

HGF and c-Met in pathogenesis of endometrial carcinoma

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1. ABSTRACT

Hepatocyte growth factor (HGF) regulates cell growth, motility, and morphogenesis of various types of cells via its receptor c-Met. In the growth of endometrium, HGF/c-Met signaling promotes the proliferation of both endometrial epithelial cells and stromal cells. In the onset and development of several cancers, HGF/c-Met signaling drives carcinogenesis and cancer invasion and metastasis. In endometrial carcinoma (EC), accounting for a majority of cancer-related morbidity and mortality among women, the increased expression of HGF and c-Met signaling is associated with a poor prognosis of EC patients. Thus, we will discuss the role of HGF and c-Met in the EC pathogenesis in this review.

2. INTRODUCTION

Hepatocyte growth factor (HGF) is a multifunctional cytokine that elicits diverse responses in different cells and tissues, which is originally identified as a mitogen for primary hepatocytes (1). HGF is produced as a one-chain inactive pro-protein, later cleaved into a two chain (alpha, beta) biologically active form by enzymes such as HGF activator (HGFA). Other enzymes such as thrombin, type II transmembrane enzyme matriptase, hepsin and uPAR also cleave pro-HGF into HGF (2). HGF regulates cell growth, motility, and morphogenesis of various types of cells via HGF receptor tyrosine kinase, namely c-Met (3). Met is encoded by MET gene. MET mutation and

amplification are well described in solid tumors, and c-Met is the target of numerous clinical trials aiming to personalize treatment for various types of cancers (4-8). Much evidence now points to the driving of carcinogenesis and cancer invasion and metastasis by HGF/c-Met signaling, including ovarian carcinoma, hepatocellular carcinoma, breast cancer, lung cancer and salivary gland carcinoma (9-14).

In endometrial carcinoma (EC), which is one of major causes of cancer-related morbidity and mortality among women (15), both HGF and c-Met are closely correlated with patients' prognosis. HGF expression was associated with surgical stage III and IV, while c-Met was significantly correlated with surgical stage III and IV, histologic Grade 3, and shorter survival (16). Recently, Bishop and colleagues (17) observed that total expression of HGF and c-Met was increased in patients with EC compared with patients with atrophic endometrium, but no difference in p-c-Met expression. They also found that the higher c-Met and HGF expression in EC patients is, the lower overall survival they have (17). Patients with expression of HGF as well as fibroblast growth factor have a higher risk of recurrence compared with those without these expressions (18). Since the closely association between both HGF and c-Met and EC prognosis, we will discuss the role of HGF and c-Met in the EC pathogenesis in this review.

3. HGF AND c-Met IN ENDOMETRIAL STROMAL CELLS

The endometrial stromal cells can produce HGF, which stimulates the invasion of EC cells *in vitro* (19). Through *in vitro* study found that HGF doesn't support clonogenicity of stromal cell from ovulating women undergoing hysterectomy for fibroids or adenomyosis (20), exogenous stimulation with HGF alone can significantly enhance the cell proliferation of endometrial stroma from women with endometriosis (21). Considering the relationship between HGF and endometrial stromal cells, knowledge on the HGF/c-Met in endometrial stromal cells may provide better understanding the role of HGF and c-Met in EC.

The expression of estrogen receptors and progesterone receptors are associated with EC pathogenesis and patients' prognosis (22,23). HGF and Met expression and function can be regulated by both estrogen and progesterone. Both the protein and mRNA expressions of HGF and Met in mouse uterus were high at proestrus, drastically decreased at estrus, remained low at metestrus, and increased again at diestrus stage, which were regulated by estrogen and progesterone in mice uterus, suggesting that HGF plays a role in cyclic endometrial remodeling by promoting cell proliferation via autocrine/paracrine mechanisms (24).

In the study on endometriosis with women, both endogenous and exogenous HGF can stimulate the Met receptor expressed in endometrial stromal cells, and promote invasion of stromal cells. The stromal cell invasion stimulated by HGF was partly due to the induction of urokinase-type plasminogen activator, a member of the extracellular proteolysis system (25). These findings suggesting a positive feedback that endometrial stromal cells produce HGF, which stimulates proliferation and invasion of stromal cells via an autocrine pathway. And the invasion is partly stimulated by urokinase-type plasminogen activator.

