

Shared Biology Underlying Benign Endometrial Diseases and Endometrial Cancer: Current Knowledge and Future Prospectives

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Abstract

The endometrium is thought to serve as the precursor tissue for diseases of the uterus such as endometrial cancer, adenomyosis, and endometriosis. More specifically, endometrial glands are proposed to be the source of developing endometrial cancer within the uterine body while ectopic endometrial glands and surrounding stroma which develop within the myometrium give rise to adenomyosis, and those that establish outside of the uterus give rise to endometriosis. While adenomyosis and endometriosis are benign diseases, they do share several cellular characteristics with endometrial cancer including enhanced cell survival/proliferation, migration and invasion. Further, the pathophysiology of these diseases is driven by unopposed estrogen and each exhibit various degrees of progesterone resistance and altered downstream expression and/or function of genes relevant to epithelial-to-mesenchymal transition, tissue remodeling and transcriptional signaling. In this review we summarize our current understanding on differences and similarities in major cell signaling pathways among endometrial cancer, adenomyosis and endometriosis. In closing, we emphasize the necessity for additional studies to delve deeper into common attributes in the pathophysiology of these diseases towards the goal of identifying novel, non-hormonal therapies for their treatment.

Keywords: Endometrial cancer, Adenomyosis, Endometriosis, Protease, Protease inhibitor, Tissue remodeling, Epithelial-to-mesenchymal transition, Steroid receptor, Transcription factor

Introduction

The uterus is an essential female organ required for the propagation of all mammalian species. The uterus is composed of two major tissue layers, the endometrium, which is the inner layer as is further classified as the functionalis or basalis layer whose major functions are to provide the site of attachment of implanting embryos and to give rise to a new functionalis layer with regeneration of the endometrial lining which occurs with each menstrual cycle. The myometrium is the muscular tissue component of the uterus which is critical for contractions during labor and delivery. The endometrial lining is composed of three major cell types, the endometrial luminal epithelial cells, the glandular epithelial cells and the stromal cells. Endometrial cancer [1,2] develops when endometrial glands become hyperplastic and invasive

developing first within the endometrium (**Stage IA; Figure 1**) and then spreading to the underlying myometrium (**Stage IB; Figure 1**) with both limited to the uterine body. Stage II tumors typically invade into cervical stromal connective tissue, but without invading beyond the uterus, while stage III tumors may invade local or regional structures beyond the uterus including the lymph nodes. Adenomyosis is defined as growth of endometrial epithelial glands and surrounding stroma which develop within the myometrium (**Figure 1**) while endometriosis is composed of both glands and stroma which develop ectopically in the pelvic cavity (**Figure 1**). In the case of endometriosis, these lesions can develop throughout the pelvic cavity with the majority of lesions developing on the ovary, the peritoneal lining and in the cul-de-sac. Endometrial cancer cells, adenomyotic epithelial and stromal cells and endometriotic epithelial and stromal cells all exhibit

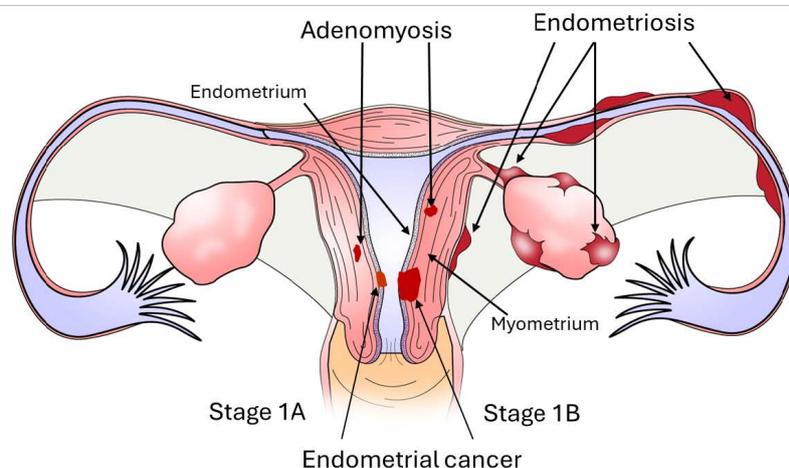


Figure 1. Graphic depiction of endometrial cancer, adenomyosis, and endometriosis localization within the female reproductive tract.

characteristics of enhanced estrogen signaling and reduced progesterone action including augmented cell proliferation, migration and invasion. Key players in the pathophysiology include the sex steroid receptors, mediators of epithelial-to-mesenchymal transition (which contribute to cell migration and invasion), proteases and protease inhibitors and transcription factors. In the following paragraphs, we examine the expression of steroid receptors, epithelial-mesenchymal transition proteins, proteases, protease inhibitors, and transcription factors among these three endometrial diseases. To do so, we evaluated the literature through a search of the PUBMED/MEDLINE database. Search terms included publications with “endometrial cancer”, “adenomyosis” and “endometriosis” in the title. Each disease was separately assessed in conjunction (and) with “steroid receptor”, or “epithelial-mesenchymal-transition”, or “protease”/“protease inhibitor” or “transcription factor” in the article title.

Steroid Receptors Expression in Malignant and Benign Endometrial Diseases

Endometrial cancer

Both the level of expression and cellular localization of the steroid receptors, estrogen receptor and progesterone receptor are critical for normal responses of the endometrium to the sex hormones estrogen and progesterone, respectively [3]. Estrogen receptor (ER) is known for its role in increasing cell proliferation during the proliferative phase of the female menstrual cycle, while progesterone receptor (PR) is known to block estrogen-induced proliferation of endometrial glands and promote stromal cell proliferation and differentiation.

However, these steroid receptors have differing patterns of expression in endometrial cancer and diseases of the uterus [4–6]. A systematic review and meta-analysis by Zhang and colleagues [5] strongly support the notion that in subjects with endometrial cancer there is an inverse relationship between the levels of ER and PR and survival. More recently, a collaborative study by a European Network for Individualized Treatment of Endometrial Cancer [6], identified distinct clinical outcomes based upon level of ER and PR expression level. Cutoff values of 0–10% ER/PR positive was associated with unfavorable outcomes, 20–80% was associated with intermediate outcomes (defined as) while 90–100% was associated with favorable outcomes. Di Nezza and colleagues further explore how reduced PR expression may impact the pathophysiology of EC. In this study they discovered that progesterone inhibits the expression of matrix metalloproteinases (MMPs), thus suppressing mechanisms such as extracellular matrix degradation and the processing of growth factors and cytokines that aid and promote cancer cells to invade [7]. Fujimoto and colleagues observed a decrease in the mRNA levels of ER- α and ER- β , and an upregulation in ERR α in relation to clinical stage, myometrial invasion, and dedifferentiation (**Table 1**) [8]. On the other hand, some studies postulate that in cancer patients who are obese, there is an upregulation of steroid receptors. This signifies a possible link between the two. For example, patients with positive PR expression were most often young and obese [9], and additionally, those who were obese had a higher probability of having an ER or PR-positive tumor [10]. From these studies it is clear that low ER and PR expression is associated with advanced endometrial cancer and poor outcomes.

Table 1. Steroid receptors in endometrial cancer.

