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REVIEW ARTICLE

Regulation of epithelial–mesenchymal transition in endometrial cancer: connecting PI3K, estrogen signaling, and microRNAs

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Abstract Endometrial cancer (EC) prognosis is dependent on many factors such as time of diagnosis, histological type, and degree of invasion. Type I EC has a more favorable prognosis as it is less prone to myometrial invasion, which is believed to be the first step in the metastatic cascade. Type II EC displays a more aggressive and motile phenotype, and therefore has a poorer prognosis. Recent work suggests that despite the epithelial nature of Type I and Type II endometrial tumors, both are capable of undergoing an epithelial–mesenchymal transition (EMT), which may facilitate myometrial invasion and metastasis. Activation of the PI3K/Akt pathway has been shown to contribute to EMT through the upregulation of EMT-associated factors. Recent research has also linked estrogen signaling and microRNAs to the regulatory mechanisms that drive EMT in EC. Understanding the intricate relationships between these pathways will provide a better understanding of metastatic progression in EC.

Keywords Endometrial cancer · Epithelial–mesenchymal transition · Phosphoinositide 3-kinase · MicroRNA · Estrogen receptor alpha · G protein-coupled receptor 30

Introduction

Currently, endometrial cancer (EC) is the most common gynecologic malignancy of the female genital tract in developed Western countries [1]. While Eastern countries have a lower incidence of EC, there is still an observed overall increase in its prevalence and fatality [2]. Specific to the United States, it is expected that over 60,000 new cases and over 10,000 deaths will occur 2016, making it the 4th most common neoplasia in women [3].

Like all cancers, prognosis of EC is dependent on many factors including time of diagnosis, progression of tumor differentiation, and degree of invasion [4]. Severity of prognosis is also dependent on histological type. Currently, EC is generalized into two categories (Type I and Type II) based on the clinicopathologic or endocrine features observed upon diagnosis [5]. It should be considered that this dualistic model is criticized in the literature, stemming from The Cancer Genome Atlas which now elucidates a range of mutations associated with EC, defining four distinct categories of EC [6]. The four categories are defined as: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high [7]. Further, this work describes how the newly defined categories fall into the dualistic model used clinically, citing microsatellite instability hypermutated, copy-number low, and copy-number high tumors as often diagnosed as Type I and POLE ultramutated tumors are classically diagnosed as Type II [7]. While this review recognizes the merit of this method of diagnosis, the dualistic model is used throughout the literature. To further complicate this, many patient tumors actually show heterogeneity and combined overlapping molecular and pathological features that challenge the current classification system [8]. The most relevant notion from the Cancer Genome Atlas is the identification of shared genomic features between EC and the basal-like breast cancer subtype. Thus, providing merit to the application of breast cancer characteristics to EC.

About 80 % of ECs are histologically classified as Type I EC [5]. Type I EC is characterized by minimal myometrial invasion, arising from atypical complex hyperplasia, and typically affects pre- and perimenopausal women [9].

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Type I EC is characterized by the expression of estrogen receptor-α (ERα), and risk factors include hyperestrogenism and obesity [9]. In contrast, Type II EC likely has a strong genetic tie, occurring mostly in postmenopausal non-obese women. Additionally, these tumors exhibit a motile phenotype, and are irresponsive to high estrogen stimulation due to the lack of ERα expression [9]. Due to the aggressive nature described, Type II tumors carry a larger risk of metastasis.

Metastasis is described as the spread of a primary tumor to a distal tissue or organ unrelated to the tissue of origin, and is believed to occur in a stepwise process involving local invasion, intravasation, systemic dissemination of tumors cells, extravasation, and colonization (to form micrometastases and eventually clinically relevant macrometastases) [10]. As 90 % of cancer deaths are related to metastasis, understanding the regulatory mechanisms that govern this process is crucial to increasing patient survival. It is hypothesized that the process of metastasis is initiated by epithelial–mesenchymal transition (EMT), ultimately resulting in local invasion. EMT is described as the process in which epithelial cells lose their cell–cell adhesion, and gain a new migratory and invasive mesenchymal phenotype (Fig. 1), [11]. Currently, EMT is not well understood in EC relative to other malignancies including breast, colon, and prostate cancer [12]. It is likely that there are tissue specific mechanisms, however due to the aforementioned connection between EC and basal-like breast cancer, many of the common hallmarks of EMT and EMT-inducing transcription factors are relevant in EC. This mini-review aims to provide a summary of current advancements made in understanding signaling and regulatory pathways involved in EMT in endometrial cancer.

