Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 420891, 12 pages
http://dx.doi.org/10.1155/2015/420891

Review Article

EMT-Inducing Molecular Factors in Gynecological Cancers

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Received 18 November 2014; Accepted 14 January 2015

Academic Editor: Xin-yuan Guan

Gynecologic cancers are the unregulated growth of neoplastic cells that arise in the cervix, ovaries, fallopian tubes, uterus, vagina, and vulva. Although gynecologic cancers are characterized by different signs and symptoms, studies have shown that they share common risk factors, such as smoking, obesity, age, exposure to certain chemicals, infection with human immunodeficiency virus (HIV), and infection with human papilloma virus (HPV). Despite recent advancements in the preventative, diagnostic, and therapeutic interventions for gynecologic cancers, many patients still die as a result of metastasis and recurrence. Since mounting evidence indicates that the epithelial-mesenchymal transition (EMT) process plays an essential role in metastatic relapse of cancer, understanding the molecular aberrations responsible for the EMT and its underlying signaling should be given high priority in order to reduce cancer morbidity and mortality.

1. Introduction

Epithelial-mesenchymal transition (EMT) is the conversion of epithelial cells to a mesenchymal phenotype, characterized by a loss of epithelial markers, such as E-cadherin, β-catenin, occludin, claudin, plakophilin, cytokeratin, and desmoplakins [1–3], and a gain of mesenchymal markers, such as N-cadherin, vimentin, and fibronectin [1, 3]. Studies have shown that dysregulation of certain transcription factors, oncogenes, tumor suppressors, miRNAs, and growth factor signaling can trigger the initiation of EMT, which is considered a major contributor to the poor prognosis in gynecological cancer.

Ovarian cancer is the most lethal gynecological cancer and tumor metastasis is responsible for its large disease mortality rate. The American Cancer Society (ACS) estimates 21,980 new cases of and 14,270 deaths from ovarian cancer in the USA in 2014 [4]. Ovarian cancer can start from epithelial cells, germ cells, and stromal cells. Platinum complexes and taxanes are usually the first treatment option given. However, about 20~30% of patients show resistance to the platinum-based chemotherapy [5, 6] and about 70~90% of patients who responded to the treatment experience a recurrence of cancer within a window of months to years [5, 7].

The ACS estimates 12,360 new cases of and 4,020 deaths from cervical cancer in the USA in 2014 [4]. Cervical cancer starts in a woman's cervix, which connects the lower part of the uterus to the vagina. HPV types 16, 18, and 31 cause most cervical cancers and vaccinations against HPV as well as the usage of condoms during sexual contact play a role in preventing HPV transmissions. The ACS recommends the administration of a Pap test every 3 years for women aged 21–29 and every 5 years for women aged 30–65 to detect malignancies and cervical intraepithelial neoplasias; early detection is key for good prognosis. While the incidence of cervical cancer has decreased in the past 40 years, it continues to be one of the most common gynecologic cancers in women [2].

Uterine cancer is commonly called endometrial cancer because it mostly starts in the endometrium, the inner lining of the uterus. The development of endometrial cancer is most prevalent in postmenopausal women. For populations within this category, it is highly recommended to have a pelvic exam every year and to report any vaginal bleeding as soon as possible to prevent the cancer metastasis. The ACS estimates 52,630 new cases of and 8,590 deaths from endometrial cancer in the USA in 2014 [4].

Table 1: Factors involved in EMT of gynecological cancers.

	Cervical cancer	Ovarian cancer	Endometrial cancer	Vulvar cancer	Vaginal cancer
Transcriptional regulators	Snail/Slug/Smuc Zeb1/Zeb2 Twist1/Twist2 E47	Snail Zeb1/2 Twist1 KLF4 ETV5 HMGA2	Snail/Slug Zeb1 Twist1/Twist2 KLF17 ETV5 HMGA2	Snail/Slug Twist2	
Growth factors	TGF-β EGF	TGF-β EGF /HB-EGF VEGF HGF FGF	TGF-β EGF VEGF IGF1		
Oncogenes	HPV16 E6/E7 Sam68 AEG1 FTS	PIK3CA AKT2	BMI-1		
Tumor suppressors	Klotho SFRPs	P53 SFRPs RASAL2	P53		
miRNAs	miR-200 family miR-155 miR-361-5p	miR-200 family miR-181 miR-20a miR-214	miR-200 family miR-155 miR-130		
Other molecular factors	β1-integrin receptors MMPs 7/9 IL6 RhoC Gelsolin TBLR1 TACC3 KCC3 EphB2 Nogo-B TNF-α	β1-integrin receptors MMP 9 IL6 RhoC MUC4/16 ET-1 BMP4 CCR7 TG2 PAK1 MTA1 Sema3E Gb2 FN1	ERα TrkB PR	ERα/β	