Steroid Receptor	Expression	References
ER- β	Downregulated in EC	[8]
ER- α	Downregulated in EC	[8]
ERR- α	Upregulated in EC	[8]
ER	Inverse relationship between ER and survival Higher in obese patients	[5] [9,10]
PR	Inverse relationship between PR and survival Inhibits MMPs, suppresses growth factors and extracellular matrix degradation Higher in obese patients	[5] [7] [9,10]

Adenomyosis

Compared to EC, there is limited information on ER and PR expression in adenomyosis as well as inconsistencies between findings regarding steroid receptor expression in adenomyosis. For example, Tamaya and colleagues evaluated steroid receptor levels in ten cases of adenomyosis utilizing Scatchard plot analysis [11]. It was found that the expression of both ER and androgen receptor (AR) was detected in each case, while PR was not detected in the majority of cases. Similarly, using tissue microarray and dendrogram cluster analysis, Jian-Jun Wei and colleagues found that the larger the tumor size, the more downregulated ER and PR expression was [12]. A morphometric investigation and evaluation of cytokeratin, vimentin, and steroid receptor content was conducted by Donnez and colleagues to compare what they initially thought to be endometriotic nodules of the rectovaginal septum with peritoneal endometriosis [13]. By the end of the study, a new type of adenomyoma was categorized, specifically rectovaginal adenomyoma, and their results demonstrated that the expression of ER and PR content in this type of lesion was significantly lower compared to eutopic endometrium tissue [13].

In contrast to other studies, Maria Sztachelska and colleagues, in a study in which the function and expression of ER and PR

were evaluated confirmed the presence of ER and PR at both gene and protein levels and an upregulation of membrane progesterone receptors α and β [14]. Another study found that ER β expression was significantly high in adenomyotic lesions but declined with increasing lesional fibrosis, while there was no significant difference in ER α expression in comparison to control tissues. They determined that with increased fibrosis in ectopic endometrium, estrogen signaling decreases [15]. Mehaseb and colleagues detected reduced levels of ER- α in eutopic and ectopic (adenomyosis) endometrium in subjects with adenomyosis compared to those without, while ER- β expression was increased in adenomyotic functionalis glands during the proliferative phase. Similar to ER- α expression, PR-A and PR-B expression in the basalis stroma, and inner and outer myometrium were reduced compared to controls [16] (Table 2).

Endometriosis

A Scatchard plot analysis was utilized by Tamaya and colleagues to determine the expression levels of steroid receptors in endometriosis [11]. In comparison to normal endometrium tissue, the ER and PR levels were lower in endometriosis tissues. An immunohistochemical analysis carried out by Nisolle and colleagues assessed the differences in proliferative activity throughout the menstrual cycle

Table 2. Steroid receptors in adenomyosis.

Steroid Receptor	Expression	References
ER	While its expression has been detected, it is decreased in adenomyoma comparison to eutopic tissue.	[11–13,15]
ER- α	Reduced levels in eutopic and ectopic endometrium	[16]
ER β	Decreased expression as lesional fibrosis increases Elevated expression during proliferative phase	[15] [16]
PR	While its expression has been detected, it is decreased in adenomyoma comparison to eutopic tissue. Downregulation detected	[12,13] [16]
mPR α	Upregulated in adenomyosis	[14]

between eutopic and ectopic endometrium [17]. It was observed that while the eutopic endometrium was not proliferatively active during the late secretory phase, the ectopic endometrium was, and instead of decreasing, PR expression in the glandular epithelium and ER expression in the glandular epithelium and stroma stayed consistent (**Table 3**). A study by Pluchino and colleagues using tissue microarray and immunohistochemistry demonstrated that in endometriosis, ER- α , PR, AR, and aromatase were expressed [18]. Specifically, as the severity of the symptoms experienced by patients was evaluated, it was determined that ER- α was linked to the differences in severity, with higher levels being more severe. Fazleabas and colleagues discovered through RT-PCR and immunocytochemistry that while PR and ER- α were expressed in both eutopic and ectopic endometrium, ER- β was only found in ectopic endometriotic lesions, thus signifying its upregulation in the disease [19]. Aromatase was additionally detected, but specifically ten months after the baboons were inoculated with menstrual endometrium to induce experimental endometriosis. In a study that examined both the expression of ER- α and ER- β , low expression levels of ER- α , and higher levels of expression of ER- β were observed [20]. The expression of steroid receptor coactivators has been found to differ between eutopic and ectopic tissue samples as well.

Epithelial-to-Mesenchymal Transition (EMT) Proteins in Malignant and Benign Endometrial Diseases

Endometrial cancer

Epithelial-mesenchymal transition (EMT) induces the spread of many diseases and cancers, including endometrial cancer (EC). EMT occurs when the epithelial cells transform into mesenchymal cells as they gain migratory and invasive characteristics [21]. The cells lose their cell polarity and cell-to-cell adhesion. E-cadherin (CDH1), a protein that regulates cellular signaling and tumor suppression, is a biomarker of EMT. In general, it is downregulated in EMT. Zhou and colleagues observed that a high expression of E-cadherin in EC, which was caused by an upregulation of SOX17, is linked to a better prognosis (**Table 4**) [22]. As mentioned earlier, ZEB1, or Zinc finger E-box binding homeobox 1 (ZEB1) is a transcription factor linked to EMT. Xiao and colleagues silenced ZEB1 and observed that this decreased cell migration and invasion [23]. They also found that the β -catenin/TCF4 signaling feedback stimulated ZEB1 transcription. ZEB2, along with SLUG, are overexpressed in EC, and act as predictors of higher FIGO stages [24]. In one study, it was found that bone morphogenetic protein 2 (BMP2) induced EMT by activating

Table 3. Role of steroid receptors in endometriosis.

Steroid Receptor	Expression	References
ER	Lower expression in endometriotic tissue.	[11]
	Instead of decreasing during the late secretory phase, levels remained constant	[17]
PR	Lower expression in endometriotic tissue	[11]
	Instead of decreasing during the late secretory phase, levels remained constant	[17]
ER- α	The higher its expression, the more severe the disease	[18]
	Lower expression	[20]
ER- β	Upregulated in endometriosis	[19,20]

Table 4. EMT proteins in endometrial cancer.

EMT Proteins	Expression	References
E-cadherin	Higher expression is linked to a better prognosis	[22]
	When migration was inhibited, its expression increased	
ZEB1	Induces EMT	[23]
ZEB2	Higher expression linked to higher FIGO stages	[24]
Snail	Linked to a worse prognosis	[26]
SLUG	Higher expression linked to higher FIGO stages	[24]
BMP2	Triggers EMT by SLUG or SNAIL	[25]
Piwil1	Causes an increase in mesenchymal markers and suppresses E-cadherin	[27]

factors such as SLUG or SNAIL [25]. Snail has been linked to a worse prognosis for EC [26]. Pivwil1 is an oncogene-like stem cell protein that is upregulated in EC. Chen and colleagues were able to determine that Pivwil1 has a role in increasing mesenchymal markers and suppressing E-cadherin, which results in an EMT-like phenotype [27].

