptidome. The ERAPs remove the N-terminal residues from the antigenic precursor peptides and generate optimal-length peptides (i.e., 8–10-mers) to fit into the MHC class I groove. Both are Zn-metallopeptidases sharing about 50% amino acid identity (Tsujimoto and Hattori 2005). ERAP1 adopts two conformations: one closed and active and another open and with low activity (Stamogiannos et al. 2015). The transition between both the states is mediated by substrate binding to a regulatory site distinct from the catalytic site, in such a way that short peptides cannot reach the latter. This explains the unique molecular ruler mechanism of ERAP1—peptides of 9–16 residues, but not shorter, are efficiently trimmed (Chang et al. 2005). Both ERAPs, however, cannot trim peptide bonds involving proline. ERAPs can destroy the putative HLA class I ligands by reducing the length of antigenic peptides below

Table 1. *Experimental evidence of the relationship between HLA class I and endometriosis*

	Objective	Methods	Results	References
1	To investigate whether HLA-G polymorphisms may influence susceptibility to endometriosis and its progression	- PCR-RFLP - Allelic discrimination methods with TaqMan SNP Genotyping Assays	- The HLA-G rs1632947:GG genotype was associated with protection against the disease and its severe stages - HLA-G rs1233334:CT protected against progression	Bylińska et al. (2018)
2	To investigate an association between HLA-C genotype and the occurrence of endometriosis	- Sequence-based typing method	- The occurrence of HLA-C*03:03*01 was increased in endometriosis than in control groups	Chou et al. (2020)
3	To study the association between HLA genotypes and endometriosis	- PCR-MPH method	- Significant positive association with endometriosis was observed for HLA-B7	Kitawaki et al. (2002)
4	To evaluate the sHLA-G levels in the blood sera of women with deep endometriosis and ovarian endometrioma throughout the menstrual cycle and to compare with the levels of sHLA-G in the blood sera of women with ovarian cancer	- ELISA test	- The level of sHLA-G concentration in the blood serum of patients with deep endometriosis fluctuates throughout the menstrual cycle, and during the proliferative and secretory phases, it remains at a high level comparable to that found in patients with ovarian cancer	Mach et al. (2010)
5	To assess whether the HLA-G is involved in the pathophysiology of endometriosis or disease progression	- ELISA test - Immunohistochemistry assays	- Higher concentrations of sHLA-G in the serum but not in the peritoneal fluid were observed in women with advanced endometriosis compared to the control group - *In situ*, expression of HLA-G protein was also higher in ectopic but not in eutopic endometrium of women with advanced endometriosis compared to the control group	Rached et al. (2019)
6	To assess whether HLA class I expression on eutopic and ectopic endometrial cells modifies susceptibility to lymphocyte-mediated lysis	- Immunofluorescence - Flow cytometry	- The HLA-B7 allele inhibits the cytotoxic activity, suggesting that the growth of ectopic endometrial cells might be under a genetic control	Semino et al. (1995)
7	To compare the expression of HLA class I in endometrial samples from patients with and without endometriosis	- Immunohistochemical assays	- A significantly higher expression of HLA I in the endometriosis group than in controls, both in the glandular cells and in the stromal cells, was observed	Vernet-Tomás et al. (2006)
8	To explore the role of DNA methylation in endometriosis	- Direct bisulfite sequencing - qRT-PCR	- DNA hypermethylation in the intron VII of the HLA-C*07 gene appears to regulate the expression of HLA-C*07 - The aberrant DNA methylation in this region was positively correlated with the occurrence of endometriosis	Zhao et al. (2023)

DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; HLA, human leukocyte antigen class I; HLA-C, HLA-G, PCR-MPH, polymerase chain reaction-based microtiter plate hybridization; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; qRT-PCR, quantitative reverse transcription polymerase chain reaction; sHLA-G, soluble HLA-G; SNP, single nucleotide polymorphism.

the threshold of 8–10 amino acids when they are overactive. A study by Saveanu et al. (2005) indicated that ERAP1 and ERAP2 were colocalized *in vivo* and linked in complexes. This implies a concerted peptide trimming by the ERAP1 and ERAP2 complexes in the ER. On the other hand, the loss of both enzymes is a frequent event significantly associated with the lack of HLA class I surface expression (Hammer et al. 2007).