According to the ACS, about 4,850 new cases of and 1,030 deaths from vulvar cancer will occur in the USA in 2014 [4]. Cancer of the vulva is a rare disease. It forms in a woman's external genitalia and makes up 3 to 5% of all gynecologic malignancies [8]. Most vulvar cancers occur in older women after the development of precancerous variations called vulvar intraepithelial neoplasias (VIN) that last for several years before developing into cancer. It also can affect younger women infected with HPV types 16, 18, 33, and 35 [9].

Vaginal cancer is unusual and accounts for less than 2% of gynecologic malignancies with an expected 3170 new cases and 880 deaths in the United States in 2014 [4]. About 70% of cases of vaginal cancer are squamous cell carcinomas, which begin in the epithelial lining of the vagina. The main risk factors are HPV subtypes 16 and 18. In order to prevent this type of cancer, vaccination and the routine Pap test are highly recommended.

An increase in cellular survival, migration, invasion, metastasis, recurrence, and drug resistance is observed in gynecological cancers and may be due to EMT [2, 10–14]. Therefore, we strongly believe that investigating the dysregulation of molecular networks responsible for EMT and its consequences may be critical to a better understanding of the etiology of the cancers and development of new therapeutic modalities. In this review, we will discuss the current knowledge regarding factors involved in EMT in each of the gynecological cancers (Table 1).

2. Transcription Factors

Several studies have shown the importance of the Snail family of transcription factors in inducing EMT in cervical cancer, endometrial cancer, ovarian cancer, and vulvar cancer [1, 3, 9, 15]. The Snail family consists of zinc finger-containing transcription factors and includes Snail (SNAI1), Slug (SNAI2), and Smuc (SNAI3) [1]. In cervical cancer cells, Snail inhibits the expression of claudins, occludin, and thrombomodulin [1, 16, 17]. Snail and Smuc have both been

associated with lymph node metastasis [15]. In endometrial cancer cells, Snail is overexpressed in both primary and metastatic tumors, and both Snail and Slug reduce E-cadherin expression [3]. Overexpression of Snail in ovarian cancer cells induced mesenchymal markers, such as tea-shirt zinc finger homeobox (TSHZ1), collagen type Vα, and fibrillin-1 (FBN-1), while suppressing E-cadherin, myosin-5C, keratin-18, keratin-8, annexin-A3, and suppressor of tumorigenicity 14 (ST14) [18]. In vulvar cancer, both Snail and Slug inhibit the expression of E-cadherin and increase the expression of vimentin [9].

Zeb1/2 (collectively known as SIP1) are two-handed zinc factors that have been shown to cause EMT. In cervical cancer cells [1] and ovarian cancer cells [19], both transcription factors reduce the expression of E-cadherin. Zeb1 also induced the upregulation of vimentin in cervical cancer [2]. Its nuclear expression in cervical cancer cells was positively associated with increased invasiveness, pelvic lymph node metastasis, and late FIGO staging [20]. In ovarian cancer cells, overexpression of Zeb1 induced mesenchymal markers TSHZ1 and FBN1, thus promoting EMT [18]. In endometrial cancer, Zeb1 decreased the expression of E-cadherin [3].

Twist1/2 are basic helix-loop-helix transcription factors sharing 66% structural homology and repress E-cadherin expression in cervical cancer [1, 21]. Twist1 is a master regulator of EMT in cervical cancer and its expression is a poor prognostic factor [1, 22]. Its elevated expression has also been associated with chemo- and radiotherapy resistance in cervical cancers [22, 23]. Twist2 expression in cervical squamous cell carcinoma patients is a predictor for metastatic potential [1, 24]. Expression of these transcription factors in cervical cancer cells is responsible for the activation of AKT and β-catenin pathways and for the preservation of stem cell-like characteristics of the cells [1, 25]. Twist overexpression has been demonstrated in invasive endometrial carcinomas and is associated with a lower patient survival rate [3, 26]. It represses the expression of E-cadherin [3]. In ovarian cancer, Twist1 overexpression promotes the expression of N-cadherin and reduces the expression of keratin-8 and E-cadherin [18]. Twist2 plays a role in the induction of EMT in vulvar cancer and has been shown to downregulate E-cadherin [9].

