Reproductive Sciences
1-9

DOI: 10.1177/1933719116660847
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Genes Linked to Endometriosis by GWAS Are Integral to Cytoskeleton Regulation and Suggests That Mesothelial Barrier Homeostasis Is a Factor in the Pathogenesis of Endometriosis

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Abstract

Endometriosis, defined by the presence of ectopic endometrial lesions, is a common disease in reproductive-age women that profoundly affects patients' quality of life. Various pathogenic models have been proposed, but the origin of endometriosis remains elusive. In this article, we propose that the mesothelial barrier, which protects the underlying stroma from endometrial transplants present in retrograde menstrual fluid, can be compromised by activation of the epithelial to mesenchymal transition (EMT) repair mechanism that lead to temporary loss of barrier integrity. Absent of the mesothelial barrier, endometrial cells can more readily adhere to the underlying peritoneal stroma and establish endometrial lesions. The hypothesis is based on the clinical and experimental observations that correlate the location of endometrial lesions with areas of mesothelial damage, together with genetic evidence that 4 genes associated with endometriosis are direct regulators of the actin-cytoskeleton, which coordinates mesothelial barrier integrity. It supports past observations that implicate the peritoneum in the pathogenesis of endometriosis and unifies previously disparate theories that endometriosis may be triggered by infection, mechanical damage, and inflammation since each of these mechanisms can induce EMT in the mesothelium. If the hypothesis is correct, inhibition of EMT in the mesothelial barrier provides a novel paradigm for the prevention and treatment of endometriosis.

Keywords

endometriosis, pathogenesis, cytoskeleton, mesothelium, epithelial to mesenchymal transition, genetic predisposition

Introduction

Endometriosis affects 6% to 10% of women during their reproductive years with symptoms including pelvic pain, dyspareunia, dysmenorrhea, and infertility.[1] The clinical awareness of endometriosis dates back to antiquity,[2,3] and it was John Sampson who coined the term "endometriosis" nearly a century ago, proposing that it was caused by homologous transplant of endometrial tissue present in retrograde menstrual fluid.[4] While Sampson's theory is still widely favored, the inciting cellular and molecular mechanisms that lead to endometriosis have largely remained unresolved.

There is compelling evidence that environmental and lifestyle factors affect endometriosis risk.[5] There is also mounting evidence from epidemiologic studies in twins and families, and more recently from genome-wide association studies (GWAS), that genetic factors contribute to the risk.[6] In the present study, we review the functional role of the top 4 genes that we have associated with endometriosis by GWAS to determine whether a mechanistic relationship exists between the genes. The study was performed with the expectation that the identification of a shared pathway or cellular mechanism would indicate how genetic factors contribute to the pathogenesis of endometriosis.

Endometriosis Gene Selection

Our laboratory has previously reported results from a large endometriosis GWAS conducted in a Caucasian population from the United States.[7] In the study, we reported association with several novel candidate regions and replicated several genetic associations previously observed in Japanese and British/Australian populations.[8-10] More recent studies have since been published that further validate several of the genomic regions in association with endometriosis.[11-14] Genome-wide

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Table 1. Endometriosis-Associated Genes With Independent Replication.[a]

	Original Study[7]			Meta-Analysis				
Gene	SNP	*P*	OR	SNP	*P*	OR	Distance to Gene (kb)	Supporting References
WNT4[b]	rs2235529	8.5×10^{-9}	1.29	rs7521902[13]	1.8×10^{-15}	1.18	Intron	7-13
CDC42[b]	rs2235529	8.5×10^{-9}	1.29	rs7521902[13]	1.8×10^{-15}	1.18	31	7,8
ID4	rs6907340	9.7×10^{-8}	1.20	rs7739264[13]	1.9×10^{-10}	1.10	34	7,10,13
VEZT	rs3596	6.7×10^{-6}	1.16	rs10859871[11]	7.2×10^{-20}	1.19	3′ untranslated region	7,10,11,13

[a]The table shows the GWAS association values to the 4 most strongly associated genes from the original study together with association statistics for the most strongly associated SNPs discovered in independent studies and calculated by meta-analysis.
[b]WNT4 and CDC42 are both included here, since their genetic association are equally strong.

