Clin Transl Oncol
DOI 10.1007/s12094-012-0866-3

EDUCATIONAL SERIES – BLUE SERIES

ADVANCES IN TRANSLATIONAL ONCOLOGY

The EMT signaling pathways in endometrial carcinoma

Eva Colas · Nuria Pedrola · Laura Devis · Tugçe Ertekin · Irene Campoy · Marta Llauradó · Marina Rigau · Mireia Olivan · Marta Garcia · Silvia Cabrera · Antonio Gil-Moreno · Jordi Xercavins · Josep Castellvi · Angel Garcia · Santiago Ramon y Cajal · Gema Moreno-Bueno · Xavier Dolcet · Francesc Alameda · Jose Palacios · Jaime Prat · Andreas Doll · Xavier Matias-Guiu · Miguel Abal · Jaume Reventos

Received: 4 June 2012 / Accepted: 11 June 2012

Abstract Endometrial cancer (EC) is the most common gynecologic malignancy of the female genital tract and the fourth most common neoplasia in women. In EC, myometrial invasion is considered one of the most important prognostic factors. For this process to occur, epithelial tumor cells need to undergo an epithelial to mesenchymal transition (EMT), either transiently or stably, and to differing degrees. This process has been extensively described in other types of cancer but has been poorly studied in EC. In this review, several features of EMT and the main molecular pathways responsible for triggering this process are investigated in relation to EC. The most common hallmarks of EMT have been found in EC, either at the level of E-cadherin loss or at the induction of its repressors, as well as other molecular alterations consistent with the mesenchymal phenotype-like L1CAM and BMI-1 up-regulation. Pathways including progesterone receptor, TGFβ, ETV5 and microRNAs are deeply related to the EMT process in EC.

Introduction

Endometrial cancer (EC) is made up of a biologically and histologically diverse group of neoplasms characterized by their distinct pathogeneses. These differential characteristics

E. Colas · N. Pedrola · L. Devis · T. Ertekin · I. Campoy · M. Llauradó · M. Rigau · M. Olivan · M. Garcia · A. Doll · J. Reventos (✉)
Biomedical Research Unit, Vall d'Hebron Research Institute and University Hospital, Barcelona, Spain
e-mail: jreventos@ir.vhebron.net

E. Colas · N. Pedrola · L. Devis · T. Ertekin · I. Campoy · M. Llauradó · M. Rigau · M. Olivan · M. Garcia · A. Doll · J. Reventos
Universitat Autònoma de Barcelona, Barcelona, Spain

S. Cabrera · A. Gil-Moreno · J. Xercavins
Servei de Ginecologia, Hospital Vall d'Hebron, Barcelona, Spain

J. Castellvi · A. Garcia · S. R. y Cajal
Servei de Patologia, Hospital Vall d'Hebron, Barcelona, Spain

G. Moreno-Bueno
Departamento de Bioquímica-IIB CSIC-UAM, IdiPAZ and Fundación MD Anderson Internacional, Madrid, Spain

X. Dolcet · X. Matias-Guiu
Servei de Patologia, Hospital Arnau de Vilanova, Lleida, Spain

F. Alameda
Servei de Patologia, Hospital del Mar, Barcelona, Spain

J. Palacios
Servicio de Patología, Hospital Virgen del Rocío, Sevilla, Spain

J. Prat
Servei de Patologia, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

M. Abal
Complejo Hospitalario de Santiago de Compostela, Santiago de Compostela, Spain

J. Reventos
Department de Ciències Bàsiques, Universitat Internacional de Catalunya, Barcelona, Spain

Journal : Large 12094 | Dispatch : 14-7-2012 | Pages : 6
Article No. : 866 | ☐ LE | ☐ TYPESET
MS Code : CLAT-D-12-00875 | ☑ CP | ☑ DISK