It has been shown that the expression of transcription factor Kruppel-like factor 17 (KLF17) induces the expression of Twist in endometrial cancer cells [27]. This led to the subsequent activation of EMT, increased cell invasion, and drug resistance [27]. Both Twist and KLF17 are upregulated in endometrial cancer cells [27]. KLF4, a transcription factor related to KLF17, acts as a tumor suppressor by inhibiting cell proliferation, migration, and invasion through attenuating transforming growth factor-β (TGF-β) induced EMT in ovarian cancer cells [28].

Ets variant 5 (ETV5) belongs to the polyoma enhancer activator 3 (PEA3) family of transcription factors and has been found to induce EMT in endometrial cancer cells by increasing the transcription of Zeb1 [14]. Endometrial cancer cell lines that had undergone EMT accompanied by modified cell adhesion molecules and cytoskeleton reorganization were found to have upregulated ETV5 [14, 29]. ETV5 has also been shown to increase the transcription of matrix metalloproteinases 2 (MMP2) and HEP27, which allow for cellular invasion by degrading extracellular matrix and prevent apoptosis in tumor cells, respectively [14, 30, 31].

There is new evidence that E47 and high-mobility group AT-hook 2 (HMGA2) could play a role in inducing EMT in gynecologic cancers. E47 is a basic helix-loop-helix transcription factor that represses the expression of E-cadherin in cervical cancer cells [1]. HMGA2 represses the expression of E-cadherin in endometrial carcinoma cells [3, 32] and is inversely correlated with the expression of tumor suppressor lumican (LUM), an inhibitor of EMT, in ovarian cancer [33].

3. Growth Factors

TGF-β has been suggested to be associated with the progression of ovarian [34, 35], endometrial [14], and cervical cancers [1]. Overexpression of TGF-β (TGF-β1, TGF-β2, and TGF-β3) in ovarian cancer activates a TGF-β receptor/Ras-Related C3 botulinum toxin substrate 1 (RAC1)/Smad-dependent signaling pathway [36, 37] and in cervical cancer activates mitogen-activated protein kinases (MAPK), Smad, Wnt, tumor necrosis factor-α (TNF-α), and nuclear factor-κB (NF-κB) pathways [2, 38], promoting EMT.

Epidermal growth factor (EGF) has been shown to be a potent EMT inducer in a variety of solid tumors, including cervical [39], ovarian [10], and endometrial [14] cancer. In ovarian cancer cells, EGF binds to the EGF receptor (EGFR), thus inducing EMT activation through phosphorylation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT3) pathway. Yagi et al. also showed that heparin-binding epidermal growth factor-like growth factor (HB-EGF) is involved in ovarian cancer metastasis through EMT [40]. Lee et al. have reported that the chronic treatment of EGF in cervical cancer cells increased phosphorylation of GSK-3β, a regulator of Snail [41], inducing EMT [39]. The chronic treatment of EGF in cervical cancer cells has been shown to increase phosphorylation of glycogen synthase kinase-3 (GSK-3β), a regulator of Snail [41], thus inducing EMT [39]. The suppression of EGF signaling in endometrial cancer cells with EGF inhibitor AG1478 represses EMT and cellular migration and invasion [24].

High levels of hepatocyte growth factor (HGF) and its tyrosine kinase receptor (cMET) are found in malignant ovarian cysts and ascitic fluid from women with ovarian carcinomas [42]. HGF, through activation of the MAPK and phosphatidylinositide-4,5-bisphosphate 3-kinase (PI3K)/AKT pathways, promotes phosphorylation of p70S6K, which induces EMT in ovarian cancer cells by increasing expression of Snail and MMP9 [43, 44].