EMT in endometrial cancer

It is well understood that hormone responsive endometrial cancers typically arise from the glandular epithelium [1], but despite the epithelial nature of the tumor, Type I EC can undergo a true EMT to adopt characteristics that facilitate local invasion and ultimately metastasis [13]. Common hallmarks of EMT have been found in EC, including E-cadherin loss (via suppression by the EMT-inducing transcription factor Twist) and other molecular alterations consistent with the mesenchymal phenotype, such as L1 cell adhesion molecule (L1CAM) [14] and B lymphoma mouse Moloney leukemia virus insertion region 1 (BMI-1) upregulation [2]. LICAM can also be transcriptionally induced by TGFβ, a potent inducer of EMT [15].

In breast cancers, presence of the estrogen and progesterone receptors (ER and PR, respectively) are associated with the epithelial phenotype, resulting in less aggressive tumors and a better prognosis [16]. Similarly, well-differentiated endometrial cancers also retain expression of ER and PR, while advanced stage ECs are poorly differentiated tumors and lack one or both of these receptors. Previous studies have described genetic pathways in breast cancer that regulate the process of EMT through an indirect inactivation of estrogen receptor alpha (ERα) [4]. Thus, loss of ERα in metastases from an ERα positive primary tumor suggests a role for EMT in breast cancer progression [16]. Consequently, it is logical to conclude that Type I EC undergoes an EMT to become more invasive. At this time, it is unclear whether or not there is a connection between EMT and loss of ERα in EC, though evidence for this relationship is presented later in this review.

The PI3K/Akt pathway and its role in facilitating EMT

The phosphatidylinositol 3-kinase (PI3K) signaling pathway has many roles, including regulation of cancer cell survival, proliferation, motility, and metabolism [17]. There are currently three established classes of PI3Ks, yet only class 1A PI3Ks are associated with the majority of human cancers [18]. PI3K is a dimeric enzyme consisting

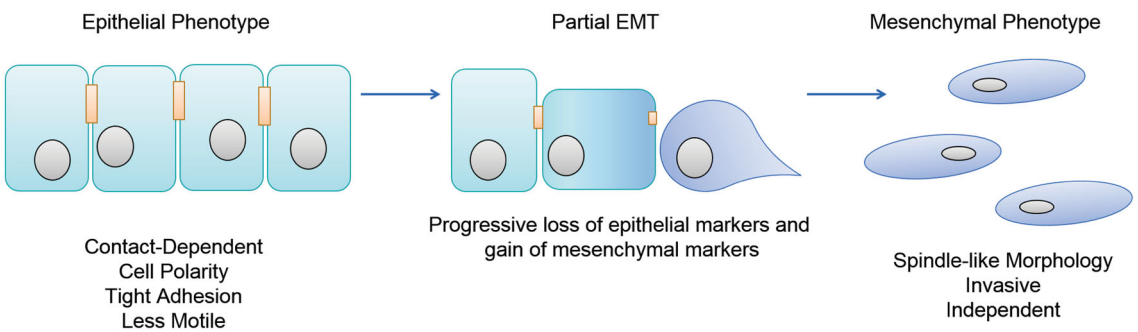

Fig. 1 Schematic of epithelial–mesenchymal transition. Epithelial cells undergoing an epithelial–mesenchymal transition display a progressive loss of epithelial characteristics such as tight cellular junctions and apical-basal polarity, and gain mesenchymal characteristics such as a spindle-like morphology and increased invasive properties. These cells are, therefore, more likely to undergo local myometrial invasion, and may eventually lead to the establishment of distal metastases