have been classified into a dualistic model, first proposed by Bokhman [1]. Nowadays, this model is being challenged, since tumors seen in daily practice occasionally show overlapping or combined morphologic and molecular characteristics between both types, in addition to ambiguous features [2]. Nevertheless, we still follow this classification as it is currently used in the clinical practice. Type I, or estrogen-dependent endometrioid ECs, represent the most common subtype. This type usually develops in peri- and early postmenopausal women. It is an estrogen-associated lesion often seen in conjunction with endometrial hyperplasia. The histological subtypes that correspond to endometrioid adenocarcinoma and its variants, as well as mucinous adenocarcinoma, are allocated to this group. Type II, or non-endometrioid ECs, tend to affect older, postmenopausal women and are a non-estrogen-associated lesion. These cancers are not preceded by endometrial hyperplasia, though they can occasionally arise in endometrial polyps or from precancerous lesions, endometrial intraepithelial carcinoma, or in the vicinity of atrophic endometrium [3]. The most virulent histologic subtypes, such as papillary serous, clear cell carcinomas, and carcinosarcomas are to be found in this group [4]. The clinicopathological differences between the two types are paralleled by specific genetic alterations, with type I showing microsatellite instability and mutations in PTEN, PIK3CA, K-RAS, and CTNNB1 (beta-catenin) and type II exhibiting TP53 mutations and chromosomal instability [5].

Epidemiologically, EC is ranked as the most common gynecologic malignancy of the female genital tract and the fourth most common neoplasia in women after breast, colorectal and lung cancer. Recent data from the US estimates that 47,130 new cases of EC will be diagnosed in 2012, but only 8,010 deaths are expected [6]. According to these statistics, EC is considered to be a good prognosis cancer, since it is usually detected in its initial stages by the presentation of disease-related symptoms. In its early stages, EC is confined to the endometrium and can be treated by hysterectomy with or without adjuvant treatment resulting in survival rates around 96 % at 5 years. However, 30 % of all EC cases are still diagnosed at regional or distant stages, and are related to lower survival rates, 67 and 16 %, respectively. When comparing the epidemiologic data of both EC types, type I lesions are generally diagnosed at an earlier stage and possess a more favorable prognosis than those of type II. Generally, type II are more aggressive tumors that are commonly diagnosed in advanced stages and often recur, despite aggressive treatment [7].

In order to tackle the causes of mortality associated with EC, it is necessary to understand how this cancer disseminates. EC spreads by direct extension through the myometrium, in an exfoliation of cells that are shed through the fallopian tubes, lymphatic dissemination, and/or hematogenous dissemination [8]. The most common route of spread is the direct extension of a tumor to the myometrium. In this review, we will focus on the mechanisms that initiate this local invasion, as this invasion is considered one of the most important prognostic factors for type I and type II ECs, usually correlating with lymphatic spread, risk of recurrence, and overall survival rate. In the multistep process that characterizes myometrial invasion, the initial events are delineated by the dissociation of tumor cells from the epithelial layer of the endometrial glands and the penetration through the basement membrane into the adjacent connective tissue, i.e., the myometrium [7]. This process is similar in other types of cancer, and many authors [8, 9] have pointed out that for this process to occur, epithelial tumor cells need to undergo an epithelial to mesenchymal (EMT) transition, either transiently or stably, and to differing degrees.

Epithelial to mesenchymal transition (EMT)

EMT is a well-described process whereby epithelial cells lose their polarity and cell–cell contacts, undergoing a dramatic remodeling of the cytoskeleton and acquiring a migratory phenotype, which activates a mesenchymal-like gene expression program. The epithelial cells form a sheet or layer of cells that are tightly connected laterally by specialized junction structures, including adherens junctions, desmosomes, hemidesmosomes, tight junctions and gap junctions. Among these, adherens junctions play a particularly important role in assembling and constructing lateral epithelial cell–cell adhesions. The epithelial cells also establish an aligned, apical–basal polarity through their association with a lamina layer at their basal surface, which ensures that the cells are only able to migrate laterally, maintaining their position within the epithelium [10]. Upon receiving specific signals, EMT occurs. Mesenchymal cells are defined by three major characteristics in their cellular phenotype and their behavior (Fig. 1): (1) a loss of strong epithelial adhesive cell–cell contacts and the acquisition of a dispersed, spindle-shaped morphology with migratory protrusions, (2) changes in the differentiation markers from cell–cell junction proteins, i.e., E-cadherin and cytokeratin intermediate filaments (specific to epithelial cells) to vimentin filaments and fibronectin, and (3) an increased motility for invasion through the extracellular matrices. All three changes are not necessarily observable during an EMT; however, the single cell acquisition of the ability to migrate and invade the extracellular matrices is considered to be a functional hallmark of EMT. Hence, mesenchymal cells are able to detach, penetrate through the

Journal : Large 12094 Dispatch : 14-7-2012 Pages : 6
Article No. : 866 LE TYPESET
MS Code : CLAT-D-12-00875 CP DISK