Adenomyosis

In a study by Zheng and colleagues in which the role of focal adhesion kinase (FAK) was evaluated, they determined that it is upregulated in adenomyosis and may regulate the EMT through the FAK/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway (Table 5) [28]. Many studies have discovered a link between E-cadherin and EMT in adenomyosis. When decreased, migration and invasion are induced [29]. N-cadherin, on the other hand, is found to be upregulated in adenomyosis, specifically when EMT is induced, which is why it is considered a characterization of a mesenchymal phenotype [29,30]. More specifically, Yoo and colleagues proposed that β -catenin activates TGF- β induced EMT, as there was a strong correlation between β -catenin and TGF- β 2 in women with this disease [31]. Overall, β -catenin activity promotes EMT in adenomyosis. High activity levels of Notch1, a transmembrane receptor in which its signaling pathway regulates cellular signaling, were observed by Bourdon and associates in adenomyosis-induced mice. As Notch1 activation correlated with elevated levels of immune and EMT markers, including E-cadherin, Vimentin, Tgf β , Snail1, and Slug, Snail3, it was concluded that Notch1 activation corresponds with the atypical expression of these markers in the progression of adenomyosis [32]. SPARC-related modular calcium binding 2 (SMOC2) is an extracellular matrix-associated protein. Its overexpression results in the upregulation of N-cadherin and alpha-SMA – another mesenchymal marker – as well as

the downregulation of E-cadherin. This suggests that SMOC2 promotes EMT [33]. Hu and colleagues aimed to determine the role of transmembrane glycoprotein neuropilin 1 (NRP1) in EMT by infecting endometrial cells with NRP1 retroviruses so as to upregulate NRP1. A mesenchymal phenotype, downregulation of E-cadherin, upregulation of alpha-SMA and N-cadherin, and enhanced migration were observed. In contrast, NRP1 shRNA inhibited EMT. This signifies its possible role in the EMT and the progression of adenomyosis [34]. Similar to endometrial cancer, several EMT proteins are misexpressed in adenomyosis. ZEB1 is elevated in endometrial adenomyosis tissue, and its upregulation is modulated by SKP1 and SKP2 [35] in eutopic adenomyosis endometrial stromal cells. Qi and colleagues [29] reported that Notch1, N-cadherin, Snail and Slug were upregulated in eutopic endometrial tissue from adenomyosis patients compared to normal endometrium while E-cadherin expression was reduced.

Endometriosis

Like endometrial cancer and adenomyosis, E-cadherin expression is reduced in endometriosis (Table 6). Gaetje and associates first reported that endometriotic epithelial cells lack E-cadherin expression which was associated with cell invasion *in vitro* and that E-cadherin negative epithelial cells were increased in endometriotic tissue compared to controls [36]. Sirtuin 1 (SIRT1) is a protein that deacetylates transcription factors to impact gene expression. When overexpressed in endometriotic epithelial cells, it inhibits oncogene induced senescence and is therefore able to trigger EMT [37]. Enhancer of Zeste homolog 2 (EZH2) has been identified as an enzyme that promotes EMT in endometriosis. Its overexpression upregulated Snail, Slug, and vimentin expression, while it downregulated E-cadherin. When inhibited, the opposite occurred, resulting in the restoration of the epithelial

Table 5. EMT proteins in adenomyosis.

EMT Proteins	Expression	References
Focal Adhesion Kinase (FAK)	Upregulated in adenomyosis; regulates EMT through FAK/PI3K/AKT pathway	[28]
E-cadherin	Inhibits EMT and migration/invasion	[29]
N-cadherin	Induces EMT and migration/invasion. Upregulated in eutopic endometrial tissue of adenomyosis patients	[29,30]
β -catenin	Induces EMT	[31]
TGF β -2	Induces EMT	[31]
SMOC2	Promotes EMT by upregulating mesenchymal markers and downregulating E-cadherin	[33]
Notch1	Upregulated	[29,32]
NRP1	Overexpression caused a mesenchymal phenotype, downregulated E-cadherin, and upregulated mesenchymal markers	[34]
ZEB1	Elevated in adenomyosis tissue; modulated by SKP1 and SKP2	[35]
Slug	Upregulated in eutopic endometrial tissue of adenomyosis patients	[29]
Snail	Upregulated in eutopic endometrial tissue of adenomyosis patients	[29]

Table 6. EMT proteins in endometriosis.

EMT Proteins	Expression	References
E-cadherin	Reduced expression	[36]
SIRT1	Triggers EMT by inhibiting apoptosis	[37]
EZH2	Overexpression induces EMT by upregulating mesenchymal markers	[38]
MMP9	Higher concentration in EMT patients than healthy controls	[39]
TWIST1	Induces EMT	[40]
SLUG	Overexpressed	[40]
SNAIL	Overexpressed	[40]
β-catenin	Activates Snail; knockdown inhibits estrogen-induced Snail mediated EMT	[41]
ZEB1	Overexpression induced migration and EMT	[42]

phenotype of the EECs and a reduction in migration and invasion [38]. Huang and colleagues evaluated the role of matrix metalloproteinase-9 (MMP-9) through a statistical analysis and discovered that there is a higher concentration of MMP-9 in EMT patients, and these concentrations are proportional to the stage of the disease [39]. Regarding the mesenchymal markers, TWIST1, SNAIL, and SLUG were overexpressed, while CDH1, or E-cadherin, expression was downregulated. MYC is another protein associated with endometriosis. It was concluded that both TWIST1 and MYC induce EMT, resulting in the development of endometriotic lesions [40]. Snail was additionally found to be activated by β-catenin/TCF-3 in endometriosis. β-catenin knockdown resulted in the inhibition of oestrogen-induced Snail mediated EMT [41]. Wu and colleagues determined that ZEB1 has a vital role in inducing endometriosis, as it was overexpressed, along with EMT markers Vimentin and N-cadherin. When ZEB1 was downregulated, migration, invasion, and EMT of the Ishikawa cells were inhibited [42].

In summary, among the three diseases, E-cadherin expression appears to be reduced, while ZEB1, Snail and Slug expression are elevated in each case and associated with cell migration/invasion.

Protease/Protease Inhibitor Expression in Malignant and Benign Endometrial Diseases

Endometrial cancer

Proteases play a crucial role in regulating endometrial diseases, which can be used to the advantage during treatment. For example, Huang and colleagues determined that ubiquitin-specific protease 31 (USP31) can be used to foretell a prognosis. Those with lower levels of USP31 will most likely have a worse prognosis, and vice versa [43] (Table 7). Another protease serves a similar function. The expression of HtrA serine peptidase 1 (HtrA1) is inversely related to tumor grade. Its downregulation increased the invasiveness of

papillary serous EC cell lines, and its upregulation decreased their invasive ability [44]. Another important group of proteases is cathepsins, which are generally found within lysosomes. In comparison to normal endometrium, an upregulation of Cathepsin B has been observed in EC tissues. When suppressed, it resulted in a decrease in proliferation [45]. It has also been found to be correlated with the FIGO stage of EC [46]. Cathepsin D additionally could aid in the prognosis through immunohistochemical detections [47]. Lower levels of expression are correlated with a worse prognosis [48]. Skrzypczak and associates collected data supporting the possibility that cysteine protease cathepsin L (CTSL2) may have a role in the progression of EC. It was highly expressed, and it had a positive correlation with the expression of growth regulatory genes [49]. One study discovered that the caseinolytic mitochondrial matrix peptidase proteolytic subunit (CLPP) plays a vital role in the proliferation of type I EC cancer tissue. Its upregulation in EC suggested that it may also play a role in removing damaged mitochondrial proteins [50]. Another protease that may affect EC and its prognosis is hepsin, a type II transmembrane serine protease. There is an inconsistency of findings regarding its role in endometrial cancer. Matsuo and colleagues concluded that it is overexpressed in EC, and the higher its level of protein expression, the more advanced the cancer is [51]. However, Nakamura and colleagues determined that Hepsin, the gene that encodes for the protein hepsin, instead inhibits cell growth [52].