Vascular endothelial growth factor (VEGF) is an angiogenesis stimulator and its increased expression is associated with tumor growth in endometrial [14] and ovarian cancers [45]. VEGF allows cancers to grow by enabling the development of new blood vessels for nutrient and oxygen supply and metastatic spread. Ptaszynska et al. showed that, in metastatic ovarian cancer cells, VEGF stimulates the expression of protein autotaxin (ATX) [45], a potent motility factor, which produces the bioactive lysophospholipid (LPA) responsible

for regulating cellular migration, cell-cell interactions, and inhibiting apoptosis [46]. Furthermore both VEGF and TGF-β1 could be responsible for aberrant expression of Ras homolog gene family, member C (RhoC), which is involved in the EMT of ovarian cancer cells [47]. In endometrial cancer, Mirantes et al. showed that VEGF and insulin-like growth factor-1 (IGF1) activate Snail, Slug, Twist, and E47 [3].

Fibroblast growth factor 2 (FGF2), which is a member of the FGF family, induces ovarian cancer cell invasion by the activation of the PI3K/Akt/mammalian target Of rapamycin (mTOR) and MAPK/extracellular signal-regulated kinase (ERK) signaling pathways. This subsequently increases the expression of Slug and ZEB1, which are responsible for E-cadherin downregulation [48].

4. Tumor Suppressors

p53 is a well-known tumor suppressor that acts as an inhibitor of EMT [49]. p53 gain-of-function mutants (R273H, R175H, or C135Y) showed downregulation of miR-130b and subsequently increased the expression of Zeb1 and induced EMT in endometrial cancer [50]. Loss-of-function of p53 was also observed in 96% of high-grade serous ovarian cancers [51]. In fact, loss of p53 through Twist activation [52] or its abrogation is associated with mammalian DNA methyltransferase (DNMT) and promoter methylation that represses E-cadherin [53], promoting EMT.

Klotho, a single-pass transmembrane protein, was originally identified as a suppressor of aging [54] and acts as a modulator for insulin [55] and insulin-like growth factor-1 receptor (IGF-1R) [56] signaling and a coreceptor for FGF23 [57]. Mice lacking Klotho have a short lifespan [54] while high levels of Klotho increase lifespan [58]. Studies have demonstrated its role as a tumor suppressor [56, 59, 60]. Klotho has been shown to be downregulated in cervical cancer due to epigenetic silencing of the promoter region [61] and its downregulation is associated with cervical cancer invasiveness [62]. Overexpression of Klotho in cervical cancer cells upregulates E-cadherin and downregulates N-cadherin, Slug, and Twist [62]. In addition, overexpression of Klotho inhibits cell motility and invasiveness by suppressing expression of MMP-7 and MMP-9 and the Wnt/β-catenin pathway [62].

Secreted frizzled-related proteins (SFRPs) are extracellular signaling molecules that inhibit the Wnt pathway [63] and are methylated in cervical cancer cells [2, 64]. Overexpression of SFRPs reduces the expression of Twist, Slug, and Snail and upregulates E-cadherin, thus reducing the invasive ability of cervical cancer cells [2, 65]. In ovarian cancer, an *in vitro* study conducted by Su et al. shows that silencing SFRP5 through methylation induces EMT through Twist and activates AKT2 [66].

RAS protein activator-like 2 (RASAL2), a GTPase activating protein (GAP) that has been identified in ovarian cancer as a tumor suppressor, plays an important role in EMT and metastasis [67]. Reduced levels of RASAL2 mRNA activate the Ras-ERK pathway *in vivo* and *in vitro* [67]. Mutations in RAS are very common in malignant diseases and increase the pathological grades of the disease by suppressing E-cadherin and elevating vimentin expression [67], suggesting that downregulation of RASAL2 may promote EMT activation [67].

5. Oncogenes

HPV types 16, 18, 33, and 35 have been associated with the development of cervical and vulvar cancers [9]. HPV 16 E6/E7 oncoproteins induce the development of cervical intraepithelial neoplasias [2, 68]. Transfection of normal human foreskin keratinocytes with HPV16 E7 induced the EMT program [1, 69] and cervical cancer cells transfected with HPV16 E6/E7 oncogenes experienced downregulation of E-cadherin and upregulation of vimentin [2, 70]. Lastly, exposure to low-dose estrogen and FGF along with HPV16 E7 transfection induced the production of invasive cervical cancer cells [2, 70].