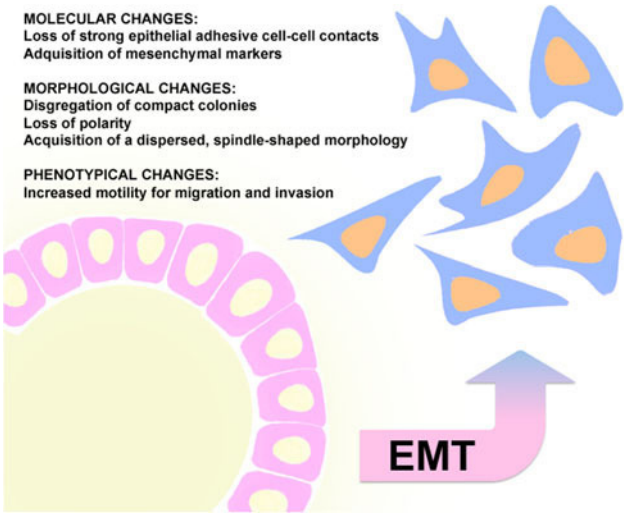

Fig. 1 General features of epithelial to mesenchymal transition (EMT). Schematic diagram of the main molecular, morphological and phenotypical changes occurring in EMT

basement membrane and infiltrate surrounding tissues to then metastasize at secondary sites [11, 12]. To reach successful dissemination, EMT must be triggered in epithelial cells through an appropriate signaling pathway. Cancer cells must also develop complex interactions to integrate stimuli from their surrounding microenvironments [13, 14].

Several transcription factors have emerged in recent years that trigger the down-regulation of E-cadherin and, consequently, produce EMT in different types of cancer. These transcription factors include the transforming growth factor-β (TGFβ), epidermal growth factor (EGF), insulin growth factor 1 (IGF-1), interleukin, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), integrin/integrin-linked kinase (ILK), notch, fibroblast growth factor (FGF) and Wnt/β-catenin signaling pathways [15–18]. Most of these signals exert their action on E-cadherin repression through the modulation of a set of pleiotropically acting transcription factors, including members of Snail (Snail and Slug) and basic helix-loop-helix (E47 and Twist) families, as well as two double zinc finger and homeodomain (Zeb1 and Zeb2) factors [9]. These repressors are expressed in various combinations in a number of malignant tumor types and have been shown in experimental models of carcinoma formation to be causally important for programming invasion [10, 19]. Hence, these repressors are recognized as key inducers of EMT.

EMT in EC invasion

In EC, hallmarks of EMT have been reported either at the level of E-cadherin loss or at the induction of its repressors. On one side, Hurt et al. [20] and Singh et al. [21] have described high levels of Zeb1 in relation to gynecologic carcinoma progression, and Kyo et al. [22] have observed a pattern of twist expression preferentially at the 'marginal regions' of ECs, which was inversely correlated with E-cadherin expression. Snail was also proposed to play a role in EC progression and was correlated with reduced estrogen-receptor α expression [23]. On the other side, several reports [24, 25] have associated negative E-cadherin expression, increased nuclear β-catenin, and loss of α-catenin with the acquisition of aggressive biological behavior, especially in high-grade tumors. Furthermore, some studies have demonstrated a correlation between reduced E-cadherin and the presence of lymph node metastasis and/or adverse patient outcomes [26–30].

Independently of the most common features of EMT described above, other molecular alterations have been consistent with this phenotype. For example, L1CAM expression was inversely correlated to the expression of hormone receptors and E-Cadherin and was found to be associated with poor prognosis [31]. L1CAM up-regulation was mimicked in EC cell lines treated with the EMT inducer TGFβ1 and blocked when Slug was depleted. In line with this result, L1CAM presents two functionally active promoter sites containing β-catenin/TCF-LEF and E-boxes, respectively, indicating that its expression can be regulated by TGFβ1, but also by Wnt/β-catenin [32]. Conversely, the over-expression of a self-renewal gene, called BMI-1, has been found in multiple human cancers, including gastric cancer [33], lung cancer [34], breast cancer [35], prostate cancer [36], ovarian cancer [37], and EC [38]. BMI-1 up-regulation has been found to contribute to the EMT-derived invasive phenotype in EC cells, and its silencing reverts EMT and reduces EC cell invasion [39].