Matrix metalloproteinases (MMPs) are key proteases which degrade the extracellular matrix and contribute to cell migration and invasion [53]. Among the numerous MMPs, MMP-2 and MMP-9 have been the most studied in endometrial cancer. Aglund and colleagues [54] first reported that overexpression of both MMP-2 and MMP-9 were associated with poor patient survival. More recent studies have demonstrated *in vitro* functionality of MMP2 and MMP9 using cell assays. SPOCK2, which was reported to be lower in endometrial cancer, was demonstrated *in vitro* to mediate

cell proliferation, invasion and migration by mediating MMP2 (and MT1-MMP) expression and action [55], while Wang and colleagues [56] demonstrated that MMP2 could be inhibited by over-expression of the mature form of IL-37 (IL137bΔ1-45) decreased cell migration and invasion by inhibiting MMP2 expression. Targeting of MMP-9 to reduce cell proliferation, migration and/or invasion was demonstrated in three independent studies. Ruan and associates [57] demonstrated that miR-183 up-regulation in endometrial cancer cells targets MMP-9 expression to augment cell proliferation and invasion *in vitro*, while Zhao and colleagues [58] reported that the long non-coding RNA, GATA6-AS, is reduced in endometrial cancer tissue and cell lines and that its overexpression *in vitro* augments cell proliferation, reduced cell apoptosis by mediating MMP-9 expression.

The net result of protease action is a combination of expression of the protease as well as that of the respective protease inhibitors [59]. Thus, several of the inhibitors of the aforementioned proteases have been examined in the context of EC. The expression of protease inhibitors has been found to significantly impact the progression of endometrial cancer. Plasminogen activator inhibitor type 1 (PAI-1) inhibits

proteases important in fibrinolysis. A study found high levels of PAI-1, as well as PAI-1 4G/5G polymorphism, in the blood of endometrial cancer patients, indicating a vital role in EC. The higher the PAI-1 level, the higher the grade [60]. Another protease inhibitor that is upregulated in EC is SERPINA3. Yang and colleagues discovered that it modulates the G2/M checkpoint of the cell cycle and additionally inhibits cell death [61]. Human epididymis protein 4 (HE4) is a protease inhibitor that can signify a worse prognosis for EC patients [62]. Its expression increases with the clinical stage. When overexpressed, proliferation is promoted and malignant phenotypes are enhanced [63]. The upregulation of protein Z-dependent protease inhibitor (ZPI), as well as its cofactor protein Z (PZ), in EC cells also indicate that they play a role in endometrial cancer [64]. They were not expressed in normal tissues. On the other hand, hepatocyte growth factor activator inhibitors HAI-1 and HAI-2 are downregulated in EC. Their decrease is associated with a worse prognosis. Nakamura and colleagues observed that they have an inhibitory effect on EC cell migration and invasion, which is achieved through decreasing matrilysin and hepsin levels. These protease inhibitors reduced ER and PR signal transduction, reduced the expression of mesenchymal markers, and increased that

Table 7. Proteases and protease inhibitors in endometrial cancer.

Proteases	Expression	References
USP31	Downregulated in EC; inverse relationship with prognosis	[43]
HtrA1	Downregulated in EC; inverse relationship with tumor grade	[44]
Cathepsin B	Upregulated in EC	[45,46]
Cathepsin D	Downregulated in EC; can be used to assess prognosis	[47,8]
CTSL2	Upregulated in EC; may cause the progression of EC	[49]
CLPP	Increased expression; may play a role in removing damaged mitochondrial proteins	[50]
Hepsin	Inhibits cell growth	[51]
	Upregulated in EC	[52]
MMP-2	Upregulated in EC	[54]
	Inhibition reduces cell proliferation, migration, invasion	[55,56]
MMP-9	Upregulated in EC	[54]
	Inhibition reduces cell proliferation, migration, enhances apoptosis	[57,58]
Protease Inhibitors	Expression	References
PAI-1	High expression; associated with grade of cancer	[60]
SERPINA3	Upregulated: regulates G2/M checkpoint and inhibits apoptosis	[61]
HE4	Overexpression associated with worse prognosis	[62,63]
ZPI	Upregulated	[64]
HAI-1 & HAI-2	Downregulated; their expression inhibits proliferation	[65]
Bortezomib	Increased mRNA expression of caspases-3 and caspases-9; decreased mRNA expression of bcl-2	[66]
TIMP-2	Elevated in blood serum	[67]
TIMP-1	Decreased expression	[67]
	Increased expression	[68]

of epithelial markers [65]. Lastly, bortezomib, a treatment for some cancers, may also be able to affect endometrial cancer cells. In an Ishikawa cell line, bortezomib decreased the mRNA expression of bcl-2, a protein that inhibits apoptosis, while it increased the mRNA expression of caspases-3 and caspases-9, both of which are activated during apoptosis. Thus, bortezomib was able to increase the susceptibility of Ishikawa cells to chemotherapy [66]. Contrary to bortezomib, the appearance of carcinoma and benign neoplasms are correlated with TIMP-2 elevation in the blood serum. On the other hand, there were lower TIMP-1 levels in endometrial cancer patients in comparison to controls and patients with polyps and hyperplasia. The researchers concluded that they cannot be considered diagnostic markers but can be used in the prognosis process [67]. Additionally, TIMP-1 was upregulated in a high risk patient group [68].

Adenomyosis

In a study that evaluated how adenomyosis impacted the coagulation and fibrinolysis system during menstruation, 50% of the patients had an increase in thrombin-antithrombin complex (TAT) and plasmin-alpha 2-plasmin inhibitor complex (PIC). According to Yamanaka and colleagues, this data indicates that adenomyosis patients are at risk of developing thrombosis, infarction, and exacerbated menorrhagia [69]. Menorrhagia could be caused by activated fibrinolysis during menstruation. Mori and colleagues investigated the effects of orally active-matrix metalloproteinase (MMP) inhibitor (ONO-4817) on mice with uterine adenomyosis. There was a lower probability that adenomyosis would progress in mice treated with ONO-4817. Mice with 1% ONO-4817 had less progression in the uteri, specifically 2.71 ± 0.93 , with the degree of pathological progression graded from 1 to 5, while the uteri that was not exposed had 4.33 ± 0.75 . Additionally, ONO-4817 inhibited the invasion of stromal cells into the gel, indicating that ONO-4817 could be potent in suppressing the development of adenomyosis [70]. Many studies have discovered that matrix metalloproteinases are upregulated in adenomyosis lesions. MMP-2 and MMP-9 specifically are most often elevated (Table 8) [71]. As a result, some have concluded

that they may play a role in the invasion of endometrial tissues into the myometrium [72]. In the endometrial stromal cells of patients with adenomyosis, there was a higher secretion of TIMP-1 in comparison to those without the disease [73]. On the other hand, in active adenomyosis, there was a lesser expression of TIMP-1, TIMP-3, and TIMP-4, a decrease in the occurrence of apoptosis, and more proliferation by glandular and stromal cells [74].