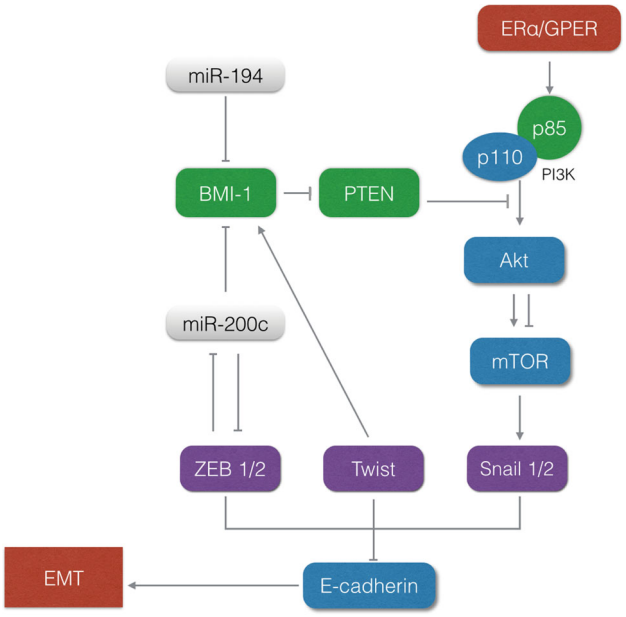

Fig. 2 Regulatory pathways that facilitate epithelial–mesenchymal transition in endometrial cancer. While PI3K/Akt signaling is a well-established regulatory pathway in many cancers, including EC, recent evidence has suggested a role for estrogen signaling in stimulating this pathway. The EMT-inducing transcription factor Snail is downstream of the PI3K signaling pathway, and works in concert with other factors such as ZEB1/2 and Twist to induce EMT through the silencing of E-cadherin. Additional regulatory factors include microRNAs, particularly miR-194 and miR-200c, which inhibit BMI-1, a known EMT inducer and inhibitor of PTEN. Together these regulatory mechanisms provide a model for EMT regulation in EC

of a regulatory p85 subunit and catalytic p110 subunit, and ultimately works to activate Akt in human cancer (Fig. 2). PI3K/Akt signaling activates the mammalian target of rapamycin (mTOR), which is the method of control over cell growth, proliferation, migration and invasion. The PI3K pathway is a therapeutic target in many cancers, and is currently being explored as a target in EC [19]. Interestingly, in both types of EC, there is clear up regulation of the PI3K pathway [20]. In Type I tumors, loss of PTEN (a tumor suppressor that inhibits the PI3K/Akt signaling pathway), and PIK3CA mutations (the gene encoding the p110 subunit) are more common (Fig. 2), [21]. Type II EC tumors are characterized by PIK3CA amplification, and PI3K signaling activation [21]. Research now suggests that beyond the known effects of the PI3K/Akt pathway in human cancers, this pathway is a central mechanism in inducing EMT in multiple cancers, including EC. A large body of data suggests that upon dysregulation, the PI3K/Akt pathway can upregulate known EMT hallmarks in EC such as BMI-1, Snail and Slug, ultimately promoting EMT [22]. These findings suggest that upregulation of the PI3K/Akt pathway can initiate EMT by silencing the universal epithelial marker, E-cadherin (as Snail and Slug directly repress this cellular adhesion protein), leading to increased motility and loss of cellular polarity [23]. Interestingly, PI3K stimulation can be modulated by estrogen signaling, presenting a link between this pathway and the histological characteristics of EC used for diagnosis.

Regulation of PI3K/Akt stimulation by estrogen signaling

ERα is widely accepted as a prognostic marker for response to hormonal therapies in breast cancer. In contrast, ERα as a prognostic marker has been suggested for over 30 years but is only recently confirmed in EC [8]. However, the mechanism in which ERα is linked to the malignant progression of EC has yet to be fully described as the complex biological effects it mediates involve interactions between multiple signaling pathways [20]. It is well supported that estrogen modulation occurs through the binding of estrogen to the estrogen receptor. The receptor then dimerizes and translocates to the nucleus where it modulates the expression of estrogen-responsive genes. Literature supports that estrogen is tied to cell proliferation events through the mediation of gene transcription [24]. However, estrogen also elicits non-transcriptional regulation involving activation of signal transducing pathways, such as the inappropriate overstimulation of the PI3K/Akt pathway in both breast cancer (MCF-7) [25] and EC cell lines [26]. As 70–80 % of EC cases are classified as Type I, which are believed to result from hyperestrogenism and therefore aberrant overexpression of ERα, it is no surprise that forced ERα overexpression contributes to a more aggressive phenotype through the stimulation of the PI3K/Akt pathway [20].