Interestingly, Stewart and Little [40] were the first to approach an immunohistochemical identification of the distinctive morphological alterations consistent with EMT features in EC. They managed to characterize the presence of microcystic, elongated and fragmented glands within EC tissues, which they named "MELFs". MELFs are specific tumor alterations, which, through immunohistochemical study, can be identified by strong CK7 expression, showing a reduction of E-Cadherin and hormone receptor and increased snail expression. Loss of hormone receptors and decreased E-cadherin immunoreactivity have been reported previously in EC [23, 41–44] and in breast carcinoma [45, 46]. Although EMT has been broadly described in EC, the molecular pathways responsible for triggering this process are still poorly delineated for this type of cancer. Here, we will review current literature pertaining to the main effectors of EMT in EC.

Journal : Large 12094 Dispatch : 14-7-2012 Pages : 6
Article No. : 866 LE TYPESET
MS Code : CLAT-D-12-00875 CP DISK

Progesterone receptor

Presence of progesterone receptors (PR) has been described as an important asset in the prognosis and treatment of EC [47, 48]. In well-differentiated EC, PR expression is usually maintained and treatment with medroxyprogesterone acetate (MPA) is usually successful. In contrast, a loss of PR expression is a negative prognostic factor and is associated with the development of a more invasive phenotype, in which MPA treatment is only occasionally successful in 15–20 % of the cases [43, 49].

Recently, Van der Host et al. [44] have postulated that a loss of progesterone signaling in progressive disease may play a role in the induction of EMT, as well as diminished T-cell infiltration. In that study, PR modulated cell lines in the presence of MPA resulted in an inhibition of migration and a down-regulation of mesenchymal markers. An assessment of the pathways involved in EMT showed that progesterone modulated cell lines presented a down-regulation of EGF, IGF-1, IL-6, integrin/ILK, PDGF, TGFβ, VEGF and Wnt/β-catenin signaling. These altered signaling pathways were also modulated in a gene expression study comparing progressive and non-progressive EC tissue samples. To date, a link between progesterone and the Wnt/β-catenin signaling pathway has been broadly described [41, 43, 50, 51], though links between progesterone and other altered pathways remain unclear.

TGFβ

TGFβ signals are largely known as tumor promoters of cellular responses, such as proliferation, survival, migration and invasion, and are related to EMT induction in other types of cancer [52]. TGFβ exerts its effect by binding to a heteromeric complex of transmembrane serine/threonine kinase, the type I (RI) and type II (RII) receptors. Following ligand binding to the receptors complex, RI phosphorylates Smad2 and Smad3. The phosphorylated Smads form a heteromeric complex with Smad4 and translocate into the nucleus to regulate TGFβ-responsive gene transcription [53].

As relates to EC, the disruption of TGFβ signaling has been observed at the early stages of carcinogenesis, leading the endometrium to divert from normal growth control [54]. In contrast, increased levels of RII and Smad4 were described in infiltrating ECs, when compared to non-infiltrating tissues at the protein level, while Smad2 and Smad4 mRNAs were down-regulated. A comparison between the molecular profiles of high risk and low risk of recurrence phenotypes for EC also pointed to a prominent role for TGFβ signaling in the acquisition of an aggressive phenotype [55]. In vitro studies confirmed that TGFβ plays a principal role at the initiation of EC invasion, through promotion of the EMT that leads to the acquisition of an invasive phenotype in Hec1a and RL95-2 cells [55, 56].

ETV5

ETV5 belongs to the PEA3 subfamily of Ets transcription factors, characterized by a sequence of 85 amino acids in an evolutionarily conserved DNA-binding domain that regulates the expression of a variety of genes by binding to a central A/GGAA/T core motif, in cooperation with other transcriptional factors and cofactors [57, 58]. Up-regulation of the ETV5 gene in EEC was described by Planagumà et al. [59] with a specific and significant increase restricted to those tumor stages associated with myometrial infiltration. Recently, ETV5 has arisen as an inducer of EMT in EC through a main regulatory effect on the Zeb1 promoter, and has also been found to induce EMT in ovarian cancer cell lines [60]. Along with ETV5 over-expression in EC cell lines, the main features of EMT were also observed. These included a modulation of cell adhesion, cell–cell contact and cellular junctions, and actin cytoskeleton reorganization. At the same time, main cellular functions were altered, as well as cell-to-cell signaling and interaction and cellular movement, as the principal modified biological processes [61].