association studies rely on the statistical analysis of a case–control population and provides a strategy to identify subtle genetic signals in large sample sets. However, GWAS is also very sensitive to differences introduced by, for example, population substructure or sampling biases. To mitigate such effects, we restricted the present study to those regions and genes we reported in our GWAS that have been independently replicated and that pass the genome-wide significance threshold of 5×10^{-8} either directly or by meta-analysis. Table 1 shows the top 3 regions and the 4 genes our experimental data suggest are the most likely to contribute to endometriosis. Like the majority of genetic variants linked to complex diseases by GWAS, these variants are not protein altering but rather are expected to be linked to a regulatory effect. The genes we consider here are those genes located nearest to the associated variants. The association signal on chromosome 1 is located within a large region of linkage disequilibrium that includes 2 genes: WNT4 and CDC42.[7] Because the association analysis supports both genes equally, both are considered in the analysis.

Functional Evaluation of 4 Genes Associated With Endometriosis

WNT4 (Wingless-Type MMTV Integration Site Family Member 4)

The WNT4 region on chromosome 1p36.12 has consistently shown strong genetic association with endometriosis in independent studies and across ethnicities.[7,8,10,12,14] WNT4 is a member of the WNT gene family, which encodes secreted signaling proteins that act as ligands to frizzled (FZD) receptors.[15] The WNT/FZD signaling pathway controls various cellular processes including proliferation, differentiation, cell-fate decisions, and migration and is a key regulatory pathway during embryonic development. The pathway has 2 branches that are referred to as the canonical and noncanonical WNT pathways. The canonical WNT pathway signals via β-catenin and the TCF/LEF family of transcriptional complexes in the nucleus where it regulates gene transcription.[16] The noncanonical pathway, also referred to as the β-catenin-independent pathway, regulates the cytoskeleton and cell polarity. WNT4 is commonly classified as a noncanonical WNT gene, even though it is able to activate both of these signaling pathways.[17] WNT4 is recognized as a central regulator in the formation of the female reproductive and renal system, along with side-branch formation in adrenal, pituitary, salivary, and mammary glands via mechanisms that depend on cytoskeletal rearrangement. WNT4 has also recently been linked to ovarian,[18] colorectal,[19] and thyroid cancer,[20] among others. WNT4 is commonly expressed in epithelial cells, and the loss of WNT4 expression in cancer is linked to EMT. Conversely, it has been shown that overexpression of WNT4 in such cells can revert the mesenchymal phenotype and inhibit cellular migration.[20] This is in line with early observations by Stark et al who concluded that Wnt4 in mice acts as an autoinducer of the mesenchyme to epithelial transition (MET) that underlies nephron development.[21]

CDC42 (Cell Division Control Protein 42 Homolog)

CDC42 has garnered less attention as an endometriosis gene than its genomic neighbor WNT4, yet genetically it is an equally strong candidate, as it is located on the same 150-kb linkage-disequilibrium block as WNT4.[7] Human CDC42 is a small GTPase of the Rho family that can hydrolyze guanosine triphosphate (GTP), and serve as intracellular signal transducers that link extracellular signals (including WNT4) to intracellular responses. The 3 signature members of the Rho family (RHOA, RAC1, and CDC42) are evolutionarily ancient with homologs in plants and yeast. CDC42, like most other small G proteins, switch between a resting GDP-bound state and an active GTP-bound state. Rho-family GTPases are known for their role in cell–cell adhesion and actin polymerization, and CDC42 in particular is known for its role in modulating filamentous actin in the cytoskeleton. The cytoskeleton is the intracellular matrix, composed of actin, intermediate filaments, and microtubules, that supports cell shape, function, and association with extracellular connective tissue.[22] The cytoskeleton can also actively contract, thereby deforming the cell and the cell's environment and allowing cells to migrate. CDC42 plays an essential role in this process. It is necessary for the formation of lamellipodia and filopodia required in cell migration and invasion.[23] It is now firmly established that CDC42, together with other Rho GTPases, perform this function as part of the cellular reprogramming during EMT.[24] Changes in CDC42 expression have been

extensively studied as part of oncogenic transformation, and CDC42 is commonly overexpressed in several types of human cancers including non-small-cell lung cancer, colorectal adenocarcinoma, melanoma, breast cancer, and testicular cancer.[25] Evidence is extensive that both elevated expression of CDC42 and histologic changes typical of EMT correlate with poor survival across a wide range of cancers.[26,27]