In the upstream of HGF/c-Met signaling, hormones or inflammatory factors can regulate this signaling. In the study also on endometriosis, the production of HGF by endometrial stromal cells can be regulated by interleukin (IL)-6 and tumor necrosis factor alpha (TNF-alpha) (26). In endometrium of the ovine uterus, through HGF mRNA expression wasn't regulated, Met mRNA expression was up-regulated by progesterone (27). In addition,

human heat-shock protein 70 can stimulated the production of HGF by macrophages derived from women with endometriosis, and can enhance the growth of endometrial stromal cells (28).

When bovine endometrial stromal cells (BESCs) were treated with HGF and IL-1alpha at the same time, the production of metalloproteinase (TIMP)-2 was up-regulated (29). Through TIMP-2 mRNA was not augmented by HGF singly, HGF can induce mRNA expression of membrane type-1 matrix metalloproteinase (MMPs) (29). When stimulated with HGF, bovine trophoblast cell line BT-1 produced an increased level of both proMMP-9 and TIMP-1 (29). In EC, the protein expressions of TIMP-2 and MMP-9 are higher in grade III carcinoma cells than those in grade II or in grade I, and the MMP-9 expression is also correlated with invasion/metastasis trend (30). Thus, HGF, which is produced from endometrial stromal cells, plays a key role in the EC development.

The endometrial stromal cells have a diverse role in regulating endometrial epithelial cells. Endometrial stromal cells regulate gap-junction function in normal human endometrial epithelial cells but not in endometrial carcinoma cells (31). Moreover, HGF is potentially involved in endometrial epithelial-stromal interactions and chorioallantoic stromal-trophectodermal interactions (32). These findings suggest a diverse role of endometrial stromal cells in regulating function of endometrial epithelial cells. In addition to endometrial stromal cells, HGF produced from endometrial stromal cells can promote the proliferation and migration of endometrial epithelial cells (33). The receptors of HGF were found to express in endometrial epithelia (24), especially c-Met (35). The role of endometrial stromal cells in endometrial epithelial cells may contribute to further understanding on the function of endometrial stromal cells in EU via secreting factors such as HGF.

Though knowledge on HGF and c-Met in endometrial stromal cells mostly bases on benign lesion such as endometriosis, it may provide information on the role of HGF and c-Met in hyperplastic lesions, even hystero carcinoma in uterus.

4. HGF AND c-Met IN ENDOMETRIAL CARCINOMA

In EC, several genes have been found to be related with the susceptibility (36-39). HGF is involved

into EC at the gene level. In human EC RL95-2 cells, the mouse HGF gene promoter containing 70 base pairs of the 5'-flanking sequences were active by transient transfecting chimeric plasmids (40). By such transient transfection of chimeric plasmids into RL95-2 cells, mouse HGF gene was found to have two putative estrogen responsive elements (ERE) respectively reside at -872 in the 5'-flanking region and at +511 in the first intron, suggesting that ERE elements of the mouse HGF gene can confer estrogen action to either homologous or heterologous promoters (41).

In human EC cell lines from endometrium, HGF can significantly influence the steady-state levels of the 8 kb c-Met mRNA, and the 8 kb c-Met mRNA undergoes rapid degradation with a half-life of less than 30 minutes, suggesting that the expression of the c-Met proto-oncogene resembles that of an immediate early response gene (42). In rat tissues of 10 endometrial adenocarcinomas and 1 endometrial squamous cell carcinoma, the Met gene is located in the core of each amplified region and was amplified most recurrently at a great high level (43). And moreover, the amplified sequences of Met and co-expression of Met and the normally silent HGF gene was found in that tumor tissue (43).