Concomitant with EMT, the up-regulation of ETV5 in EC also regulated the MMP2 [62] and HEP27 [63] promoter regions. The former protein is a matrix metalloproteinase, which is primarily responsible for the degradation of the helical domains of type IV collagen, i.e., the principal collagen of basement membranes that allows tumor cells to infiltrate surrounding tissues. The latter is a member of the superfamily of short-chain dehydrogenases/reductases that protect tumor cells against apoptosis, which is induced by oxidative stress generated during the invasive process.

In our work, we have also identified a number of proteins involved in the acquisition of invasive capabilities by ECs [64], such as lipoma-preferred partner (LPP), which acts as a novel co-regulatory partner of ETV5 in the transcriptional regulation of the EMT process. LPP is reorganized from cell–cell contacts to focal adhesions when EMT is induced by ETV5, and it translocates to the nucleus ahead of external stimuli, establishing cross-talk between the tumor cells and their surrounding microenvironments [61].

Interestingly, our group linked TGFβ and progesterone receptor pathways with ETV5 by means of a proteomic analysis that compared EC cells stably over-expressing ETV5 with both control, non-transfected cells and cells that had been transfected with the empty vector [63] (Fig. 2).

Journal : Large 12094 Dispatch : 14-7-2012 Pages : 6
Article No. : 866 LE TYPESET
MS Code : CLAT-D-12-00875 CP DISK

MicroRNA

Several reports have shown the importance of certain microRNAs in modulating EMT. These microRNAs represent a class of small, non-coding RNAs with important regulatory functions in diverse biological processes [65, 66], including cancer [67]. In EC, and specifically in the carcinosarcoma histology from type II EC, Castilla et al. [68] managed to identify specific microRNA signatures that distinguished epithelial from mesenchymal areas. Among the 377 microRNAs assayed, 14 microRNAs were found differentially expressed. The most strongly up-regulated microRNA was miR-155, indicating that this miRNA participated in EMT. The role of this microRNA in EMT had been previously suggested in vitro, in relation to TGFβ. TGFβ-treated normal murine mammary gland epithelial cells underwent EMT, and miR-155 was found to be significantly up-regulated. The ectopic expression of miR-155 also disrupted tight junction formation and promoted cell migration and invasion [69]. Another key finding of this study in carcinosarcomas was the marked down-regulation of all five members of the miR-200 family in the mesenchymal cells. Several studies have demonstrated the miR-200 family to be a powerful marker and determining factor of the epithelial phenotype of cancer cells. In EC cell lines, a member of this family, miR-200c, has been confirmed to maintain the epithelial phenotype by targeting Zeb1 and Zeb2 and, moreover, to actively repress a program of mesenchymal and neuronal genes involved in cell motility and anoikis resistance [70, 71]. Regarding microRNAs regulation in other types of EC, Dong et al. [39] unveiled that miR-194 inhibited the EMT of EC cells by targeting the oncogene BMI-1.

Only seven of more than 24,000 entries for "endometrial cancer" in PUBMED correspond to "endometrial cancer" and "EMT." This data underscores the necessity of more research on this topic. It is crucial for us to understand the molecular mechanisms of myometrial invasion, as it represents one of the most important prognostic variables of EC.

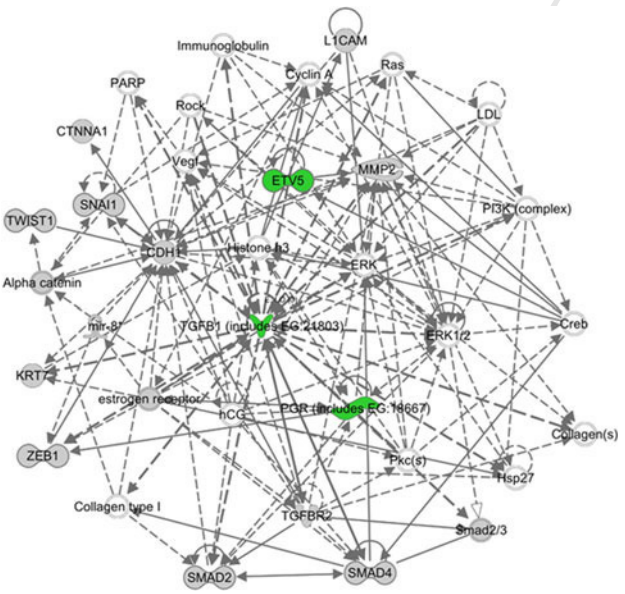

Fig. 2 Epithelial to mesenchymal transition (EMT) networks in endometrial carcinoma (EC). To obtain the interaction network, we selected genes differentially expressed in EC that have been related to EMT, and we used Ingenuity Pathways Analysis software to plot direct and indirect interactions