ID4 (Inhibitor of DNA Binding 4, Dominant Negative Helix-Loop-Helix Protein)

ID4 it is one of 4 *inhibitor of DNA binding* (ID) genes that structurally belongs to the basic helix-loop-helix transcription factor (bHLH) gene family.[28] The ID proteins are characterized by having a helix-loop-helix domain, which allows them to heterodimerize with other members of the bHLH family. However, unlike functional transcription factors, the ID proteins lack a DNA-binding domain. Thus, when an ID protein dimerizes with a functional bHLH transcription factor that has a DNA-binding domain, it acts as dominant negative by preventing DNA binding.[29] ID1 to ID3 are alike and have been classified as oncogenes, whereas ID4 functions like a tumor suppressor.[30] The function of the ID proteins has been extensively studied in the context of the bHLH transcription factor TCF3 (*Transcription Factor 3*, - also named E2A and E47). TCF3, like other TCF/LEF transcription factors, dimerizes in the nucleus, which allows them to bind to DNA E-box motifs and switch on their target genes.[31] The ID proteins can inhibit the transcriptional activation by competing for dimerization and sequestering TCF/LEF in nonfunctional ID heterodimers. ID4 can apply the same strategy to sequester ID1 to ID3, thus reactivating the TCF/LEF transcriptional complexes, which explains the tumor suppressor activity observed for ID4.[32] The genetic association between endometriosis and ID4 is anchored around an single-nucleotide polymorphism (SNP; rs6904518) located about 40-kb upstream of ID4[7] in an unusually complex regulatory region that include a CpG island, several DNaseI hypersensitivity clusters, H3K27Ac and a H3K4me marks, and transcription factor Chromatin Immunoprecipitation (ChIP) sites. ID4 is ubiquitously expressed in adult tissues and is inversely correlated with malignant progression in several tissues,[30] and ID4 has been shown to regulate components of the actin cytoskeleton in basal-like breast cancer cells.[33] It is also noteworthy that ID4 expression is inversely correlated with CDC42 expression during malignant progression and that ID4 can be epigenetically regulated by CDC42 via promotor methylation.[34] The ID4 expression has also been found to be coregulated with WNT4 expression in progesterone-induced side-branching of mammary ducts in a process that depends on cytoskeletal remodeling of epithelial cells.[35]

VEZT (Vezatin, Adherens Junction's Transmembrane Protein)

Vezatin is a multipass transmembrane protein that is ubiquitously expressed. It is an essential part of the multiprotein

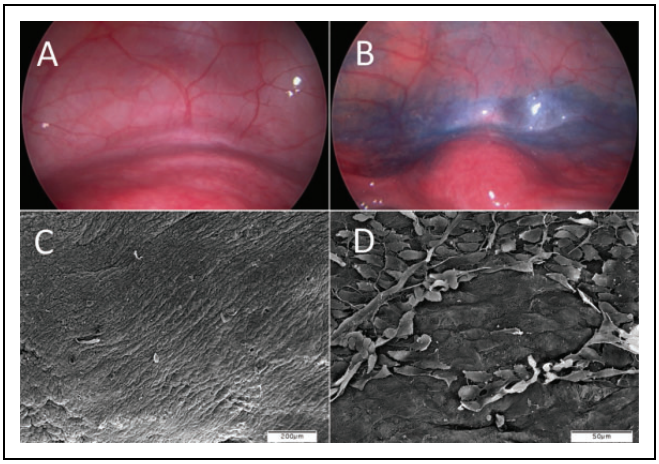

Figure 1. Panels A and B show laparoscopic views in women with chronic pelvic pain before and after application of methylene blue. Endometrial lesions are more commonly observed in blue-stained areas. Panels C and D show scanning electron microscopy images (size bars in the lower right corners). Panel C shows normal, nonstaining peritoneum. The mesothelial cells in this panel are tightly connected forming a healthy and intact epithelial sheet. Panel D shows a section obtained from a blue-stained area that shows a compromised epithelial layer with loosely connected cells together with scattered endometrial cells. The figure is modified from Lessey et al with permission from Dr B. Lessey.[46]