Endometriosis

There are a variety of proteases that regulate endometriosis. For one, Porter and associates supported their hypotheses that cysteine cathepsins promote tissue invasion and lesion establishment, and when inhibited it could block the attachment of endometriotic lesions with the data collected from their study. Cathepsins L and K were significantly upregulated in the endometriotic lesions of both mice and humans in comparison to other tissues, and when inhibited by E-64, there were much less attached endometriosis lesions [75]. Cathepsin G concentration was additionally significantly higher in endometriosis tissues (Table 9) [76]. Calcium-activated neutral protease 7 (CAPN7) is a protease that upregulates MMP-2, thus promoting human endometrial stromal cell (hESC) migration and invasion [77]. Thrombin also activated MMP-2 in endometriotic stromal cells (ESCs). This was suppressed by thrombin inhibitor d-phenylalanyl-l-prolyl-l-arginine chloromethyl ketone (PPACK). The researchers concluded that the thrombin system stimulates the inflammatory response of endometriotic cells and mitogenic activity [78]. Kusama and associates discovered that thrombin induces transformations similar to epithelial-mesenchymal transition (EMT) and fibroblast to myofibroblast transdifferentiation [79].

Tissue remodeling is an important process regulated by MMPs and TIMPs. There are conflicting observations regarding the concentration of MMP-2 in endometriotic tissues. Tang and associates discovered that the promoter regions of MMP2, as well as MMP3 and MMP7, underwent notable changes in endometriotic lesions in comparison to eutopic tissue during

Table 8. Proteases and protease inhibitors in adenomyosis.

Proteases	Expression	References
MMP-2	Elevated expression	[71]
MMP-9	Elevated expression	[71]
Protease Inhibitors	Expression	References
TAT	Increases risk of developing thrombosis, infarction, and exacerbated menorrhagia	[69]
ONO-4817	Suppressed development of adenomyosis	[70]
TIMP-1	Higher secretion in those with adenomyosis than those without.	[73]
	Decrease in expression	[74]
TIMP-3 & TIMP-4	Decrease in expression	[74]

Table 9. Proteases and protease inhibitors in endometriosis.

Protease	Expression	References
Cathepsins L & K	Upregulated; when inhibited, less endometriotic lesions can attach	[75]
Cathepsin G	High concentrations	[76]
CAPN7	Upregulates MMP-2 and promotes migration and invasion of hESC	[77]
MMP-2	Decreased Overexpressed, promotes migration and invasion, related to decrease in TIMP-2	[80] [81,82]
MMP-9	upregulated	[83]
MT5-MMP	High transcript levels in peritoneal endometriosis; leads to increase in tissue remodeling	[84]
MMP-1	Expression detected in red peritoneal and ovarian endometriosis; linked to tissue remodeling and bleeding	[85]
USP7	Upregulated, regulates DNMT1, promotes migration and invasion	[86]
USP10	Activates Raf-1/MEK/ERK signaling pathway and promotes proliferation and suppresses apoptosis	[87]
HtrA1	Downregulated	[78]
Thrombin	Activates MMP-2; promotes changes resembling EMT and FMT	[78]
Protease Inhibitors	Expression	References
Protease inhibitor	During the luteal phase, downregulated in uterine cavity, upregulated in PT	[89]
SLPI	Upregulated in peritoneal fluid	[90,91]
Alpha 1-AT	Decreased in mice that underwent ovariectomy; could induce inflammation	[92]
Kallistatin	Downregulation correlated with decrease in severity; increases ROS levels, modulates caspase 3 signaling and MnSOD	[93]
A2M	Suppressed blastocyte and mouse embryo development	[94]
TIMP-1	Downregulated in endometriosis. In early endometriosis, no significant difference in expression	[95,96]
TIMP-2	Downregulated in advanced endometriosis	[99]
TIMP-3	Promoter regions changed significantly during proliferative phase	[80]
TIMP-4	Promoter regions changed significantly during proliferative phase	[80]

the proliferative phase [80]. Chen and colleagues found that MMP2 expression decreased with disease [81], while Malvezzi and colleagues observed that in infertile women, its levels increased in stage III/IV in comparison to women with stage I/II endometriosis [82]. MMP-9 is overexpressed in endometriotic tissues [83]. Additionally, there is elevated expression of membrane-type 5 metalloproteinase (MT5-MMP) in eutopic endometrium and a greater amount of transcript levels in most peritoneal lesions [84]. An immunohistochemistry demonstrated strong staining in luminal epithelial cells. Put together with the results of an rt-PCR, it was deduced that MT5-MMP expression leads to an increase in tissue remodeling and cell migration. In red peritoneal and ovarian endometriosis, MMP1 mRNA expression was detected, but not in black peritoneal and rectovaginal lesions [85]. Its expression was also linked to tissue remodeling and

bleeding, with a possible role in the secondary shedding and reimplantation of endometriotic lesions.

The development of endometriosis may be regulated by Ubiquitin Specific Protease 7 (USP7). It is upregulated in ectopic endometrial stromal cells (EECs), promoting irregular behavior and regulating the expression of DNA methyltransferase 1 (DNMT1), a protein that when silenced, suppresses the oncogenic characteristics caused by USP7 [86]. Furthermore, the overexpression of ubiquitin-specific protease 10 (USP10) is also linked to migration, proliferation, and suppression of apoptosis. Chen and colleagues believe it accomplishes this by activating the Raf-1/ERK kinase (MEK)/ extracellular signal-regulated kinase (ERK) signaling pathway [87]. Finally, one protease that is instead downregulated in endometriosis is high temperature requirement A1 (HtrA1).

The researchers determined that it had a direct correlation with TGFβ1 [88].

A multitude of studies have also discovered many protease inhibitors that may influence or cause the onset and progression of endometriosis. A comparative study conducted by Fazleabas evaluated the general concentration of protease inhibitors in women with endometriosis. It was observed that during the luteal phase, there was a decrease in protease inhibitor concentration in the uterine cavity, but an increase in the peritoneal fluid [89]. Next, both the secretory leukocyte protease inhibitor (SLPI), which inhibits human leukocyte elastase, and its gene were significantly upregulated in the peritoneal fluid of women [90,91]. In the endometriosis-like grafts of mice that underwent a unilateral ovariectomy (uOVX), the expression level of alpha1-antitrypsin (alpha1-AT) decreased, which Tamura and colleagues suggested may induce inflammation. It also blocked interleukin-8 expression (IL-8; [92]). Mao and associates assessed the role kallistatin (KS) plays in endometriosis. It had low levels of expression, which decreased with the severity of the disease. It was found that it has the ability to increase intracellular reactive oxygen species (ROS) levels, and it additionally, modulates caspase 3 signaling and manganese superoxide dismutase (MnSOD), which together inhibit the progression of the disease [93]. Recently, the production of alpha-2 macroglobulin (A2M), a broad-spectrum plasma protease inhibitor, in human endometrium was reported. Sayegh and colleagues studied its expression and effects on mouse embryo development. Strong signaling expression was detected in the secretory endothelium compared to proliferative endothelium. The blastocyte development of mouse embryos *in vitro* was suppressed at A2M concentrations of 400-400 mmol/L. It also inhibited mouse embryo development [94]. TIMP-1, the tissue inhibitor of metalloproteinases-1, was found in a multitude of studies to have reduced expression in endometriosis [95,96]. Madjid and colleagues discovered that in the endometrial cells of subjects with decreased TIMP-1 expression had a higher risk of endometriosis [97]. However, one study did not determine a statistical significance between the difference in expression of TIMP-1 in the eutopic endometrium of subjects with early endometriosis and subjects with a healthy endometrium [98]. In late endometriosis, TIMP-2 is downregulated, which could signify an increase in MMP-2 as endometriosis advances [99]. Additionally, the promoter regions of TIMP3 and TIMP4 underwent notable changes in endometriotic lesions in comparison to eutopic tissue during the proliferative phase [80].