Both Type I and II ECs have been shown to be related to PI3K/Akt activation through estrogen stimulation, though Type II EC lacks ERα. Studies have shown that for both subtypes, estrogen binds to p85, the known regulatory site of the class 1A PI3K consisting of p85/p110 in the PI3K/Akt pathway (Fig. 2), [20]. First observed in breast cancer [20], binding at this site ultimately causes the activation of the Akt pathway [26], which is known to regulate multiple EMT markers, thus establishing a clear correlation between PI3K/Akt activation and EMT. The reported interactions between ERα and PI3K suggest one mechanism for the enhancement of a more aggressive phenotype for Type I EC, though both types upregulate EMT markers through the PI3K/Akt pathway.

However, there is also a clear correlation established between poor ERα expression and an aggressive phenotype, due to the nature of Type II EC which lacks this receptor and is more prone to invasion of surrounding tissues [8]. Low levels of ERα have been associated with increased expression of multiple EMT markers (Snail1/2,

Twist, ZEB 1/2), and a functional link between ERα loss and EMT activation has been supported in other cancer types, namely breast cancer [27, 28]. Yet, regardless of ERα status, there is a clear contradiction considering estrogen triggers PI3K/Akt activation in both Type I and II EC cell lines [26]. Studies show that blocking Akt activation by a PI3K inhibitor in Type I and Type II EC cell lines offers new hints for alternative therapies for EC [26]. This is critical for Type II EC, as this further supports the hypothesis that both types of EC have been shown to be controlled by targeting the PI3K/Akt signaling cascade [26]. Though this seems contradictory, PI3K/Akt activation is only ERα-dependent in Type I EC cell lines [26]. This suggests that the PI3K pathway may be stimulated by estrogen through an alternative receptor in Type II EC.

Lack of ERα expression in most Type II ECs has led to the assumption that these tumors must be estrogen-independent [29], but it is clear from aforementioned work that estrogen somehow stimulates the PI3K/Akt pathway in Type II EC. Of recent importance, GPER (also referred to as GPR30) has been shown to bind estrogen along with other antiestrogens including tamoxifen, and has been recently considered the third estrogen receptor [30]. GPER is a 7-transmembrane spanning G protein-coupled receptor (GPCR) that is localized predominantly to intracellular membranes [31]. A recent study has shown that in the Type II EC cell line Hec50, estrogen signaling via GPER resulted in the activation of downstream kinase pathways, mainly PI3K/Akt [31]. Thus, GPER stands as the current alternate mechanism in which Type II EC tumors can maintain responsiveness to estrogen [31]. Supporting this hypothesis in a clinical setting is evidence that GPER overexpression occurs more frequently in high-grade, invasive endometrial tumors, and overall survival for these patients is poorer [32].

In conclusion, it is clear that estrogen stimulation of the PI3K/Akt pathway plays an important role in cancer progression for both Type I and II EC. However, the effect of this pathway is specific for each subtype. It is likely that ERα overexpression is required for endometrial tumor initiation, and the adaptation of a more aggressive phenotype. However, as seen in breast cancer, loss of ERα can also initiate an EMT [33], and some research suggests that loss of ERα indicates an EMT signature in endometrial cancer [8]. Considering the newly described role of GPER, it is likely that loss of ERα is necessary for the tumor to progress, but stimulation of the PI3K/Akt pathway can still force an EMT via estrogen stimulation through GPER.

MicroRNA regulation of EMT in endometrial cancer

Recent studies have shown that noncoding microRNAs act as crucial modulators of EMT [16, 34, 35]. MicroRNAs are short, 20–24 nucleotide RNA molecules that repress gene expression by binding to the 3′ untranslated region (3′ UTR) of their target mRNA, which leads to translational inhibition or degradation of the mRNA transcript [36]. The relationship between microRNAs and EMT is widely studied in a variety of cancers, however the role of microRNAs in the EMT of EC is poorly understood [1]. Due to tissue specificity, it is inappropriate to draw conclusions from known microRNAs in related carcinomas. Therefore, this review focuses on miR-194 and miR-200c, which have been well studied and emerged as regulators of EMT in EC.