Src-associated substrate in mitosis of 68 kDa (Sam68) is a member of the signal transducer and activator of RNA (STAR) family of RNA-binding proteins [71] and is involved in various cellular processes, including T cell receptor [72] and insulin receptor signaling [73], transcriptional regulation [74], mRNA processing [75], TNF-induced NF-κB activation, and apoptosis [76]. Li and colleagues have shown that Sam68 is overexpressed in cervical cancer cell lines and tissues and its expression is associated with pelvic lymph node metastasis [77]. Also, its cytoplasmic subcellular localization is associated with poor overall survival of cervical cancer patients [77]. Depletion of Sam68 inhibits migratory and invasive potential of cervical cancer cells as well as the expression of vimentin and fibronectin, possibly through suppressing the Akt/GSK3β/Snail pathways [77].

Astrocyte-elevated gene 1 (AEG1) was identified as an HIV-inducible gene in astrocytes [78] and has been implicated in the development, progression, and pathogenesis of various tumors [79–81]. Overexpression of AEG1 resulted in downregulation of E-cadherin and upregulation of N-cadherin and vimentin, thus increasing invasive capability of cervical cancer cells [2, 82]. Also, it is suggested that AEG1 could potentially play a role in the resistance of cervical cancer cells to paclitaxel and cisplatin chemotherapy [2, 82].

Fused-toe homologue (FTS) was originally identified as a gene deleted in the Fused toes mouse mutation [83]. FTS has been involved in uterine cervical carcinogenesis and correlates positively with staging and grading of cervical cancer [2, 84]. Induction of FTS expression reduces expression of E-cadherin and claudin and upregulates expression of N-cadherin and Slug [2, 85]. Knockdown of FTS inhibits EGF-induced EMT and migratory ability of cervical cancer cells [2, 85].

B lymphoma mouse Moloney leukemia virus insertion region 1 (BMI-1) activates EMT in many human cancers and is overexpressed in endometrial cancer [86]. Endometrial cancer cells expressing endogenous BMI-1 show increased invasive ability in comparison to those not expressing endogenous BMI-1 [86]. Those expressing BMI-1 expressed spindle-like, fibroblast morphology, reduced E-cadherin

expression, and increased vimentin expression [86]. miR-194 targets BMI-1 and silences its effects, reversing the invasive ability of cells, increasing E-cadherin expression, and decreasing vimentin expression [86]. Furthermore, knockdown of BMI-1 inhibited *in vitro* cell proliferation [86].

6. miRNA

miRNAs are small noncoding RNAs that bind target mRNAs and inhibit gene translation [87]. Studies have shown that the miR-200 family, consisting of miR-141, miR-200a, miR-200b, miR-200c, and miR-429, play a crucial role in EMT. miR-200 is a master regulator of cervical cancer and ovarian cancer EMT [2, 51]. Downregulation of miR-200 in mesenchymal cells of uterine carcinosarcomas and ovarian cancer cells increases the expression of Zeb1/2 [3, 51, 88, 89]. A study conducted by Lei et al. has shown that miR-155 functions as a tumor suppressor in cervical cancer cells [90] and other studies have shown its oncogenic role in a variety of human cancer cells and tumors [91–93]. They also reported that overexpression of miR-155 suppresses the migratory/invasive capability of cervical cancer cells and EGF-induced EMT through upregulation of p53 and downregulation of Smad2 [90]. Interestingly, miR-155 was found to be overexpressed in endometrial cancer cells and to induce EMT [14]. It is thought that its mode of action is related to TGF-β. When normal murine mammary gland epithelial cells were treated with TGF-β, they underwent EMT and also upregulated miR-155 [14, 94]. The ectopic expression of miR-155 led to increased cellular invasiveness and inhibited the formation of tight junctions [14, 94]. Future work should be done to pinpoint the differences in pathways that cause miR-155 to be an EMT suppressor in cervical cancer but an EMT activator in endometrial cancer. miR-361-5p is elevated in cervical cancer cells and promotes cell proliferation, lymph node invasion, and metastasis through EMT [2, 95]. miR-214 [96] and miR-20a [97] promote EMT by downregulation of PTEN in ovarian cancer. Also miR-181a acts as an inducer of TGF-β by Smad7 inhibition and promotes EMT in epithelial ovarian cancer [98].