epithelial adherens junction complex that includes E-cadherin (CDH1). Specifically, it is believed that vezatin mediates the recruitment of myosin VIIA (MYO7A) to adherens junctions, hereby linking adherens junction to the cytoskeleton in a manner that complements E-cadherin's link to actin via β-catenin and α-catenin. Inhibition of vezatin results in a strong diminution in E-cadherin messenger RNA. Expression of both VEZT and CDH1 are required to maintain epithelial homeostasis. The genetic association between endometriosis and vezatin (VEZT) is anchored around an SNP (rs3596) located in the 3′-untranslated region of VEZT, but the association signal encompasses the entire VEZT gene, including the 300 base pair 5′ regulatory region that is shared in a head-to-head fashion with *FYVE, RhoGEF and PH Domain Containing 6* (FGD6). The VEZT-FGD6 promotor belongs to a group of promotors that are called bidirectional or divergent promotors particularly common in mammals. Bidirectional promotors often couple protein-coding genes involved in the same biological process.[36] In fact, FGD6 contains a RhoGEF domain that can activate resting Rho GTPases by exchanging bound GDP for free GTP and that preferentially targets CDC42. Further, a recent study reported that FGD6 can bind CDC42 directly and that FGD6 in an osteoclast model system regulates the actin-cytoskeleton and cell adhesion by activating CDC42 at different intracellular locations.[37] A detailed view of the bidirectional promotor between VEZT and FGD6 is shown in Supplementary Figure 1. The function of the 4 endometriosis genes and their role in EMT is summarized in Table 2.

Table 2. Biologic Functions of the 4 Genes Associated with Endometriosis.[a]

Gene	Description	Role	EMT Effect
WNT4	Extracellular signaling molecule that act as ligand to transmembrane frizzled (FZD) receptors	Regulates cytoskeleton via CDC42 in the noncanonical WNT pathway and nuclear transcription via TCF/LEF in the canonical WNT pathway	Expression of WNT4 reverses EMT and stabilizes epithelial integrity
CDC42	Intracellular regulator of the actin cytoskeleton	Polymerizes actin molecules into filamentous actin providing cytoskeletal structure. Essential in filopodia and lamellipodia formation	Overexpression of CDC42 correlates with EMT and is commonly seen in various cancers
ID4	Transcription factor-like molecule that regulates transcription	Dimerizes with TCF/LEF bHLH transcription factors inhibiting their function. Can also bind to ID1-ID3 hereby sequestering them	Generally classified as a tumor suppressor gene with reduced expression correlating with EMT and poorly differentiated cancers
VEZT	Transmembrane protein essential in adherens junctions	Adherens junctions provide the anchor points that link the cytoskeleton to the cell membrane	Reduced expression of VEZT is linked to EMT

[a]The table lists 4 genes that are genetically associated with endometriosis and summarizes their biological roles together with their effect in relation to EMT.

The Mesothelial Barrier

To understand the pathogenic model we propose for endometriosis, it is important to understand the function and properties of the mesothelial lining that cover all surfaces in the peritoneal cavity.