Both miR-194 and miR-200c target and suppress BMI-1, which ultimately inhibits PTEN, and therefore both work to preserve the epithelial phenotype in EC (Fig. 2). BMI-1 is a self-renewal gene and is overexpressed in many cancers including breast, lung, prostate, ovarian and recently in EC [37]. BMI-1 is directly activated by Twist, and is known to suppress PTEN making it crucial for the maintenance of the stem-like phenotype in cancer [38]. Specific to EC, it has been shown that silencing of BMI-1 in the invasive mesenchymal-type EC cell line Hec-50B, resulted in re-expression of the epithelial marker E-cadherin and downregulation of the mesenchymal marker vimentin, leading to reduced cell invasion [2]. It has also been shown that transfection of miR-194 into EC cells directly targets BMI-1 and can reverse an EMT signature [2]. Similarly, inhibition of miR-194 in Hec-1A cells resulted in a 50 % decrease in cell motility [39], supporting the hypothesis that miR-194 inhibits EMT and helps to maintain the epithelial phenotype. With regard to clinical significance, miR-194 levels were decreased in patients with advanced stage Type I EC compared to early stage, and higher levels of miR-194 correlated with better patient survival independent of histological type [40].

Similarly, the miR-200 family of microRNAs is a modulator of EMT-associated factors such as BMI-1 and E-cadherin, ultimately governing the preservation of an epithelial phenotype in multiple cancers, including EC [41, 42]. Of specific interest is miR-200c, which directly targets and inhibits the transcription factors ZEB1 and ZEB2, which are known to bind to the E-cadherin promoter and prevent gene expression (Fig. 2), [43]. Therefore, miR-200c integrity is crucial in cancer progression since it acts as a key modulator in both preventing the silencing of E-cadherin, but also preventing BMI-1 upregulation. Loss of E-cadherin was observed in aggressive, high grade, undifferentiated endometrial tumors, which also correlated with ZEB1 overexpression and a marked loss of miR-200c [44]. Interestingly, a role for estrogen regulation of miR-200c has been proposed [45], and high levels of the miR-200 family member miR-

200a were observed in ERα positive breast tumors [46]. In addition to ZEB1, miR-200c has also been shown to target fibronectin and moesin in EC which are involved in migration, and TrkB which confers anoikis resistance [47]. Therefore, loss of miR-200c during EMT would directly influence the expression of mesenchymal markers involved in tumor cell detachment, migration, and resistance to anoikis. Understanding and identifying microRNAs that work to maintain an epithelial phenotype are crucial, as microRNAs are now being explored as therapeutic targets.

Conclusions

Considering that both Type I and Type II EC have been shown to invade surrounding tissues, EMT clearly plays an important role in the progression of the disease. While EMT is governed by common markers, such as Snail, Twist, and ZEB 1/2, more research is needed to understand the complex relationships between these factors and their role in facilitating EMT in EC specifically. Furthermore, EMT has been associated with a cancer stem cell phenotype, and while this was not discussed in this review, elucidating whether or not this relationship exists in EC will provide a stronger framework for understanding tumor progression and recurrence. As research moves forward, the PI3K/Akt pathway continues to be a central mechanism initiating an EMT in EC. Upon its dysregulation, the PI3K/Akt pathway can upregulate classic EMT hallmarks such as BMI-1, Snail and Slug (which directly repress E-cadherin), resulting in a more motile phenotype. It is well supported that the PI3K pathway can by regulated by estrogen for both EC subtypes, which complicates the understanding of the relationship between clinicopathological subtype and cellular mechanisms as Type II EC lacks ERα. The discovery of GPER now provides a mechanism in which both Type I and II EC can stimulate PI3K/Akt activity to force malignant progression of the tumor. This now provides the possibility of a universal mechanism for EC treatment as PI3K pathway inhibitors do exist. Also of known interest are two microRNAs, miR-194 and miR-200c, both of which are understood to preserve the epithelial phenotype. Introducing these two components into the web of pathways and EMT hallmarks proposes two potential methods of maintaining the epithelial phenotype and potentially suppressing the PI3K/Akt pathway in the context of EMT in EC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent and research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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