7. Other Molecular Factors

Endothelin-1 (ET-1) is a vasoconstrictor peptide that binds two G-protein-coupled transmembrane receptors (ET_A and ET_B) [99, 100] and has been implicated in EMT in ovarian tumors [100]. In particular, elevated levels of ET-1 activate ET_A receptor, which activate an integrin-linked kinase- (ILK-) mediated signaling pathway. This causes the inhibition of GSK-3β and the E-cadherin promoter and increased levels of β-catenin, N-cadherin, and Snail, which drives the cells to a fibroblastoid and invasive phenotype [100]. Also, Colas et al. showed that, in endometrial cancer, ILK signaling activates Snail, Slug, Twist, and E47, promoting EMT [14].

Bone morphogenetic protein 4 (BMP4) belongs to the TGF-β superfamily proteins and is highly expressed in ovary cell types [101]. BMP4 in ovarian cancer cells induces EMT via the (BMP4)/anaplastic lymphoma kinase (ALK) pathway, increasing the expression of mRNA and protein levels of Snail and Slug and downregulating E-cadherin [19, 101, 102].

Transmembrane protein receptors, such as integrin, are also involved in cervical [103] and ovarian tumor progression [104]. Integrins consist of 18α and 8β subunits and they play a major role in cell migration [105]. In cervical cancer, αv β3 and αv β6 are associated with decreased patient survival [103]. In ovarian cancer, it has been found that α5β1 integrin binds to fibronectin to induce EMT [37].

MMPs are a family of zinc-required matrix-degrading enzymes. Several groups have found that the increased expression of MMPs can predict tumor aggressiveness and poor patient survival [106, 107]. A study has shown that cervical cancer cells treated with MMP7 and MMP9 adopt mesenchymal characteristics with high migratory ability [2, 108]. The inhibition of MMP expression causes the inhibition of Vim1, fibronectin, and Snail expression [2, 108]. This suggests that MMPs play a direct role in inducing EMT processes.

Mucins 4/16 (MUC4/16) are identified as tumor antigens in epithelial ovarian cancer. Overexpression of MUC16 in epithelial ovarian cancer downregulates E-cadherin and upregulates N-cadherin and vimentin, thus promoting tumor metastasis [22]. In ovarian cancer cells, MUC4 overexpression upregulates Snail, focal adhesion kinase (FAK), Twist1/2, and MAPK signaling cascade proteins and downregulates E-cadherin and CK18 expression [109].

Chemokine receptor 7 (CCR7) is constitutively expressed in epithelial ovarian cancer. CCR7 and its ligand CCL19/21 participate in EMT development, thus promoting ovarian cancer metastasis [110].

Interleukin 6 (IL6) is a proinflammatory cytokine that induces EMT in cervical and ovarian cancers [2, 111]. In cervical cancer, IL6 promotes EMT activation via the STAT3 pathway [2, 112]. In ovarian cancer, increased levels of EGF stimulate IL6 secretion, which promote the mobility and resistance to chemotherapy via the JAK/STAT3, SHP-2/Ras, MAPK, and PI3K/Akt signaling pathways [111, 113].

Rho-GTPases play a key role in cervical cancer EMT due to its induction of the downregulation of cell adhesion molecules and cytoskeleton reorganization [1]. RhoC is involved in the reorganization of the actin cytoskeleton and in the regulation of cell shape, motility, and attachment [47, 114]. Stable expression of RhoC enhanced migratory, invasive, and tumor-forming abilities of cervical cancer cells [1, 115]. RhoC has been reported to be a downstream effector of Notch receptor [115]. The knockdown of RhoC and Notch receptor caused decreased expression of fibronectin and actin stress fibers during wound healing [1, 115]. Gou et al. showed that overexpression of RhoC downregulates E-cadherin and upregulates B-cadherin and α-SMA, thus promoting cell migration, invasion, and lamellipodia formation, and suggested that RhoC-mediated EMT could be initiated by TGF-β1 and VEGF [47].

Gelsolin is an actin-binding protein that is upregulated in cervical cancer cells [1, 116]. Cervical cancer patients expressing gelsolin had a decreased 5-year survival rate in comparison to those not expressing gelsolin [1, 116]. Decreased gelsolin expression caused decreased cell migration, MMP2

expression, vimentin, and upregulated E-cadherin expression in cervical cancer cells [1, 116].