The HGF secreted from endometrial stromal cells can influence the biological behaviors of EC that it induces invasion of EC cell lines *in vitro* by targeting HGF receptor Met expressed in EC cell (19). When the exon encoding the ATP-binding site of MET was deleted from the genome of EC cells, these derivative isogenic cells expressed a kinase-inactive Met (MET-KD) and were completely unresponsive to HGF, but the tumorigenic potential of MET-KD cells can be partially restored by HGF *in vivo*, further confirming the HGF/Met signaling in EC (44). Moreover, during the process of EC invasion, HGF can induce invasion of all endometrial stromal and EC cell lines (HEC-1 A, HEC-1B, or KLE) in a 3D co-culture through inducing MMP-9 mRNA expression in stromal cells and/or increased activation of MMP-2 and MMP-9 by proteolytic digestion (45). Though stromal cell-derived HGF leads to invasive growth of EC cells, the EC cells don't produce HGF instead of an HGF inducer, namely basic fibroblast growth factor, indicating a positive feedback in EC invasion (46). In addition, EC cells induce HGF production from stromal cells by TNF- α , which is stimulated by estrogen (47).

5. DOWNSTREAM OF HGF/c-Met SIGNALING IN ENDOMETRIAL CARCINOMA

In addition to EC, HGF/c-Met signaling is involved into pathogenesis of another women specifically cancer, breast cancer (48), in which Akt is involved the metastasis of the disease as downstream (49). Both EC and breast cancer are estrogen-related cancers, so is there any similar with them? Studies on EC have revealed the effect of Akt as a downstream of HGF/c-Met signaling in EC biological behaviors. In EC cell lines RL95-2 cells, HGF can induce anoikis resistance through phosphatidylinositol 3-kinase (PI3K) /Akt pathway-dependent up-regulation of cyclooxygenase-2 (COX-2) expression (50), which may contribute to EC cells anti-apoptosis. Recent study confirmed this effect of HGF/c-Met/PI3K/Akt signaling, and further demonstrates the function to induce invasion and migration in RL95-2 cells via this signaling (51). In summary, HGF/c-Met/Akt signaling participates in anti-apoptosis, invasion and migration in EC, suggesting a promising target in EC therapy.

Moreover, in EC cell lines RL95-2, HGF could induce a cDNA Mig-7 before migration, but not in normal primary endometrial epithelial cells, suggesting HGF may be involved into cell-cell contacts, which leads to cell spread (52). As far as known, Mig-7 is the only cDNA induced by HGF in EC, but further knowledge on it is still not enough. Previous study on metastasis of lung cancer revealed that Mig-7 was inhibited by partly down-regulated integrin/PI3K/Akt signaling (53), suggesting the role of Mig-7 as a downstream of PI3K/Akt signaling. So whether Mig-7 plays the similar role in HGF/c-Met/Akt signaling of EC is need to investigate in future, which may contribute more understanding on EC metastasis. Moreover, also in lung cancer, Mig-7 can control COX-2/prostaglandin E₂ -mediated metastasis (54), which could provide a thinking on whether Mig-7 is involved into PI3K/Akt signaling via COX-2 regulation in EC.

6. CONCLUSIONS

In the growth of endometrium, HGF/c-Met signaling promotes the proliferation of both endometrial epithelial cells and stromal cells. HGF stimulates proliferation and invasion of stromal cells via an autocrine pathway, while it promotes proliferation and migration of epithelial cells via c-Met. The similar effect of HGF/c-Met signaling

HGF and c-Met in endometrial carcinoma pathogenesis

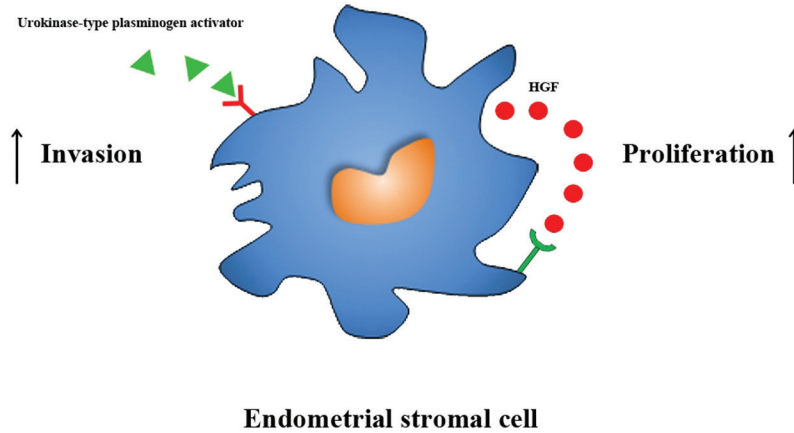


Figure 1. The positive feedback to promote proliferation and invasion of endometrial stromal cells. The endometrial stromal cells produce hepatocyte growth factor (HGF), which stimulates proliferation and invasion of stromal cells via an autocrine pathway. And the invasion can be stimulated by urokinase-type plasminogen activator.