ERAP1/ERAP2 protein expression is detected in many tissues and is induced by type I and type II interferons (IFNs) and TNF-α, suggesting that they are essential for immune control (Saric et al. 2002; Lee 2017).

The human *ERAP1* and *ERAP2* genes are located on chromosome 5q15 in opposite orientations (Lee 2017). Both genes are polymorphic with strong linkage disequilibrium (LD) across the chromosome 5q15 locus, and many functional variants appear to affect their enzymatic activity and the expression level or both. *ERAP1* variants are complex allotypes including multiple nonsynonymous single nucleotide polymorphisms (SNPs), known as haplotypes. Ten *ERAP1* haplotypes (Hap1 to Hap10) account for over 99% of the *ERAP1* variants in human populations (Reeves et al. 2013; Ombrello et al. 2015). Polymorphic amino acids are located near the catalytic site (residues 346, 349), in the peptide-binding site (residues 725 and 730) or in the interdomain regions or other locations that can affect the conformational changes associated with enzymatic activity (residues 528 and 575). Therefore, these polymorphisms may influence ERAP1 activity in multiple ways (Hanson et al. 2018; López de Castro 2018).

In contrast to *ERAP1*, nonsynonymous changes affecting the amino acid sequence of *ERAP2* seem to be limited. The polymorphism rs2549782 coding for the K392N (Lys392Asp) change affects the ERAP2 activity. The N392

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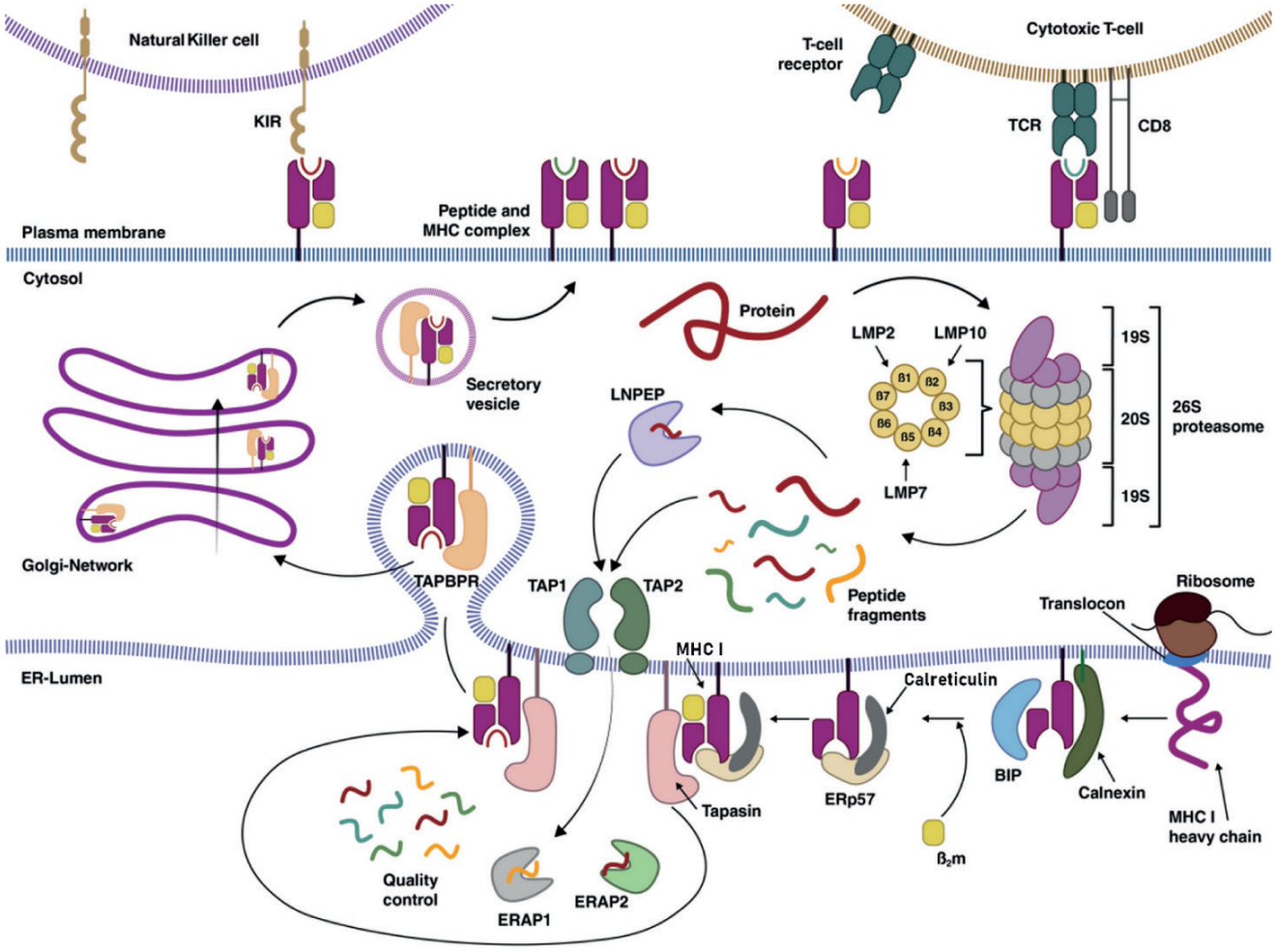