Cell surface receptor tyrosine kinase (TrKB) and its ligand, brain-derived neurotrophic factor (BDNF), are upregulated in endometrial carcinoma in comparison to normal epithelial cells [117]. High TrKB levels are associated with EMT phenotype and lymph node metastasis, and its knockdown resulted in the decreased migratory and invasive abilities of the endometrial cancer cells [117].

The expression of transducin β-like-related 1 (TBLR1), a transcriptional cofactor, in cervical cancer cells induces the expression of Vim1 and fibronectin while reducing the expression of β-catenin [2, 118]. It activates the NF-κB and Wnt/β-catenin pathways to upregulate expression of Snail and Twist [2, 118]. Furthermore, TBLR1 expression has been shown to induce the invasiveness of cervical cancer cells [2, 118].

Transforming, acidic coiled-coil protein 3 (TACC3) plays a role in the interaction of actin with microtubules and regulates the centrosome during cell mitosis. We have demonstrated that EGF/EGFR signaling is critical for TACC3-mediated EMT in cervical cancer [119].

K+/Cl− cotransporters (KCC) play an important role in the regulation of cell volume and cytoplasmic chloride, transepithelial transport [120, 121], and cervical tumorigenesis [122, 123]. Hsu et al. have reported that KCC3, one of the KCC isoforms (KCC1–KCC4), is significantly elevated in primary cervical carcinomas and its overexpression causes EMT, accompanied by cell morphological changes, downregulation of E-cadherin and β-catenin, upregulation of vimentin, and enhancement of cell proliferation and invasiveness in cervical cancer cells [124].

Erythropoietin-producing human hepatocellular carcinoma (Eph) receptor B2 is a member of the largest family of receptor tyrosine kinases in the human genome [125] and is phosphorylated when its ligand binds, subsequently triggering downstream signaling cascades [126]. Gao et al. have reported that EphB2 is overexpressed in cervical cancer and its expression is associated with tumor progression [127]. In addition, ectopic expression of EphB2 in cervical cancer cells results in an increase in cell migration/invasion and EMT signature fibroblast-like morphology, loss of cell-to-cell contact, and downregulation of E-cadherin. Its ectopic expression also resulted in upregulation of mesenchymal markers (vimentin, CDH2, and fibronectin) and EMT inducers (Snail1, Snail2, and Twist2), as well as an acquisition of stem cell properties via activation of the R-Ras pathway, whereas its depletion has an opposite effect [127].

Nogo isoforms (Nogo-A, Nogo-B, and Nogo-C) belong to the reticulum superfamily and share a conserved reticulum homology domain (RHD), which contains a 66 aa loop domain, Nogo-66 [128]. Nogo-B was identified as a novel human apoptosis-inducing protein [129] and its overexpression has been shown to induce apoptosis through endoplasmic reticulum stress-specific signaling pathways [130] and to play a role in cell adhesion and migration [131, 132]. Nogo-B expression is elevated in cervical cancers and its expression is correlated with the degree of cervical cancer metastasis [128]. Overexpression of Nogo-B in cervical cancer cells promotes cell migration, invasion, and EMT and inhibits cell adhesion [128]. Nogo-B interacts with Fibulin-5, a member of the Fibulin family [133] which contains a conserved Arg-Gly-Asp (RGD) motif that binds to integrins, mediates endothelial cell adhesion, and suppresses angiogenesis [134]. Downregulation of Fibulin-5 inhibits cell migration/invasion, upregulates E-cadherin, and downregulates mesenchymal markers (N-cadherin and vimentin) as well as EMT inducers (Snail, Twist1, Zeb1, and Zeb2) [128].

Estrogen receptors α (ERα) and β (ERβ) have been recognized in the normal vulvar epithelium [135, 136]. Zannoni et al. showed that changes in both ERα and ERβ expression, likely due to low estrogen, induce EMT in vulvar squamous cell carcinomas, which is associated with a significant reduction in the expression of E-cadherin [136]. In endometrial cancer the reduction of ERα correlated with the activation of Wnt, Sonic hedgehog, and TGF-β signaling and reduced patient survival [137]. In ovarian cancer, 17β-estradiol (E2) promotes EMT via an ERα-dependent pathway [138]. In the presence of E2, Snail and Slug are significantly upregulated while E-cadherin is downregulated [138].