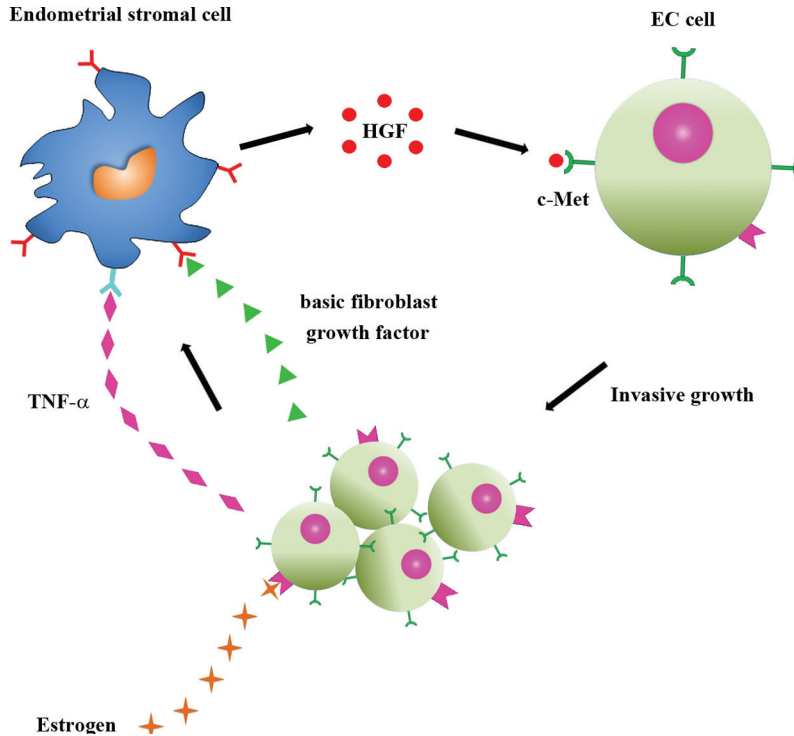


Figure 2. The endometrial carcinoma (EC) cells induce HGF production. The endometrial stromal cells secrete hepatocyte growth factor (HGF), which leads to invasive growth of EC cells via binding to c-Met. In turn, EC cells produce basic fibroblast growth factor to induce the HGF secretion. In addition, EC cells induce HGF production from stromal cells by TNF-alpha, which is stimulated by estrogen.

in EC cell lines has been observed, which can be stimulate by inflammatory factors or estrogen. In the downstream of HGF/c-Met signaling, PI3K/ Akt is a significant one in the anti-apoptosis,

invasion and migration in EC. However, recently knowledge about HGF/c-Met in EC pathogenesis remains many questions. For instance, is there any other factors regulating HGF/c-Met signaling

in proliferation and migration of EC cell? Which factors regulate HGF/c-Met/PI3K/Akt in EC pathogenesis? During the cancer cells invasion and migration, whether HGF/c-Met is involved into cancer cells colonization or angiogenesis? Answer those questions may contribute further understanding on the role of HGF/c-Met signaling in EC, and therefore the EC pathogenesis. Further understanding on HGF/c-Met in EC may provide more knowledge on EC pathogenesis and a promising therapeutic target in EC.

7. ACKNOWLEDGEMENTS

This work was supported by Department of Pathophysiology, Tongji Medical College, Huazhong University of Science and Technology.