Fig 1. *The antigen-processing pathway via MHC-I. De novo synthesized MHC-I heavy chain associates with the BIP and calnexin and then binds to β2m. Calnexin is replaced by its soluble counterpart, calreticulin, and this complex is linked by the disulfide isomerase ERp57. Tapasin bridges this MHC-I complex to TAP (Thomas and Tampé 2017). During the immune response, new subunits with increased activity of LMP2, LMP7, and LMP10 are formed under the influence of cytokines (Ferrington and Gregerson 2012; Leone et al. 2013). After protein degradation by the immunoproteasome in the cytosol, peptide fragments are transferred to the lumen of the ER (ER-Lumen) by transporters TAP1 and TAP2 (Thomas and Tampé 2017), where they are trimmed by heterodimeric aminopeptidases ERAP1 and ERAP2 (Lankat-Buttgereit and Tampé 2002; Evnouchidou et al. 2014; López de Castro 2018; Evnouchidou and van Endert 2019). Peptides can also be trimmed by the LNPEP aminopeptidase in the cytosol (Saveanu et al. 2009; Segura et al. 2009; Weimershaus et al. 2012; Agrawal and Brown 2014). Peptide/MHC-I complexes can leave the multicomponent PLC with the assistance of TAPBPR (McShan et al. 2022) and finally are transferred via the Golgi-Network to the cell surface. Their antigenic cargo is inspected by cytotoxic T cells (Scholz and Tampé 2005; Trowitzsch and Tampé 2020) and NK cells (Lee 2017; Compagnone et al. 2019) (created by Adobe Illustrator). β2m, β2-microglobulin; BIP, binding immunoglobulin protein; CD8; ER, endoplasmic reticulum; ERAP, endoplasmic reticulum aminopeptidases; ERp57; LMP, low molecular weight protein; LNPEP, leucyl and cystinyl aminopeptidase; MHC-I, major histocompatibility complex I; NK, natural killer; PLC, peptide-loading complex; TAP, transporters associated with antigen processing; TAPBPR, TAP-binding protein-related; TCR, T cell receptor.*

allele is in LD with the G allele of rs2248374 (allotype B), a polymorphism that favors nonsense-mediated RNA decay and impairs protein expression (Andrés et al. 2010). As a result, only the K392 variant (allotype A—rs2248374A) is expressed in most populations (Evnouchidou et al. 2012). Because both alleles of rs2248374 occur with a similar frequency in the population due to balancing selection, about 25% of individuals fail to express ERAP2. However, ERAP2 short protein isoforms of unknown function were detected in virus-infected rs2248374 GG individuals (Ye et al. 2018; Saulle et al. 2020). It should be noted that homozygotes from the B allotype have reduced levels of MHC class I expression on B cell surfaces (Andrés et al. 2010). This indicates that the rs2248374 polymorphism in the *ERAP2* gene influences the expression of MHC class I on the cells of the immune system. Moreover, Lospinoso et al. (2021) found that the ERAP2-asparagine (N) isoform, expressed in the trophoblast cell line JEG-3, significantly activates the

immune cells for killing by both cytotoxic T cells and NK cells, which may determine the success of pregnancy.