Mesothelial cells form sheet-like barriers between basal layers and luminal compartments of the body. Structurally, mesothelial cells are immobile, arranged in a cobblestone pattern and characterized by having an apical–basal polarity. Mesothelial cells adhere to their mesothelial neighbors via 4 types of adhesive structures: tight junctions, adherens junctions, desmosomes, and GAP junctions.[38] It is the tight junctions and the subjacent adherens junctions in particular that control mesothelial homeostasis and barrier properties.[39] Mesothelial barrier stability can be affected by biological insults like an inflammatory process or surgery, leading to a change in the cellular state from mesothelial homeostasis to wound healing in a process known as epithelial to mesenchymal transition (EMT). EMT is the process of transdifferentiation of epithelial cells (or in this case mesothelial cells) into mesenchymal cells. It is a common and natural process that is particularly well known from embryonic development and wound healing. EMT has been shown to contribute pathologically to fibrosis, cancer development, and metastasis.[24,40] With morphological characteristics opposite those of epithelial cells, mesenchymal cells are motile and characterized by a front–rear polarity, and they are often detached from their mesenchymal and mesothelial neighbors.[41] A patch of mesothelial cells that has undergone EMT no longer provides the sheet-like protective barrier between the basal layer and the luminal space, leaving the underlying basal layers temporarily exposed. EMT is a transient process that is invoked (or highjacked) under special circumstances. It is complemented by mesenchymal-to-epithelial transition (MET), which describes the opposite mechanism of motile mesenchymal cells transitioning into immobile mesothelial cells. Mesothelial cells constantly monitor their environment for potential damage, which triggers wound healing via EMT. Once the damage has been healed, the mesenchymal cells revert to their mesothelial form via MET. The mechanism that is emerging for the mesothelial barrier repair process is a sensitive and plastic process, delicately balanced between mesothelial homeostasis and mesenchymal repair.[42-44]

Clinical Implications of the Mesothelial Barrier in Endometriosis

In addition to the molecular and cellular properties of the mesothelial barrier, clinical observations report macroscopic mesothelial barrier damage in areas with endometrial lesions. The first of these studies reported staining of the pelvic surfaces with methylene blue and noted that endometrial lesions are commonly found in blue-staining areas but rarely in nonstaining areas.[45] This technique is now being used to visualize very small lesions that otherwise would be ignored during surgical treatment of endometriosis. One clinical report on the use of methylene blue to detect endometriosis compared biopsies from nonstaining and staining areas by electron scanning microscopy, showing that nonstaining areas represent healthy and intact mesothelium, whereas areas receptive to methylene blue staining show gaps in the mesothelial barrier that expose the underlying extracellular matrix illustrated in Figure 1.[46]

Discussion

We have provided a functional evaluation of 4 genes that have been associated with endometriosis by GWAS based on the rationale that a shared biologic function between these genes might suggest a pathogenic mechanism. The most prominent functional link that has emerged is the involvement of all 4 genes in the regulation of the actin-cytoskeleton. The actin-cytoskeleton has not previously been implicated in the pathogenesis of endometriosis. However, this conspicuous link, taken together with the fact that endometrial lesions coincide with areas of the peritoneal surface with mesothelial damage, and that the actin-cytoskeleton plays a critical role in