In summary, each of the three diseases exhibit signs of tissue remodeling and invasion. Not surprisingly, increases in protease expression has been reported in each of these diseases while the expression of protease inhibitor expression is less consistent, some report reduction while others have been reported to be elevated.

Transcription Factor Expression in Malignant and Benign Endometrial Diseases

Endometrial cancer

A variety of transcription factors have been found to significantly impact endometrial cancer through their regulation of gene expression. Firstly, Yang and colleagues evaluated the effect the knockdown of E2F1 has on EC, and it was discovered that it inhibited invasion and metastasis, thus allowing one to conclude that it regularly promotes a malignant phenotype (**Table 10**) [100]. Another study supports this conclusion, as it identified a strong correlation of E2F1 with EC [101]. This study additionally found that HMGA1 and PGR are closely correlated with EC. A different form of E2F1, E2F7, was highly expressed in EC, and its silencing may suppress the effect RAD51AP1 overexpression has on cell growth [102]. It is important to note that many endometrial-mesenchymal transition (EMT) proteins mentioned in an earlier section, such as Notch1 [103], SNAIL [104] and SLUG [105], are also transcription factors, and their expression, whether its elevated or lowered, plays a significant role in the development of endometrial cancer, adenomyosis, and endometriosis.

HMGA2 is a transcription factor known to promote cancer. One study observed its upregulation in endometrial cancer, which was linked to a worse prognosis, as its overexpression promoted proliferation, migration, invasion, and drug resistance. HMGA2 knockdown had the opposite effects [106]. Another transcription factor in which its upregulation was observed in EC is T-Box transcription factor (TBX2). Ding and colleagues discovered it enhanced cell resistance to chemotherapy by regulating the nuclear factor erythroid 2-related factor (NRF2) pathway [107]. It was additionally found to suppress ferroptosis by upregulating ferroptosis suppressor protein 1 (FSP1; [108]. Transcription factor 19 (TCF19), known to be differentially expressed in microsatellite stable and unstable, was linked to a worse prognosis and immune exhaustion signature in endometrial cancer patients. It promoted tripartite motif-containing 14 (TRIM14) transcription, which induced tumorigenicity [109]. Repressor Element 1 (RE1) silencing transcription factor (REST), on the other hand, was downregulated in human EC samples. While it was highly expressed in the cell lines, the decrease in expression is linked to an increase in proliferation [110].

There are many significant transcription factors in endometrial cancer that are a part of the forkhead box family. To start, FOXP1, a P subfamily, was differently expressed in human samples based on the phase of the menstrual cycle and the grade of malignancy. There was a reduction in its immunostaining during the early secretory stage in the basal [111]. Additionally, its expression was reduced in the nucleus

Table 10. Transcription factors in endometrial cancer.

Transcription Factor	Expression	References
E2F1	Knockdown inhibited invasion and migration Closely correlated with EC	[100] [101]
E2F7	Highly expressed. Silencing could suppress proliferative effects of RAD51AP1	[102]
HMGA2	Upregulation associated with worse prognosis. It promoted proliferation, migration, invasion, and drug resistance	[106]
TBX2	Upregulated in EC; enhances cell resistance by regulation of NRF2; upregulates FSP1 to suppress ferroptosis	[107,108]
TCF19	Linked to worse prognosis	[109]
REST	Downregulation linked to proliferation	[110]
FOXP1	Lowered expression in early secretory phase, and in nucleus and cytoplasm of grade 3 EC	[111]
FOXO1	Inhibits proliferation and migration; may target SREBP1 (it induces tumorigenesis) which was downregulated	[112]
FOXA1	Could be tumor suppressor because its downregulation promoted proliferation	[113]
HOXA10	Downregulation induced development of EC hyperplasia in animals	[115]
HOXB9	Upregulated in EC; linked to worse prognosis	[116]
KLF2	Expression inhibits EC proliferation by suppressing NPM1	[117]
KLF12	Overexpressed in EC; increases proliferation and decreases apoptosis	[118]
KLF17	Induces EMT and cell invasion. Transactivates TWIST1 expression	[119]
ETV4	Controls EC development and ER signaling	[120]
ETV5	Overexpression leads to EMT; regulates NID1 and NUPR1	[121]
SIRT1	Overexpression of SIRT1 leads to proliferation, migration, invasion, and an inhibition of apoptosis; enhances deacetylation of FOXO3	[114]
ATF3	Downregulated; expression can inhibit proliferation, JunB expression, and promote apoptosis	[122]
ATF4	Overexpressed	[123]
NFAT5	Expression increases with grade	[124]
NF1C	Inhibited proliferation, motility, and invasion of HECs	[64]

and cytoplasm of grade 3 EC in comparison to grades 1 and 2. This study concluded that FOXP1 is specifically involved in estrogen dependent ECs as well. Next, the overexpression of forkhead transcription factor 1 (FOXO1) was observed to inhibit cell proliferation, migration, invasion, and tumorigenesis. In these cells, sterol regulatory element-binding protein 1 (SREBP1), another transcription factor, was downregulated, which may signify that FOXO1 targets SREBP1 [112]. SREBP1 is usually upregulated in EC and promotes tumorigenesis. Another transcription factor of the forkhead box family is forkhead box A1(FOXA1). When downregulated, Abe and colleagues observed that proliferation was promoted. Thus, FOXA1 could potentially be a tumor suppressor [113]. FOXO3 was found to be associated with SIRT1 [114]. SIRT1 induces FOXO3 deacetylation and activity. Overexpression of SIRT1 leads to proliferation, migration, invasion, and an inhibition of apoptosis. Two transcription factors of the homeobox gene family were found to play a role in EC. When HOXA10 was downregulated, endometrial hyperplasia began to

develop in animals [115]. On the other hand, elevated levels of HOXB9 indicated a worse prognosis, as it was upregulated in EC and associated with histological grade and lymph node metastasis [116]. Two transcription factors of the Kruppel-like transcription family were detected. The expression of Kruppel-like factor 2 (KLF2) resulted in the inhibition of EC proliferation through the suppression of nucleophosmin 1 (NPM1) transcription [117]. On the other hand, Kruppel-like factor 12 (KLF12) was found to be overexpressed in EC, which was associated with an increase in proliferation and tumor size, a decrease in apoptosis [118]. Additionally, Dong and colleagues demonstrated that when Kruppel-like factor 17 (KLF17), a transcription factor, induced EMT and cell invasion, the expression of TWIST1 increased [119]. This is because KLF17 transactivates TWIST1 expression by binding to its promoter. Interestingly, ETV4 has been found to control ER activity, a key oncogene of endometrial cancer, as well as the development of EC [120]. ETV5 is overexpressed in Hec1A EC cells and has been found to induce the EMT [121]. The study additionally