Other polymorphisms, such as rs10044354, or SNPs in strong LD with it, may influence the expression of ERAP2 (Kuiper et al. 2014). A polymorphism located in the *ERAP2* promoter region, rs7586269, was associated with opposite changes in the expression of ERAP1 and ERAP2 so that decreased expression of ERAP2 correlated with increased ERAP1 expression, suggesting a concerted regulation of the expression of both genes by this SNP (Paladini et al. 2018).

ERAP1 and *ERAP2* polymorphisms and expression induce significant changes in multiple MHC-I-bound peptidomes. These changes are MHC allotype-specific and reflect the separate roles in their processing of the MHC-I ligands (López de Castro 2018). Perhaps the polymorphism of these genes influencing the expression of proteins, their activity, and substrate specificity may be related to a predisposition to endometriosis. The inability to form the correct HLA class I complexes with the appropriate peptides may result in a lack of immune response by $CD8^+$ lymphocytes and NK cells, contributing to the attachment of the ectopic endometrium to various sites of female organs. To date, there are no studies on *ERAP* polymorphism and expression in ectopic endometrium tissues such as the peritoneum, ovaries, and fallopian tubes. Therefore, it remains unclear whether this variation influences disease development, its association with the location of endometriotic lesions, and, subsequently, its connection to disease severity. The only pregnancy-related disease in which the role of ERAP has been studied is preeclampsia (PE). Xu et al. (2020) revealed that ERAP1 expression was significantly elevated in placental tissues of PE, and hypoxia increased ERAP1 expression in trophoblast. Moreover, ERAP2 is also a good candidate to contribute to the development of PE and other pregnancy-related diseases because of its involvement in the regulation of the immune response, pro-inflammatory cytokine production, and blood pressure. The fetal *ERAP2* SNP rs2549782 genotype was associated with a higher risk for PE in African American women (Vanhille et al. 2013). A study by Seamon et al. (2020) revealed that the ERAP1 protein was upregulated in the first-trimester placentae in comparison to placentae at delivery from both normotensive and PE women. In turn, ERAP2 protein expression was similar in normotensive women at delivery compared to expression in the first trimester. Our research also indicated the role of *ERAP1* and *ERAP2* gene polymorphisms in recurrent implantation failure following *in vitro* fertilization (Piekarska et al. 2022) and in recurrent miscarriage following natural conception (Wilczyńska et al. 2019). Moreover, an increased level of plasma ERAP2 protein was associated with miscarriage after *in vitro* fertilization (Piekarska et al. 2021). It should be noted that a large group of these patients were women suffering from endometriosis.

It is quite intriguing that the aminopeptidases ERAP1 and ERAP2 that reside in the ER are released into the peripheral blood. Moreover, studies are demonstrating their ability to trim receptors for pro-inflammatory cytokines such as TNF-α and the type I IL-6 cytokine receptor (IL-6Rα), and the type II IL-1 decoy receptor (IL-1RII) (Cui et al. 2003a,b). Cui et al. (2002) found that ERAP1 can bind to the extracellular domain of the tumor necrosis factor receptor-1 (TNFR1), facilitating its shedding via the formation of a TNFR1/ERAP1 complex. The authors observed that overexpression of ERAP1 causes a production of soluble TNFR1, which competes with TNF receptors on the cell surface, hence attenuating TNF-α bioactivity when ERAP1 levels are increased and restoring TNF-α when levels decrease. TNF receptor shedding may also decrease the number of cell-surface receptors accessible for ligand binding. Therefore, it can be assumed that overexpression of ERAP1 may attenuate the inflammation. Furthermore, reports are showing a multifunctional role for ERAP1 and ERAP2. ERAPs participate in many biological processes including post-natal angiogenesis and regulation of blood pressure (Cifaldi et al. 2012). ERAP1 and ERAP2 cleave Angiotensin II (Ang II) into Ang III and IV (Mattorre et al. 2022).