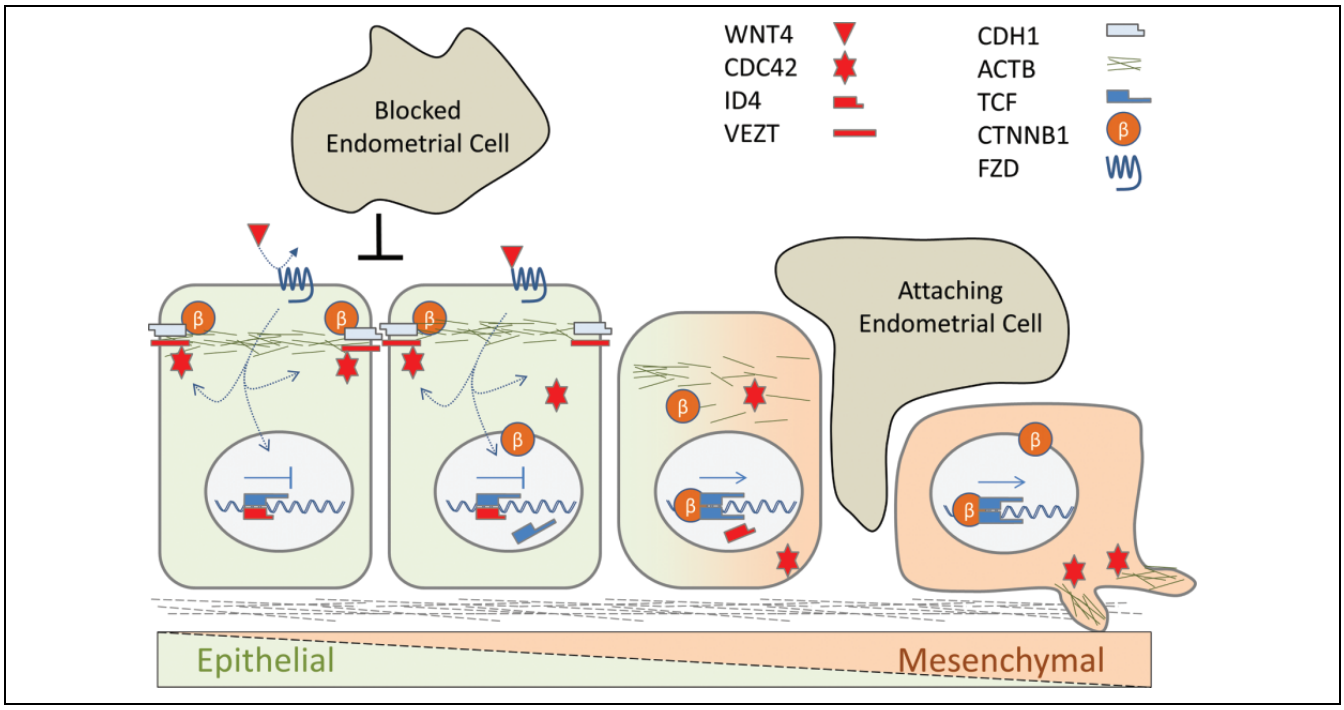

Figure 2. The figure illustrates our hypothesis that the intact epithelial sheet prevents the attachment of endometrial cells to the basement membrane, whereas injured epithelium is vulnerable to attachment and growth of endometrial cells. We propose attachment of an endometrial cell to the basal layer is the initiating step in the development of endometriosis. The epithelial to mesenchymal transition (EMT) is shown from left to right. The 2 left-most cells represent healthy epithelium with intact adherens junctions. The 2 right-most cells show cells in progressively more advanced stages of EMT. As EMT progresses, the epithelial cells lose their adherens junctions and the actin-belt (ACTB) disintegrate, and changes in transcriptional activity are observed. The once immobile epithelial cells become detached and lamellipodia and filopodia develop as illustrated in the right-most cell. The 4 endometriosis genes are represented by red-colored shapes. WNT4, an extra-cellular signaling molecule, is a ligand to the frizzled receptor (FZD) and regulates transcription via the canonical WNT pathway and actin-cytoskeleton via the Rho GTPase CDC42. Vezatin (VEZT) colocates with E-cadherin (CDH1) at the adherens junctions where they provide anchors in the cell membrane for the actin-cytoskeleton. ID4, the bHLH transcription factor inhibitor, is seen paired with the TCF transcription factor in the nucleus, where it prevents transcription. As EMT progresses, ID4 is displaced, allowing TCF transcription to take place. β-catenin (CTNNB1) has 2 distinct functions: (a) it links actin to E-cadherin at the adherens junction and (b) it facilitates TCF transcription.

mesothelial barrier homeostasis, has led us to a new model for the pathogenesis of endometriosis. In this model, women with elevated genetic risk for endometriosis are particularly prone to activation of the EMT repair mechanism that causes temporary loss of mesothelial barrier integrity, which allows endometrial cells to attach to the underlying stroma and establish endometrial lesions. The model we propose is illustrated in Figure 2 and supports experimental observations by Demir et al that menstrual effluent can induce EMT in mesothelial cells and provide an avenue for endometrial fragments to adhere to the submesothelial extracellular matrix.[47]

The 4 genes reviewed here were selected for their proximity to genetic markers linked to endometriosis by GWAS; however, only functional studies can confirm whether these genes actually contribute to endometriosis risk. The first study to address this question reported that the risk allele of rs10859871 (C) near VEZT correlates with increased VEZT expression in blood and endometrium and thus giving credence to the involvement of VEZT with endometroisis.[48]

Numerous models for the pathogenesis of endometriosis have been proposed that generally can be classified as (a) metaplasia, (b) stem cell derived, and (c) transplantation. These are shown in Figure 3 and described in detail in several reviews on the pathogenesis of endometriosis.[49-51] The model we propose belongs to the class defined by transplantation of endometrial cells present in retrograde menstrual fluid where it constitutes a new branch in this class that implicate mesothelial barrier homeostasis as the pathogenic mechanism.