discovered that ETV5 regulates the protein expression of Nidogen 1 (NID1) and Nuclear Protein 1 (NUPR1). Together, an invasive phenotype is achieved. Similarly, from the activating transcription factor family, ATF3 and ATF4 were detected. ATF3 was observed to be downregulated in endometrial cancer cells. When overexpressed, it inhibits proliferation, JunB expression, a transcription factor upregulated in EC and promotes apoptosis [122]. Liu and associates discovered that ATF4 is normally upregulated in EC cell lines, and its knockdown inhibits tumor growth [123]. Two transcription factors of the nuclear factor family were found to have different effects on endometrial cancer. Nuclear factor of activated T cells 5 (NFAT5) expression increased with grade [124], while Nuclear Factor 1-C (NF1C) inhibited the proliferation, motility, and invasion of human uterine endometrial cancer cells [63].

Adenomyosis

Compared to endometrial cancer, there is a paucity of work on transcription factors and adenomyosis. Expression of two zinc-finger transcription factors, GATA binding proteins, 2 and 6, were determined by immunohistochemistry. GATA2 had a two-fold lower expression while GATA6 a four-fold higher expression in ESCs of adenomyosis patients (**Table 11**) [125]. These levels impaired ESC decidualization. Another transcription factor that impairs decidualization is transcription factor 21 (TCF21). It achieves this by inhibiting decidual markers and cytoskeleton alterations [126]. STAT3 is a transcription factor known to play a significant role in endometrial regeneration. According to Hiraoka and colleagues, its activation promotes adenomyosis. In Stat3-deficient mice, a decrease in lesions and expression of genes associated with tissue regeneration

were observed in comparison to control mice (STAT3; [127]. In one study enacted by Li and colleagues, notably higher expressions of NF-κB DNA-binding activity, which was linked to dysmenorrhea severity, and p50 and p65 were detected [128]. It was concluded that NF-κB could be a transcription factor of great significance regarding the development of adenomyosis. Nie and colleagues additionally collected data signaling an elevation in expression of p50, p65, and p52, and a downregulation in progesterone receptor isoform B (PR-B) and a decrease in its immunoreactivity [129]. Lupicka and associates hypothesized that disturbances in stem cell differentiation of uterine tissue could be a main promoter of the development of adenomyosis. This is backed up by their data. There was a decrease in protein level of NANOG and SOX2 in stromal cells, while an elevation of OCT4 and SOX2 in the myometrial cells of dysfunctional uteri [130]. Two studies observed a decrease in mRNA and protein expression of HOXA10 [131]. Only the study conducted by Guo and colleagues observed a decrease in mRNA and protein expression of HOXA11 as well [132].

Endometriosis

In deep infiltrating endometriosis (DIE), Ganieva and associates detected a significant amount of TCF21 expression in comparison to normal tissues. Its expression increased with severity of the disease (**Table 12**), and it was also determined to play a role in the regulation of fibrosis in endometriosis [133]. Additionally, Wu and colleagues determined that TCF12 plays a role in the pathogenesis of endometriosis, as it has a higher expression in endometriotic than endometrial stromal cells, a change in its expression significantly impacted the proliferation and invasion of ESCs, and also affected the

Table 11. Transcription factors in adenomyosis.

Transcription Factor	Expression	References
GATA2	Low expression (H-SCORE)	[125]
GATA6	High expression (H-SCORE)	[125]
TCF21	Impairs decidualization	[126]
STAT3	Activation promotes adenomyosis; deficiency leads to decrease in lesions	[127]
NF-κB	High DNA-binding activity, which was linked to dysmenorrhea severity	[128]
p50	High protein expression and immunoreactivity	[128,129]
p52	High immunoreactivity	[129]
p65	High protein expression and immunoreactivity	[128,129]
PR-B	Downregulated and decrease in immunoreactivity	[129]
NANOG	Protein level decreased in stromal cells	[130]
SOX2	Protein level decreased in stromal cells, but increase in myometrial cells	[130]
OCT4	Increased protein level in myometrial cells	[130]
HOXA10	Decrease in expression	[130,131]
HOXA11	Decrease in expression	[132]

binding activities of other transcription factors like USF2, MMP9, and SF-1 [134]. Ntzeros and associates observed a difference in ZEB1 expression in the endometriotic cysts of endometrioma cases with and without DIE, which could reflect differences in their pathogenetic mechanisms [135]. Another study determined that ZEB1 could be linked to an invasive type of endometriosis. Its expression was only detected in the epithelial of endometriotic lesions, not of normal endometria, and it was most often found in the epithelial cells of invasive endometriosis [136]. AP-1 is another transcription factor that may aid in the development of invasive endometriosis, as its expression has been shown in multiple models, and it promotes invasive phenotypes [137]. There was a high activation of transcription factor nuclear factor-kappa B (NK-kappaB) in red, or active, endometriotic lesions [138]. p50 is also a part of the NF-kappaB family. In p50 knockdown mice, the size of the endometrial implants greatly decreased while NF-kappaB activation was interfered with. Additionally, NF-YA, NF-YB, and NF-YC are additional nuclear factors with

possible significant roles in this disease. NF-YA expression was found to be upregulated during the proliferative phase in eutopic endometrium. In ectopic endometrium, NF-YB and NF-YC were also upregulated [139]. Amirteimouri and colleagues suggested that because of NF-Y's regulation of ID genes, it may be behind the epigenetic changes that occur in endometrial tissues. In severe endometriosis, in which patients experienced intense pain, Badary and colleagues found significant expression through immunohistochemistry of HIF-1a [140]. Early growth response 1 (EGR) is another transcription factor detected in endometriosis tissues. It was determined to induce proliferation, migration, and invasion [141]. Transcription factors of the GATA family have been found to regulate key genes that impact endometriosis. GATA2 regulates genes important for the differentiation of stromal cells [142]. It is repressed in endometriotic cells. GATA6 on the other hand, is upregulated in endometriotic cells, inhibits GATA2 and promotes endometriotic markers. Likewise, GATA-3 promotes proliferation. In a study by Chen and colleagues,

Table 12. Transcription factors in endometriosis.