Acknowledgments The authors would like to thank Lisa Piccione for correction of the manuscript. This work has been supported by the Spanish Ministry of Science and Innovation (SAF 2005-06771; SAF 2008-03996; SAF 2010-10635-E; SAF2011-26548), CENIT Program (CENIT/01/2006) and RTICC Program (RTICC RD06/0020/0058 and RD06/0020/1034), the Catalan Institute of Health and the Department of Universities and Research, Catalan Government (2009SGR00487, 2005SGR00553), the ACCIO Program (RDITSCON07-1-0001), the Foundation La Marato de TV3 (Grant 050431), the IV Grant Fundació Santiago Dexeus Font for Clinical Investigation Projects 2009, the National Programme of Biotechnology (FIT-010000-2007-26), the Asociación Española Contra el Cáncer (AECC) and the European Commission Program Fondo Europeo de Desarrollo Regional (FEDER).

Conflict of interest None.

References

1. Bokhman JV (1983) Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 15:10–17
2. Zannoni GF, Scambia G, Gallo D (2011) The dualistic model of endometrial cancer: the challenge of classifying grade 3 endometrioid carcinoma. Gynecol Oncol. doi:10.1016/j.ygyno.2011.09.036
3. Llauradó M et al (2011) Molecular bases of endometrial cancer: new roles for new actors in the diagnosis and the therapy of the disease. Mol Cell Endocrinol. doi:10.1016/j.mce.2011.10.003
4. Amant F et al (2005) Endometrial cancer. Lancet 366:491–505
5. Yeramian A et al (2012) Endometrial carcinoma: molecular alterations involved in tumor development and progression. Oncogene. doi:10.1038/onc.2012.76
6. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62:10–29
7. Abal M et al (2007) Molecular determinants of invasion in endometrial cancer. Clin Transl Oncol 9:272–277
8. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
9. Moreno-Bueno G, Portillo F, Cano A (2008) Transcriptional regulation of cell polarity in EMT and cancer. Oncogene 27:6958–6969
10. Yang J, Weinberg RA (2008) Epithelial–mesenchymal transition: at the crossroads of development and tumor metastasis. Dev Cell 14:818–829
11. Thiery JP, Morgan M (2004) Breast cancer progression with a Twist. Nat Med 10:777–778
12. Kang Y, Massague J (2004) Epithelial–mesenchymal transitions: twist in development and metastasis. Cell 118:277–279
13. Mueller MM, Fusenig NE (2004) Friends or foes—bipolar effects of the tumour stroma in cancer. Nat Rev Cancer 4:839–849
14. Bhowmick NA, Neilson EG, Moses HL (2004) Stromal fibroblasts in cancer initiation and progression. Nature 432:332–337
15. Barrallo-Gimeno A, Nieto MA (2005) The Snail genes as inducers of cell movement and survival: implications in development and cancer. Development 132:3151–3161
16. De Craene B, van Roy F, Berx G (2005) Unraveling signaling cascades for the Snail family of transcription factors. Cell Signal 17:535–547
17. Huber M, Kraut N, Beug H (2005) Molecular requirements for epithelial–mesenchymal transition during tumor progression. Curr Opin Cell Biol 17:548–558

Journal : Large 12094 | Dispatch : 14-7-2012 | Pages : 6
Article No. : 866 | LE | TYPESET
MS Code : CLAT-D-12-00875 | CP | DISK