2.2. LNPEP

LNPEP (known also as Insulin-Regulated membrane Aminopeptidase [IRAP], and Placental Leucine Aminopeptidase [PLAP], and Angiotensinogen receptor 4 [ATR4]), with broad tissue distribution, is another aminopeptidase whose role in the pathomechanism of endometriosis has not yet been elucidated. The aminopeptidase is found both in the cytosol and endosomes, where it cleaves proteins before cysteine, leucine, and various other amino acids. Due to an additional N-terminal cytoplasmic domain, LNPEP is retained in the endosomal vesicles from where it can migrate to the cell membrane forming a type II integral membrane glycoprotein. LNPEP co-segregates with the insulin-responsive glucose transporter type 4 (GLUT4) transporter in storage vesicles that traffic to and from the plasma membrane in insulin-responsive cells (Summers et al. 1999; Descamps et al. 2020). LNPEP, located in the membrane, catalyzes the final step of converting angiotensinogen to angiotensin IV. It is also known as the AT4 receptor and is expressed in the human brain, as well as in the heart, kidneys, adrenal glands, and blood vessels. LNPEP has a positive influence on blood flow, neuroprotection, synaptogenesis, long-term potentiation, and memory consolidation and retrieval. LNPEP is also an essential component in the rennin–angiotensin system (Mattorre et al. 2022). LNPEP can be secreted in soluble form in maternal serum during normal pregnancy and plays a role in maintaining homeostasis during pregnancy. LNPEP expression has also been demonstrated by placental cells

in pregnancy. It increases progressively with gestational age and, as oxytocinase, is involved in the induction or inhibition of pain during labor (Nonn et al. 2021). LNPEP degrades other peptide hormones, such as vasopressin and angiotensin III (Paladini et al. 2020). Additionally, it is engaged in the generation of antigenic peptides for cross-presentation in endosomal compartments in MHC class I antigen processing (Saveanu et al. 2009; Segura et al. 2009; Weimershaus et al. 2012; Agrawal and Brown 2014).

The *LNPEP* gene consists of 18 exons (17 introns) on chromosome 5q15 and has two major transcript variants. The LNPEP rs4869317 T/A SNP (located in the intron 1 of the transcript variant 1, RefSeq NM_005575.3) was found to be associated with vasopressinase activity (Nakada et al. 2011). The A609T SNP interacts with the hinge domain III of IRAP. This SNP reduces the enzyme's activity by almost half (Mpakali et al. 2015).

2.3. Tapasin (TAP binding protein, Tsn)

Tapasin is a V-C1 (variable-constant) immunoglobulin superfamily (IgSF) molecule that links MHC class I molecules to the TAP in the ER. Tsn stabilizes the structure of peptide–MHC-I and promotes the dissociation of low-affinity peptides. Tapasin thus functions as an MHC-I-specific peptide editor or peptide proofreader (Tan et al. 2002; Praveen et al. 2010; Thomas and Tampé 2017, 2019; Margulies et al. 2020). It has up to four MHC class I complexes, and tapasin can bind to a single TAP molecule. This protein contains a C-terminal double lysine motif (KKAE), which is known to maintain membrane proteins in the ER. It has been found that substitutions at position K408 in the transmembrane/cytoplasmic domain of the tapasin affected the expression of MHC class I molecules at the cell surface and downregulated tapasin stabilization of TAP (Petersen et al. 2005).

Tapasin is encoded by the *TAPBP* gene, located near the MHC at 6p21.3. Alternative splicing results in transcript variants encoding different isoforms (Belicha-Villanueva et al. 2010). Among the SNPs in this gene, it would be worth examining rs3106189 C/T [5'UTR], rs1059288 A/G on 3'UTR, or rs2071888 C/G [T260R]. The first SNP, located in the promoter of the gene among the binding sites for several transcription factors, including interferon regulatory transcription factor (IRF)-1, IRF-2, and IRF-7, could influence its expression level (Shao et al. 2013). The second SNP in 3'UTR might influence microRNA (miRNA) binding. However, rs2071888 C/G (T260R) on exon 4 is in absolute LD with rs1059288 T > C on 3'UTR (Cho et al. 2013).