7. REFERENCES

1. Nakamura T, Nishizawa T, Hagiya M, Seki T, Shimonishi M, Sugimura A, Tashiro K, Shimizu S: Molecular cloning and expression of human hepatocyte growth factor. *Nature* 342(6248):440-3 (1989). DOI: 10.1038/342440a0
2. Jiang W, Hiscox S, Matsumoto K, Nakamura T: Hepatocyte growth factor/scatter factor, its molecular, cellular and clinical implications in cancer. *Crit Rev Oncol Hematol* 29(3):209-48 (1999). DOI: 10.1016/S1040-8428(98)00019-5
3. Morishita R, Aoki M, Yo Y, Ogihara T: Hepatocyte growth factor as cardiovascular hormone: role of HGF in the pathogenesis of cardiovascular disease. *Endocr J* 49(3):273-84 (2002). DOI: 10.1507/endocrj.49.273
4. Sattler M, Salgia R: C-MET and hepatocyte growth factor: Potential new targets in cancer therapy. *Curr Oncol Rep* 9:102-108 (2007). DOI: 10.1007/s11912-007-0005-4
5. Comoglio PM, Giordano S, Trusolino L: Drug development of MET inhibitors: Targeting oncogene addiction and expedience. *Nat Rev Drug Discov* 7:504-516 (2008). DOI: 10.1038/nrd2530
6. Landi L, Minuti G, D'Incecco A, Cappuzzo F: Targeting c-MET in the battle against advanced non small-cell lung cancer. *Curr Opin Oncol* 25:130-136 (2013). DOI: 10.1097/CCO.0b013e32835daf37
7. Yu S, Yu Y, Zhao N, Cui J, Li W, Liu T: C-Met as a prognostic marker in gastric cancer: A systematic review and meta-analysis. *PLoS One* 8:e79137 (2013). DOI: 10.1371/journal.pone.0079137
8. Barrow-McGee R, Kermorgant S: Met endosomal signalling: In the right place, at the right time. *Int J Biochem Cell Biol* 49:69-74 (2014). DOI: 10.1016/j.biocel.2014.01.009
9. Sheng XJ, Li Z, Sun M, Wang ZH, Zhou DM, Li JQ, Zhao Q, Sun XF, Liu QC: MACC1 induces metastasis in ovarian carcinoma by upregulating hepatocyte growth factor receptor c-MET. *Oncol Lett* 8(2):891-897 (2014). Doi not found.
10. Pavan S, Musiani D, Torchiario E, Migliardi G, Gai M, Di Cunto F, Erriquez J, Olivero M, Di Renzo MF: HSP27 is required for invasion and metastasis triggered by hepatocyte growth factor. *Int J Cancer* 134(6):1289-99 (2014). DOI: 10.1002/ijc.28464
11. Wang YC, Xu GL, Jia WD, Han SJ, Ren WH, Wang W, Liu WB, Zhang CH, Chen H: Estrogen suppresses metastasis in rat hepatocellular carcinoma through decreasing interleukin-6 and hepatocyte growth factor expression. *Inflammation* 35(1):143-9 (2012). DOI: 10.1007/s10753-011-9299-3
12. Previdi S, Maroni P, Matteucci E, Brogginini M, Bendinelli P, Desiderio MA: Interaction between human-breast cancer metastasis and bone microenvironment through activated hepatocyte growth factor/Met and beta-catenin/Wnt pathways. *Eur J Cancer* 46(9):1679-91 (2010). DOI: 10.1016/j.ejca.2010.02.036
13. Navab R, Liu J, Seiden-Long I, Shih W, Li M, Bandarchi B, Chen Y, Lau D,