Progesterone receptors (PR) have been indicated as potential EMT suppressors in endometrial cancer [14]. PR expression in endometrial cancer is a good prognostic factor for patients and is associated with successful treatment with medroxyprogesterone acetate (MPA) [14, 139]. This may be due to the fact that a loss of progesterone signaling induces EMT. It was shown that MPA treatment in PR-modulated cells downregulates the expression of mesenchymal cell markers, migration, and several signaling pathways, including EGF, IGF1, IL6, integrin/ILK, platelet-derived growth factor (PDGF), TGF-β, VEGF, and Wnt/β-catenin signaling pathways [14, 140].

Tissue transglutaminase (TG2), a multifunctional protein involved in cellular adhesion, promotes EMT [19] in ovarian carcinoma by activating NF-κB complex, which induces Zeb1 [141]. It also upregulates MMP2 secretion [142] and downregulates E-cadherin [143].

p21-activated kinase (PAK1), a serine/threonine protein kinase, coordinates cell morphology and motility [144] and is targeted by miRNA 222 [145]. PAK1 is highly expressed in primary ovarian cancer and downregulates E-cadherin through Snail [87].

Metastasis-associated gene 1 (MTA1) is considered a critical factor in tumor metastasis [146]. Knockdown of MTA1 decreased migratory, invasive, and adhesive capabilities of cervical cancer cells as well as the expression of E-cadherin and p53 [147]. In ovarian cancer, overexpression of MTA1 promotes oncogenic transformation and downregulates E-cadherin by increasing expression of Snail and Slug [148].

Semaphorin 3E (Sema3E) is a secreted molecule that controls angiogenesis [149] and tumor cell survival and serves as a ligand for Plexin D1 [150]. High levels of Sema3E are found in high-grade ovarian endometrioid carcinoma [151]. Sema3E/Plexin D1 promotes increased migratory and invasive potential and metastatic growth of ovarian endometrioid carcinoma cells [151]. Furthermore, Sema3E/Plexin D1 induces EMT through nuclear localization of Snail and PI3K

and ERK/MAPK signaling pathways, which play an important role in the Sema3E/Plexin D1-mediated EMT process in ovarian endometrioid carcinoma cells [151].

GRB2-associated-binding protein 2 (Gab2), a member of the Gab/DOS family of scaffolding adapter proteins [152], is highly expressed in ovarian cancer [153]. Overexpression of Gab2 reduced expression of E-cadherin and increased Zeb1 expression and cell migratory and invasive abilities through the activation of the PI3K pathway in ovarian cancer cells [153].

8. Conclusion

Metastasis is the major cause of death from all gynecological cancers. Many studies have found that EMT plays a central role in cancer metastasis by deregulating the molecular network. This allows the downregulation of epithelial markers, upregulation of mesenchymal markers, and increased migration, invasion, cell survival, metastasis, and recurrence.

The knowledge of all factors that contribute to the activation of EMT opens a door to new therapeutic strategies that can inhibit metastasis in all gynecological cancers. Several studies have found that EMT could be pharmacologically targeted. Selumetinib, a small molecule MEK inhibitor, is able to suppress EMT in patients with frequent low-grade serous epithelial ovarian cancer [154]. ILK inhibitors, KP392, QLT0267, and T315, can suppress ILK- EMT activity in epithelial ovarian cancer [155]. *In vitro* studies have also shown that the EGF inhibitor, AG1478, causes EGF-induced EMT in cervical, ovarian, and endometrial cancer [155]. Additionally, it has been found that inhibitors of FAK (focal adhesion kinase, induced by MUC4-overexpressing cells) [109], ETaR (zibotentan), and TG2 (KCC-009) suppress EMT in ovarian cancer [155]. Furthermore, vaccines and antibodies against mucins (MUC16) can limit tumor metastasis in ovarian carcinoma [113]. New improvements have been made in targeting EMT via epigenetic or miRNA control in epithelial ovarian cancer. For example, restoration of the miR-200c family negatively regulates the EMT process [154]. HPV vaccine targeting HPV16 E6/E7 antigens in patients with high-grade cervical dysplasias actually caused regression of the dysplasias [156]. Lapatinib, a drug used in endometrial cancers, blocks EGFR tyrosine kinase, thereby preventing EGF signaling [157]. The rapid understanding of molecular dysregulation involved in EMT activation creates the hope for future approaches to more personalized treatments that will have a positive impact on survival rate.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Loredana Campo and Catherine Zhang contributed equally.

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