18. Thiery JP, Sleeman JP (2006) Complex networks orchestrate epithelial–mesenchymal transitions. Nat Rev Mol Cell Biol 7:131–142
19. Micalizzi D, Farabaugh S, Ford H (2010) Epithelial–mesenchymal transition in cancer: parallels between normal development and tumor progression. J Mammary Gland Biol Neoplasia 15:117–134
20. Hurt EM, Saykally JN, Anose BM, Kalli KR, Sanders MM (2008) Expression of the ZEB1 (deltaEF1) transcription factor in human: additional insights. Mol Cell Biochem 318:89–99
21. Singh M et al (2008) ZEB1 expression in type I vs type II endometrial cancers: a marker of aggressive disease. Mod Pathol 21:912–923
22. Kyo S et al (2006) High Twist expression is involved in infiltrative endometrial cancer and affects patient survival. Hum Pathol 37:431–438
23. Blechschmidt K et al (2007) The E-cadherin repressor snail plays a role in tumor progression of endometrioid adenocarcinomas. Diagn Mol Pathol 16:222–228
24. Shih H-C et al (2004) Immunohistochemical expression of E-cadherin and beta-catenin in the normal and malignant human endometrium: an inverse correlation between E-cadherin and nuclear beta-catenin expression. Anticancer Res 24:3843–3850
25. Scholten AN, Aliredjo R, Creutzberg CL, Smit VTHB (2006) Combined E-cadherin, alpha-catenin, and beta-catenin expression is a favorable prognostic factor in endometrial carcinoma. Int J Gynecol Cancer 16:1379–1385
26. Sakuragi N et al (1994) Decreased E-cadherin expression in endometrial carcinoma is associated with tumor dedifferentiation and deep myometrial invasion. Gynecol Oncol 53:183–189
27. Moreno-Bueno G et al (2003) Abnormalities of E- and P-cadherin and catenin (beta-, gamma-catenin, and p120ctn) expression in endometrial cancer and endometrial atypical hyperplasia. J Pathol 199:471–478
28. Stefansson IM, Salvesen HB, Akslen LA (2004) Prognostic impact of alterations in P-cadherin expression and related cell adhesion markers in endometrial cancer. J Clin Oncol 22:1242–1252
29. Mell LK et al (2004) Prognostic significance of E-cadherin protein expression in pathological stage I–III endometrial cancer. Clin Cancer Res 10:5546–5553
30. Leblanc M et al (2001) Alteration of CD44 and cadherins expression: possible association with augmented aggressiveness and invasiveness of endometrial carcinoma. Virchows Arch 438:78–85
31. Huszar M et al (2010) Up-regulation of L1CAM is linked to loss of hormone receptors and E-cadherin in aggressive subtypes of endometrial carcinomas. J Pathol 220:551–561
32. Pfeifer M et al (2010) L1CAM expression in endometrial carcinomas is regulated by usage of two different promoter regions. BMC Mol Biol 11:64
33. Lee H et al(2012) Immunohistochemical analysis of polycomb group protein expression in advanced gastric cancer. Hum Pathol. doi:10.1016/j.humpath 2011.12.019
34. Vonlanthen S et al (2001) The bmi-1 oncoprotein is differentially expressed in non-small cell lung cancer and correlates with INK4A-ARF locus expression. Br J Cancer 84:1372–1376
35. Guo B-H et al (2011) Bmi-1 promotes invasion and metastasis, and its elevated expression is correlated with an advanced stage of breast cancer. Mol. Cancer 10:10
36. Glinsky GV, Berezovska O, Glinskii AB (2005) Microarray analysis identifies a death-from-cancer signature predicting therapy failure in patients with multiple types of cancer. J Clin Invest 115:1503–1521
37. Zhang F, Sui L, Xin T (2008) Correlations of BMI-1 expression and telomerase activity in ovarian cancer tissues. Exp Oncol 30:70–74
38. Honig A et al (2010) Overexpression of polycomb protein BMI-1 in human specimens of breast, ovarian, endometrial and cervical cancer. Anticancer Res 30:1559–1564
39. Dong P et al (2011) MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. Mol Cancer 10:99
40. Stewart CJR, Little L (2009) Immunophenotypic features of MELF pattern invasion in endometrial adenocarcinoma: evidence for epithelial–mesenchymal transition. Histopathology 55:91–101
41. Hanekamp EE et al (2005) Differences in invasive capacity of endometrial cancer cell lines expressing different progesterone receptor isotypes: possible involvement of cadherins. J Soc Gynecol Invest 12:278–284
42. Dai D, Wolf DM, Litman ES, White MJ, Leslie KK (2002) Progesterone inhibits human endometrial cancer cell growth and invasiveness: down-regulation of cellular adhesion molecules through progesterone B receptors. Cancer Res 62:881–886