- Zu YF, Cescon D, Zhu CQ, Organ S, Ibrahimov E, Ohanessian D, Tsao MS: Co-overexpression of Met and hepatocyte growth factor promotes systemic metastasis in NCI-H460 non-small cell lung carcinoma cells. *Neoplasia* 11(12):1292-300 (2009).
Doi not found.
14. Tsukinoki K, Yasuda M, Mori Y, Asano S, Naito H, Ota Y, Osamura RY, Watanabe Y: Hepatocyte growth factor and c-Met immunoreactivity are associated with metastasis in high grade salivary gland carcinoma. *Oncol Rep* 12(5):1017-21 (2004).
Doi not found.
 15. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. *CA Cancer J Clin* 61(2):69-90 (2011).
DOI: 10.3322/caac.20107
 16. Wagatsuma S, Konno R, Sato S, Yajima A: Tumor angiogenesis, hepatocyte growth factor, and c-Met expression in endometrial carcinoma. *Cancer* 82(3):520-30 (1998).
DOI:10.1002/(SICI)1097-0142(19980201)82:3<520::AID-CNCR14>3.0.CO;2-3
 17. Bishop E A, Lengyel ER, Yamada SD, Montag A, Temkin SM: The expression of hepatocyte growth factor (HGF) and c-Met in uterine serous carcinoma. *Gynecol Oncol* 121(1):218-23 (2011).
DOI: 10.1016/j.ygyno.2010.11.031
 18. Felix AS, Edwards RP, Stone RA, Chivukula M, Parwani AV, Bowser R, Linkov F, Weissfeld JL: Associations between hepatocyte growth factor, c-Met, and basic fibroblast growth factor and survival in endometrial cancer patients. *Br J Cancer* 106(12):2004-9 (2012).
DOI: 10.1038/bjc.2012.200
 19. Bae-Jump V, Segreti EM, Vandermolen D, Kauma S: Hepatocyte growth factor (HGF) induces invasion of endometrial carcinoma cell lines in vitro. *Gynecol Oncol* 73(2):265-72 (1999).
DOI: 10.1006/gyno.1999.5353
 20. Chan RW, Schwab KE, Gargett CE: Clonogenicity of human endometrial epithelial and stromal cells. *Biol Reprod* 70(6):1738-50 (2004).
DOI: 10.1095/biolreprod.103.024109
 21. Khan KN, Masuzaki H, Fujishita A, Kitajima M, Sekine I, Matsuyama T, Ishimaru T: Estrogen and progesterone receptor expression in macrophages and regulation of hepatocyte growth factor by ovarian steroids in women with endometriosis. *Hum Reprod* 20(7):2004-13 (2005).
DOI: 10.1093/humrep/deh897
 22. Tomica D, Ramić S, Danolić D, Knezević F, Kolak T, Balja MP, Alvir I, Mamić I, Puljiz M: A correlation between the expression of estrogen receptors and progesterone receptors in cancer cells and in the myometrium and prognostic factors in endometrial cancer. *Coll Antropol* 38(1):129-34 (2014).
Doi not found.
 23. Kreizman-Shefer H, Pricop J, Goldman S, Elmalah I, Shalev E: Distribution of estrogen and progesterone receptors isoforms in endometrial cancer. *Diagn Pathol* 9:77 (2014).
DOI: 10.1186/1746-1596-9-77
 24. Zhang X: Hepatocyte growth factor system in the mouse uterus: variation across the estrous cycle and regulation by 17-beta-estradiol and progesterone. *Biol Reprod* 82(6):1037-48 (2010).
DOI: 10.1095/biolreprod.109.079772
 25. Yoshida S, Harada T, Mitsunari M, Iwabe T, Sakamoto Y, Tsukihara S, Iba Y, Horie S, Terakawa N: Hepatocyte growth factor/ Met system promotes endometrial and endometriotic stromal cell invasion via autocrine and paracrine pathways. *J Clin Endocrinol Metab* 89(2):823-32 (2004).
DOI: 10.1210/jc.2003-030874
 26. Khan KN, Masuzaki H, Fujishita A, Kitajima M, Hiraki K, Sekine I, Matsuyama T, Ishimaru T: Interleukin-6- and