Pelvic Involvement in the Pathogenesis of Endometriosis

Sampson's transplantation theory depends on the adhesion of endometrial cells to the mesothelial barrier and their invasion into the extra-cellular matrix underneath, and thus, the mesothelial barrier homeostasis is likely an important factor in the pathogenesis of endometriosis; however, as pointed out by the authors of a recent review on the pelvic involvement in the pathogenesis of endometriosis, most research has focused on the endometrial tissue itself, while the role of the mesothelium only has enjoyed little attention.[52]

It is generally agreed that mesothelial cells provide an effective antiadhesive surface and provide an effective barrier

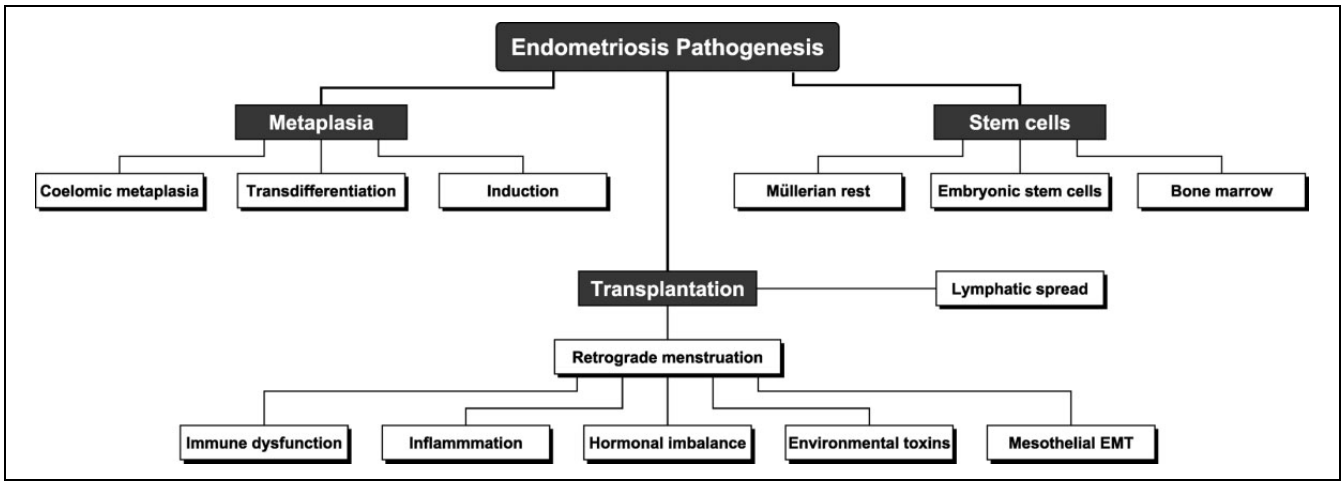

Figure 3. The pathogenic models can be categorized into 3 classes. One class concerns coelomic metaplasia of extra-uterine cells that transdifferentiate into endometrial cells. Another class concerns differentiation of stem cells derived from the basalis layer of the endometrium or possibly Müllerian remnants from embryonic development. The last and most widely supported class concerns transplantation of endometrial cells in the pelvis via retrograde menstruation. It is believed that hormonal, immunological, and inflammatory factors trigger or facilitate the actual development of endometriosis. Other factors have also been proposed that include impaired apoptotic clearance of menstrual tissues and misregulated expression of adhesion factors. The figure outlines the different models for endometriosis pathogenesis based on tree reviews.[50-52] The model we propose here belongs to the class defined by transplantation of endometrial cells present in retrograde menstrual fluid but constitutes a new branch in this class that implicates mesothelial barrier homeostasis as the pathogenic mechanism and represented in the figure as mesothelial EMT in the lower right corner.