43. Hanekamp EE et al (2002) Loss of progesterone receptor may lead to an invasive phenotype in human endometrial cancer. Eur J Cancer 38(Suppl 6): S71–S72
44. van der Horst PH et al (2012) Progesterone inhibits epithelial-to-mesenchymal transition in endometrial cancer. PLoS One 7
45. Fujita N et al (2003) MTA3, a Mi-2/NuRD complex subunit, regulates an invasive growth pathway in breast cancer. Cell 113:207–219
46. Dandachi N et al (2001) Co-expression of tenascin-C and vimentin in human breast cancer cells indicates phenotypic transdifferentiation during tumour progression: correlation with histopathological parameters, hormone receptors, and oncoproteins. J Pathol 193:181–189
47. Ehrlich CE, Young PC, Stehman FB, Sutton GP, Alford WM (1988) Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. Am J Obstet Gynecol 158:796–807
48. Jeon Y-T et al (2006) Steroid receptor expressions in endometrial cancer: clinical significance and epidemiological implication. Cancer Lett 239:198–204
49. Thigpen JT et al (1999) Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 17:1736–1744
50. Hanekamp EE et al (2003) Consequences of loss of progesterone receptor expression in development of invasive endometrial cancer. Clin Cancer Res 9:4190–4199
51. Wang Y et al (2009) Progesterone inhibition of Wnt/beta-catenin signaling in normal endometrium and endometrial cancer. Clin Cancer Res 15:5784–5793
52. Massagué J (2008) TGFbeta in Cancer. Cell 134:215–230
53. Derynck R, Zhang YE (2003) Smad-dependent and Smad-independent pathways in TGF-beta family signaling. Nature 425:577–584
54. Parekh TV et al (2002) Transforming growth factor beta signaling is disabled early in human endometrial carcinogenesis concomitant with loss of growth inhibition. Cancer Res 62:2778–2790
55. Muinelo-Romay L et al (2011) High-risk endometrial carcinoma profiling identifies TGF-β1 as a key factor in the initiation of tumor invasion. Mol Cancer Ther 10:1357–1366
56. Lei X, Wang L, Yang J, Sun L-Z (2009) TGFbeta signaling supports survival and metastasis of endometrial cancer cells. Cancer Manag Res 2009:15–24
57. de Launoit Y et al (2006) The Ets transcription factors of the PEA3 group: transcriptional regulators in metastasis. Biochim Biophys Acta 1766:79–87
58. Graves BJ, Petersen JM (1998) Specificity within the ets family of transcription factors. Adv Cancer Res 75:1–55
59. Planaguma J et al (2005) Up-regulation of ERM/ETV5 correlates with the degree of myometrial infiltration in endometrioid endometrial carcinoma. J Pathol 207:422–429
60. Llauradó M et al (2012) ETV5 transcription factor is overexpressed in ovarian cancer and regulates cell adhesion in ovarian cancer cells. Int J Cancer 130:1532–1543
61. Colas E et al (2012) ETV5 cooperates with LPP as a sensor of extracellular signals and promotes EMT in endometrial carcinomas. Oncogene. doi: 10.1038/onc.2011.632
62. Monge M et al (2007) ERM/ETV5 up-regulation plays a role during myometrial infiltration through matrix metalloproteinase-2 activation in endometrial cancer. Cancer Res 67:6753–6759
63. Monge M et al (2009) Proteomic approach to ETV5 during endometrial carcinoma invasion reveals a link to oxidative stress. Carcinogenesis 30:1288–1297
64. Monge M et al (2009) Subtractive proteomic approach to the endometrial carcinoma invasion front. J Proteome Res 8:4676–4684
65. Ebert MS, Sharp PA (2012) Roles for MicroRNAs in conferring robustness to biological processes. Cell 149:515–524
66. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116:281–297
67. Lujambio A, Lowe SW (2012) The microcosmos of cancer. Nature 482:347–355
68. Castilla MA et al (2011) Micro-RNA signature of the epithelial–mesenchymal transition in endometrial carcinosarcoma. J Pathol 223:72–80
69. Kong W et al (2008) MicroRNA-155 is regulated by the transforming growth factor beta/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. Mol Cell Biol 28:6773–6784
70. Howe EN, Cochrane DR, Richer JK (2011) Targets of miR-200c mediate suppression of cell motility and anoikis resistance. Breast Cancer Res 13:R45
71. Cano A, Nieto MA (2008) Non-coding RNAs take centre stage in epithelial-to-mesenchymal transition. Trends Cell Biol 18:357–359

Journal : Large 12094 | Dispatch : 14-7-2012 | Pages : 6
Article No. : 866 | LE | TYPESET
MS Code : CLAT-D-12-00875 | CP | DISK