- tumour necrosis factor alpha-mediated expression of hepatocyte growth factor by stromal cells and its involvement in the growth of endometriosis. *Hum Reprod* 20(10):2715-23 (2005).
DOI: 10.1093/humrep/dei156
27. Satterfield MC, Hayashi K, Song G, Black SG, Bazer FW, Spencer TE: Progesterone regulates FGF10, MET, IGFBP1, and IGFBP3 in the endometrium of the ovine uterus. *Biol Reprod* 79(6):1226-36 (2008).
DOI: 10.1095/biolreprod.108.071787
 28. Khan KN, Kitajima M, Imamura T, Hiraki K, Fujishita A, Sekine I, Ishimaru T, Masuzaki H: Toll-like receptor 4-mediated growth of endometriosis by human heat-shock protein 70. *Hum Reprod* 23(10):2210-9 (2008).
DOI: 10.1093/humrep/den195
 29. Hirata M, Sato T, Tsumagari M, Shimada A, Nakano H, Hashizume K, Ito A: Differential regulation of the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases by cytokines and growth factors in bovine endometrial stromal cells and trophoblast cell line BT-1 in vitro. *Biol Reprod* 68(4):1276-81 (2003).
DOI: 10.1095/biolreprod.102.006452
 30. Guo W, Chen G, Zhu C, Wang H: Expression of matrix metalloproteinase-2, 9 and its tissue inhibitor-1, 2 in endometrial carcinoma. *Zhonghua Fu Chan Ke Za Zhi* 37(10):604-7 (2002).
 31. Schlemmer SR, Kaufman DG: Endometrial stromal cells regulate gap-junction function in normal human endometrial epithelial cells but not in endometrial carcinoma cells. *Mol Carcinog* 28(2):70-5 (2000).
DOI: 10.1002/1098-2744(200006)28:2<70::AID-MC2>3.0.CO;2-9
 32. Chen C, Spencer TE, Bazer FW: Expression of hepatocyte growth factor and its receptor c-met in the ovine uterus. *Biol Reprod* 62(6):1844-50 (2000).
DOI: 10.1095/biolreprod62.6.1844
 33. Fukaya T, Sugawara J, Yoshida H, Murakami T, Yajima A: Intercellular adhesion molecule-1 and hepatocyte growth factor in human endometriosis: original investigation and a review of literature. *Gynecol Obstet Invest* 47 Suppl 1:11-6; discussion 16-7 (1999).
DOI: 10.1159/000052854
 34. Spencer TE, Bazer FW: Biology of progesterone action during pregnancy recognition and maintenance of pregnancy. *Front Biosci* 7:d1879-98 (2002).
Doi not found.
 35. Murakami S, Miyamoto Y, Fujiwara C, Takeuchi S, Takahashi S, Okuda K: Expression and action of hepatocyte growth factor in bovine endometrial stromal and epithelial cells in vitro. *Mol Reprod Dev* 60(4):472-80 (2001).
DOI: 10.1002/mrd.1112
 36. Dahabreh IJ, Schmid CH, Lau J, Varvarigou V, Murray S, Trikalinos TA: Genotype misclassification in genetic association studies of the rs1042522 TP53 (Arg72Pro) polymorphism: a systematic review of studies of breast, lung, colorectal, ovarian, and endometrial cancer. *Am J Epidemiol* 177(12):1317-25 (2013).
DOI: 10.1093/aje/kws394
 37. Mrozikiewicz PM, Grześkowiak E, Seremak-Mrozikiewicz A, Bogacz A, Barlik M, Semczuk A, Bartkowiak-Wieczorek J, Drews K: Importance of CYP1A1 polymorphism and its transcriptional regulation in ovarian and endometrial cancer. *Ginekol Pol* 82(12):925-32 (2011).
Doi not found.
 38. Zając A, Stachowiak G, Smolarz B, Wilczyński JR: Polymorphisms of codon 72 of the TP53 gene in endometrial carcinoma of postmenopausal women. *Postepy Hig Med Dosw (Online)* 67:1312-8 (2013).
DOI: 10.5604/17322693.1080804
 39. Hosono S, Matsuo K, Ito H, Oze I, Hirose K, Watanabe M, Nakanishi T, Tajima