Transcription Factor	Expression	References
TCF21	Highly expression in DIE; increases with severity of disease	[133,134]
ZEB1	Indicator of invasive endometriosis	[135,136]
EGR1	Induces proliferation, migration, and invasion	[141]
GATA2	Repressed in endometriosis; vital to regulation of genes that control differentiation of stromal cells	[142]
GATA-3	Promotes proliferation	[142]
GATA6	Upregulated in endometriosis; inhibits GATA2	[142]
NK-kappaB	High activation in red (active) lesions	[138]
NF-YA, B, & C	Upregulated	[139]
HIF-1alpha	Significant expression in severe endometriosis	[140]
KLF11	Under expressed in human lesions, knockout can cause proliferative lesions in mice	[145]
TFEB	Highly expressed – knockdown suppressions lesion growth	[146]
OCT4	Maintains undifferentiated state in tissues; upregulated in endometriosis; expression correlated with genes that control migration	[147] [148]
BACH2	Regulates Treg genes; upregulated	[149]
ATF4	Expression allows cells to resist ferroptosis	[150]
AP-1	Promotes invasive phenotype	[137]
p50	Part of NF-kappaB family – p50 knockdown decreased size of implants; there was disruption in NF-kappaB activation	[138]
SOX18	Upregulated – induces EMT, increase invasion and migration, deteriorates endometriosis	[144]
COUP-TF	Detected in both eutopic and endometriotic cells; might inhibit aromatase P450 in eutopic endometrial cells	[151]
SF-1	Transcription undetected in eutopic endometrial cells; can compete for same DNA-binding site to prevent inhibition caused by COUP-TF in endometriotic stromal cells	[151]
HOXA10	Reduced expression in both eutopic and ectopic tissue; reduced eutopic endometrial expression associated with infertility	[152]

cells where GATA-3 was introduced had higher proliferation rates than those without GATA-3 [143]. The cells in which it was suppressed had lower proliferation rates than others. In Ishikawa cells, SOX18 overexpression was found to induce EMT, increase proliferation, as well as progress endometriosis overtime through the growth and bleeding of tissue outside of the uterus [144]. KLF11, a gene known to be associated with disease in humans, was found to be under expressed in endometriotic tissues of humans. When Klf11 was knocked out in mice, their lesions were larger and resembled the lesions of humans with late-stage diseases. In comparison, Klf9 knockout had no significant result on the lesions of the animals [145]. According to Chen and colleagues, transcription factor EB (TFEB) is highly expressed in the endometrium. It improves the proliferative abilities of human endometrial stromal cells (HESCs). In rat models, TFEB knockdown suppresses the growth of lesions [146]. OCT4 is a transcription factor known to be an essential to upholding a tissue's undifferentiated state [147]. Chang and colleagues discovered that in endometriotic tissues, the expression of OCT4 mRNA, which was upregulated in ectopic endometriotic tissues, was associated with genes that regulate migration in the cell [148]. In women who ultimately develop endometriosis, an increase in inflammation in eutopic and ectopic endometrium is observed, which can now be linked to a disruption in the homeostasis of regulatory T cells (Treg). BACH2, a transcription factor that regulates Treg genes, is upregulated in these tissues, indicating an iron-heme overload response [149]. Additionally, the overexpression of ATF4 has been found to allow cells to resist ferroptosis that is caused by an iron overload [150]. In a comparison between chicken ovalbumin upstream promoter transcription factor (COUP-TF) and steroidogenic factor-1 (SF-1), where antibodies were employed against both, it was found that in eutopic endometrial cells, only COUP-TF bound to the nuclear receptor half-site (NRHS), while both COUP-TF and SF-1 transcripts were detected in endometriotic tissues [151]. The researchers concluded that as SF-1 expression is undetected in eutopic endometrial stromal cells, one of the transcription factors that causes the inhibition of aromatase P450 is COUP-TF. However, in endometriotic stromal cells, SF-1 can compete for the same DNA-binding site, thus stopping the inhibition caused by COUP-TF. Lastly, among the transcription factors investigated in endometriosis pathophysiology, perhaps the most-well studied is HOXA10. Lazim and colleagues recently published a systematic review on the topic [152]. Briefly, the majority of data on this topic would support the notion that sufficient data are provided to support the notion that women with endometriosis express low levels of HOXA10 compared to women without endometriosis. More specifically, low levels of eutopic endometrial HOXA10 expression was associated with infertility which may be due to altered endometrial receptivity, decidualization and/or embryo implantation failure. With respect to ectopic, endometriotic lesion tissue, HOXA10 expression is also reduced compared to eutopic endometrial tissue.

In summary, there is a vast amount of literature on transcription factor expression in each of the three diseases but little consistency among the diseases. Among those transcription factors, HOXA10 has been reported to be reduced in all three conditions, with most reports on endometriosis. The bulk of the literature reports GATA2 and GATA6 expression in endometriosis and to a lesser extent adenomyosis.

Summary

Endometrial cancer, adenomyosis and endometriosis are diseases which arise from the endometrial lining of the uterus. Each disease is characterized by augmented cell proliferation/survival, migration and invasion. Augmented estrogen action and reduced progesterone signaling is postulated to contribute these common cellular attributes among these diseases. Expression of estrogen and progesterone receptors appear to display similar patterns among the three conditions but there is less consistency in assessment of epithelial-to-mesenchymal transition proteins (such as ZEB2, EZH2) among the three diseases. With respect to EMT protein assessment, there is a larger body of work and consistency in patterns of expression for key proteins such as CDH1, SLUG, SNAIL and ZEB1 between endometrial cancer and endometriosis. As all three of these diseases exhibit differing degrees of invasiveness, which is linked to tissue remodeling, there is some consistency with respect to patterns of expression for proteases such as MMP-2 and MMP-9 which is elevated in all three diseases. With respect to protease inhibitors, TIMP-1 expression is reduced in all three diseases, while TIMP-2 expression is reduced in endometrial cancer and endometriosis. While many studies have evaluated expression of different transcription factors in endometrial cancer, adenomyosis, and endometriosis, few studies have assessed the same transcription factors. Thus, there are several factors associated with endometrial cancer, adenomyosis and endometriosis, most notably altered steroid receptor expression and imbalances in the MMP/TIMP systems.

Limitations

While the studies cited in this review provide important information on pathways associated with endometrial cancer, adenomyosis and endometrial cancer pathophysiology, there are limitations in the approaches and study designs. For example, the majority of the studies which have examined EMT markers, proteases/protease inhibitors and/or transcription factors, many have been descriptive with few studies concurrently assessing expression/localization and function using *in vitro* assays. This is extremely important especially when studying the protease/protease inhibitors. Immunohistochemical localization and Western blot analysis of protease/protease inhibitors do not provide information on function of the proteases/proteases inhibitors. Further,

few studies concurrently evaluate protease and respective protease inhibitor expression and/or ratio. Often both protease and protease inhibitor may be expressed, and it is an alteration that favors net protease activity which leads to tissue invasion/remodeling. Additionally, greater emphasis on patient demographics, inclusion, exclusion criteria, stage of disease (for endometrial cancer and endometriosis) and type of lesion (for endometriosis) must be taken into account. This in turn should minimize variability and heterogeneity of experimental outcomes allowing for more robust data.

Future Studies

Future studies may focus on further dissecting the intermediates (transcription factors) associated with impaired steroid signaling and altered MMP/TIMP expression. Clearly, compared to endometrial cancer and endometriosis, adenomyosis is the least explored of the three diseases. As adenomyosis diagnosis is increasing, more detailed examination of this disease is warranted. When embarking upon future studies, it will be essential to take into account the aforementioned limitations to increase experimental rigor and reproducibility. In turn, we anticipate this will more clearly align the similarities and differences among these three common diseases in women.

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YA and WBN wrote and edited the review article.

Conflict of Interest

The authors declare no conflict of interest.

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