2.4. TAPBPR—TAP-binding protein-related

Over 20 years ago, a gene encoding a Tsn homolog called TAPBPR was discovered that is highly conserved among vertebrates. TAPBPR is an MHC-I dedicated binding protein and has a role in facilitating high-affinity epitope selection and peptide loading in the antigen presentation pathway (Teng et al. 2002; McShan et al. 2022). This protein functions as a second MHC-I-specific chaperone and peptide proofreader. As is already known, a crucial element of MHC-I antigen presentation is the so-called PLC. It is a multisubunit machinery containing an MHC-I-specific chaperone Tsn and TAP. TAPBPR is interferon-γ (IFN-γ)-inducible (like tapasin), recognizes peptide-receptive MHC-I in the ER, and thus catalyzes peptide proofreading, which changes the order of peptides presented on MHC-I on the cell surface. Although TAPBPR has a distinct allomorphic specificity and is independent of PLC, it is thought to share a common catalytic mechanism with Tsn (Thomas and Tampé 2017). The encoded TAPBPR protein—similarly to tapasin—is composed of a signal sequence and three extracellular domains, which include a unique membrane-distal domain, an IgSF V domain and an IgC1 domain, a transmembrane domain, and a cytoplasmatic region (Teng et al. 2002). TAPBPR is now included as a new component of MHC-I antigen presentation but was initially identified with a gene locus that encoded 22% sequence identity with tapasin. TAPBPR interacts with uridine diphosphate (UDP)-glucose: glycoprotein glucosyltransferase 1 (UGGT1), which means it is directly connected to the calreticulin/calnexin cycle. Furthermore, TAPBPR uses a β-hairpin motif that recognizes the peptide-binding status. The β-hairpin, often referred to as the "jack-hairpin," is situated beneath the floor of the MHC-I peptide-binding groove. Furthermore, it interacts with a conserved residue in β2m, the conformation of which is influenced by the occupancy of MHC-I peptides (Trowitzsch and Tampé 2020).

The human *TAPBPR* gene is located at chromosome position 12p13.3 next to the paralogous *MHC* locus, between the *CD27* and *VAMP1* genes. The *TAPBPR* gene consists of 7 exons and spans 10 kb. Similar to *TAPBP*, *TAPBPR* also possesses TATA and CAATT boxes in its promoter region (Teng et al. 2002). Polymorphisms in MHC class I molecules themselves, as well as in specific components, have a very strong impact on individual disease susceptibility. Thus, it can be speculated that it contributes to the control of pathogens including primarily viral infections. In addition, it may influence the immune system's recognition of tumors. It is interesting to note that there is a strong association between TAPBPR expression and survival of patients with glioblastoma multiform (Hermann et al. 2015).

2.5. TAP

TAP is a 150-kDa heterodimeric protein complex (TAP1 and TAP2) and a member of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of transporters. TAP forms a transmembrane pore in the ER membrane.

The opening and closing of these pores depend on ATP binding and hydrolysis. In the ER, together with other elements, it forms a PLC that directs the loading of high-affinity peptides onto nascent MHC-I molecules (Lehnert and Tampé 2017). TAP also plays a pivotal role in transporting peptides into phagosomes and endosomes during cross-presentation in dendritic cells (Mantel et al. 2022). Therefore, TAP constitutes a major component in the adaptive immune response against virally or malignantly transformed cells (Leone et al. 2013; Verweij et al. 2015). TAP was found in all nucleated cells of jawed vertebrates (Lehnert and Tampé 2017).

TAP protein is encoded at chromosomal location 6p21.32 in the MHC class II region between the DQB1 and DPA1 loci (McCluskey et al. 2004). Both TAP1 and TAP2 transcription is upregulated by interferon-β (IFN-β), IFN-γ, and TNF-α (Elliott 1997). A deletion or mutation in the *TAP* gene severely affects the translocation of peptides to the ER. Therefore, several genetic and protein variants of TAP1 and TAP2 have been associated with autoimmune diseases, cancers, and infections (Lankat-Buttgereit and Tampé 2002; Leone et al. 2013; Qian et al. 2017; Tabassum et al. 2021). So far, no literature data describes the role of TAP proteins and their genetic polymorphism in endometriosis. Twelve alleles of *TAP1* and *TAP2* have been named by the HLA Nomenclature Committee (http://hla.alleles.org/alleles/classo.html) (Robinson et al. 2015). The functional consequences of the non-synonymous variants rs1057141 (I393V) in *TAP1* and rs1800454 (V379I) in *TAP2* are unknown. In contrast to this, rs241447 (T665A) present in exon 11 of TAP2 seems to be functionally relevant. One study reported that rs241447 could influence the relative proportion of alternative splicing isoforms of TAP2 differing in efficiency and specificity of transport of different peptides. Interestingly, rs241447 is in complete LD (at least in Caucasians) with the other SNP—rs241456 located in the 3'UTR of the *TAP2* gene. According to *in vitro* studies, this SNP participates in the creation of a potential binding site for hsa-miR-1270 and therefore suppresses TAP2 production in an allelic-specific manner (Wiśniewski et al. 2020).