against endometrial cell implants. However, it is clear that endometrial cells under certain pathological conditions can breach the barrier and establish endometrial lesions. It has been debated whether the lesion is established via active penetration of the mesothelial barrier[53] or whether implants preferentially adhere directly to the extracellular matrix in areas with mesothelial barrier damage.[54] We consider both processes possible, but expect that endometrial cell adhesion directly to the extracellular matrix to be more common than previously anticipated. The debate on the mesothelial barrier properties extends far beyond endometriosis and is currently being investigated in areas of pelvic cancer metastasis, post-surgical abdominal adhesions, and fibrosis following pelvic dialysis with increasing attention being paid to the role of EMT in these pathologies.[55-57]

Epithelial to Mesenchymal Transition in Endometriosis Progression

Epithelial to mesenchymal transition is a powerful and reversible process of transdifferentiation known primarily from embryonic development and cancer progression. It is reasonable to consider EMT as a potential contributor to endometriosis in connection with stress response, invasiveness, and stemness of endometriotic cells. In fact, one study that evaluated EMT state in epithelial cells from different types of endometrial lesions, including red peritoneal lesions, black peritoneal lesions, deep infiltrating endometriosis, ovarian endometriosis, and menstrual endometrium, found significant differences in the expression levels of cytokeratin, E-cadherin, and vimentin, which suggests the EMT also plays a role in the progression of endometriosis.[58]

A New Treatment Paradigm

The implication of mesothelial barrier integrity as a pathogenic factor in endometriosis opens a new paradigm for the prevention of endometriosis by inhibiting (desensitizing) EMT. It also provides impetus to investigate surgical techniques to minimize damage to the mesothelium, and to time surgery to periods when retrograde menstruation is absent, thereby reducing the risk for the establishment of new lesions. Importantly, therapeutics that have been show to inhibit and reverse EMT are largely nonhormonal and would not burden the patient with undesirable effects associated with hormonal treatments.[59]

Can the Endometriosis Genes Explain Endometriosis-Related Infertility?

A study on single-cell RNA sequence profiling of human preimplantation embryos found robust expression of CDC42 at the 8-cell stage (morula stage), together with consistent but less abundant expression of VEZT and ID4.[60] CDC42 and VEZT in particular play essential roles in trophectoderm differentiation during blastocyst development. During this process, the actin-cytoskeleton matures and all 4 types of junctions appear, allowing the embryo to morph into a tightly packed hollow sphere of polarized epithelial cells. In fact, this transition is the very first instance of MET in development. Under normal conditions, the embryo is ready for implantation at this stage. However, animal

models have shown that both VEZT-null and CDC42-null mice have defects in the organization of the actin cytoskeleton that lead to failed blastocyst development and cause the *conceptus* to die before implantation.[61,62] We suspect improper transcriptional regulation of at least CDC42 and VEZT during early embryoic development might affect proper blastocyst formation and hereby contribute to endometriosis-related infertility.

Conclusions

We provide evidence that genes repeatedly and reliably found to be associated with endometriosis are regulators of the actin-cytoskeleton and thus play a direct role in mesothelial homeostasis. We summarize how EMT temporarily and reversibly induces functional changes in the epithelial cells to conduct repair of the mesothelial barrier. We propose a new model for the pathogenesis of endometriosis where the transplantation of endometrial cells present in retrograde menstrual fluid occurs directly onto the extracellular matrix in areas of the peritoneum left exposed by EMT-induced repair. If this hypothesis is correct, it opens new avenues of endometriosis treatment by regulating the sensitivity of the EMT repair mechanism using nonhormonal compounds.

Authors' Note

HMA drafted the manuscript in discussion with KW. Both authors approved the final article. A provisional patent application has been filed by Juneau Biosciences that include the conclusions reported in the manuscript. Title: Method of Treating Endometriotic Disease by Altering an Epithelial to Mesenchymal Transition. Serial No.: 62/170,346. Filing date: June 3, 2015.

Acknowledgments

The authors would like to thank Dr. Bruce Lessey, MD, for permission to use his illustrations, Dr. Karen Miller, MD, for her critical reading of the manuscript, and Rakesh Chettier, MS, for his valuable comments.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: HMA and KW are employed by Juneau Biosciences who provided salary support for the study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: HMA and KW have direct financial interest in Juneau Biosciences.

Supplemental Material

The online supplemental figure is available at http://rs.sagepub.com/supplemental.

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