2.6. Immunoproteasome LMPs

The proteasome is a multicatalytic proteinase complex with a highly ordered ring-shaped 20S core structure. Proteasomes cleave peptides in an ATP/ubiquitin-dependent process in a non-lysosomal pathway. Among the different types of proteasomes, the immunoproteasome has the function of processing MHC class I peptides (Fricker 2020). There are three catalytic subunits within the immunoproteasome: LMP2, LMP7, and the multicatalytic endopeptidase complex subunit-1 (MECL-1 also called LMP10) responsible for the processing of proteins to peptides. The LMP2 and LMP7 subunits perform chymotrypsin-like activity and cleave at hydrophobic amino acids. LMP10 exhibits trypsin-like activity (Ferrington and Gregerson 2012; Leone et al. 2013). They are induced in the majority of cells by stimulation with IFN-γ, under conditions of oxidative or inflammatory stress (Heink et al. 2005; Shin et al. 2006; Morozov and Karpov 2018). The immunoproteasome produces a different range of peptides than the standard proteasome (Fricker 2020).

The genes encoding LMP2—*PSMB9* and LMP7—*PSMB8* are located in the MHC class II region on chromosome 6. There are two reported isoforms. These proteins have been shown to have cytoplasmic and nuclear cellular localization. The gene *PSMB10* for LMP10 is found outside the MHC class II region on chromosome 16 and is expressed as a single copy. One of the SNPs worth testing is rs17587 A/G

Table 2. *Elements of antigen processing machinery in the context of MHC I (in alphabetical order)*

	Component	Full name	Function	References
1	ERAP1 and ERAP2	Endoplasmic Reticulum Aminopeptidase 1 and 2	Trimming the antigenic peptides in the endoplasmic reticulum	Evnouchidou et al. (2014) and Evnouchidou and van Endert (2019)
2	LMP2, LMP7 and LMP10	Immunoproteasome Low Molecular Weight Proteins 2, 7, and 10	Processing of proteins to peptides in the cytosol	Ferrington and Gregerson (2012) and Leone et al. (2013)
3	LNPEP	Leucyl and Cystinyl Aminopeptidase	Trimming peptides in the cytosol	Agrawal and Brown (2014) and Segura et al. (2009)
4	MHC I	Major Histocompatibility Complex I	Presenting antigens to immune cells on the cell surface	Trowitzsch and Tampé (2020)
5	Tsn	Tapasin	Bridging the MHC I complex to transporters associated with antigen processing (TAP)	Thomas and Tampé (2017)
6	TAPBPR	TAP-Binding Protein-Related	Facilitating high-affinity epitope selection and peptide loading in the antigen presentation pathway	McShan et al. (2022) and Teng et al. (2002)
7	TAP1 and TAP2	Transporter associated with Antigen Processing 1 and 2	Transporting peptide precursors into the endoplasmic reticulum	Evnouchidou et al. (2014) and Evnouchidou and van Endert (2019)

[R60H] in exon 3 in the LMP2 protein, which can have a significant impact on immunoproteasome function (Ferrington and Gregerson 2012). It was found that MECL-1 and LMP7 deficiency resulted in reduced MHC class I expression in virus-infected mice (van Helden et al. 2011).
Table 2 summarizes information regarding the molecules involved in antigen processing.

3. Concluding Remarks

Genetic and protein changes in components engaged in antigen processing may constitute potential sites for targeting the development of many diseases. Moreover, pharmacological regulation of the activity of individual elements in the antigen-processing pathway through MHC-I is a promising way to modulate the acquired immune response, with possible applications in combating autoimmune diseases, enhancing the immune response to pathogens, and in immunotherapy of cancer, and also in the treatment of endometriosis. Inhibition of human aminopeptidases has already been identified as a potential approach to therapy of different types of cancer and nonmalignant diseases (Zervoudi et al. 2013; Hanson et al. 2019; Paldino and Fierabracci 2023).

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Competing interests

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Author's contribution statements

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