- K, Tanaka H: Polymorphisms in base excision repair genes are associated with endometrial cancer risk among postmenopausal Japanese women. *Int J Gynecol Cancer* 23(9):1561-8 (2013). DOI: 10.1097/IGC.0b013e3182a80a7e
40. Liu Y, Michalopoulos GK, Zarnegar R: Structural and functional characterization of the mouse hepatocyte growth factor gene promoter. *J Biol Chem* 269(6):4152-60 (1994). Doi not found.
 41. Liu Y, Lin L, Zarnegar R: Modulation of hepatocyte growth factor gene expression by estrogen in mouse ovary. *Mol Cell Endocrinol* 1994;104(2):173-81 (). DOI: 10.1016/0303-7207(94)90120-1
 42. Moghul A, Lin L, Beedle A, Kanbour-Shakir A, DeFrances MC, Liu Y, Zarnegar R: Modulation of c-MET proto-oncogene (HGF receptor) mRNA abundance by cytokines and hormones: evidence for rapid decay of the 8 kb c-MET transcript. *Oncogene* 9(7):2045-52 (1994). Doi not found.
 43. Walentinsson A, Helou K, Wallenius V, Hedrich HJ, Szpirer C, Levan G: Independent amplification of two gene clusters on chromosome 4 in rat endometrial cancer: identification and molecular characterization. *Cancer Res* 61(22):8263-73 (2001). Doi not found.
 44. Arena S, Pisacane A, Mazzone M, Comoglio PM, Bardelli A: Genetic targeting of the kinase activity of the Met receptor in cancer cells. *Proc Natl Acad Sci U S A* 104(27):11412-7 (2007). DOI: 10.1073/pnas.0703205104
 45. Park YH, Ryu HS, Choi DS, Chang KH, Park DW, Min CK: Effects of hepatocyte growth factor on the expression of matrix metalloproteinases and their tissue inhibitors during the endometrial cancer invasion in a three-dimensional coculture. *Int J Gynecol Cancer* 13(1):53-60 (2003). DOI: 10.1046/j.1525-1438.2003.13033.x
 46. Yoshida S, Harada T, Iwabe T, Taniguchi F, Fujii A, Sakamoto Y, Yamauchi N, Shiota G, Terakawa N: Induction of hepatocyte growth factor in stromal cells by tumor-derived basic fibroblast growth factor enhances growth and invasion of endometrial cancer. *J Clin Endocrinol Metab* 87(5):2376-83 (2002). DOI: 10.1210/jcem.87.5.8483
 47. Choi DS, Kim HJ, Yoon JH, Yoo SC, Jo H, Lee SY, Min CK, Ryu HS: Endometrial cancer invasion depends on cancer-derived tumor necrosis factor-alpha and stromal derived hepatocyte growth factor. *Int J Cancer* 124(11):2528-38 (2009). DOI: 10.1002/ijc.24238
 48. Sundaram S, Le TL, Essaid L, Freerman AJ, Huang MJ, Galanko JA, McNaughton KK, Bendt KM, Darr DB, Troester MA, Makowski L: Weight Loss Reversed Obesity-Induced HGF/c-Met Pathway and Basal-Like Breast Cancer Progression. *Front Oncol* 4:175 (2014). DOI: 10.3389/fonc.2014.00175
 49. Shi MD, Liao YC, Shih YW, Tsai LY: Nobiletin attenuates metastasis via both ERK and PI3K/Akt pathways in HGF-treated liver cancer HepG2 cells. *Phytomedicine* 20(8-9):743-52 (2013). DOI: 10.1016/j.phymed.2013.02.004
 50. Kanayama S, Yamada Y, Kawaguchi R, Tsuji Y, Haruta S, Kobayashi H: Hepatocyte growth factor induces anoikis resistance by up-regulation of cyclooxygenase-2 expression in uterine endometrial cancer cells. *Oncol Rep* 19(1):117-22 (2008). Doi not found.
 51. Yoshizawa Y, Yamada Y, Kanayama S, Shigetomi H, Kawaguchi R, Yoshida S, Nagai A, Furukawa N, Oi H, Kobayashi H: Signaling pathway involved in cyclooxygenase-2 up-regulation by hepatocyte growth factor in endometrial cancer cells. *Oncol Rep* 26(4):957-64 (2011). Doi not found.
 52. Crouch S, Spidel CS, Lindsey JS: HGF

and ligation of alphavbeta5 integrin induce a novel, cancer cell-specific gene expression required for cell scattering. *Exp Cell Res* 292(2):274-87 (2004).
DOI: 10.1016/j.yexcr.2003.09.016

53. Ho MY, Hung SW, Liang CM, Liang SM: Recombinant viral capsid protein VP1 suppresses lung cancer metastasis by inhibiting COX-2/PGE2 and MIG-7. *Oncotarget* 5(11):3931-43 (2014).
Doi not found.
54. Ho MY, Liang SM, Hung SW, Liang CM: MIG-7 controls COX-2/PGE2-mediated lung cancer metastasis. *Cancer Res* 73(1):439-49 (2013).
DOI: 10.1158/0008-5472.CAN-12-2220

Abbreviation: HGF: hepatocyte growth factor; EC: endometrial carcinoma; HGFA: HGF activator; IL-6: interleukin-6; TNF-alpha: tumor necrosis factor alpha; TIMP-2: metalloproteinase-2; MMP: matrix metalloproteina; ERE: estrogen responsive elements; MET-KD: kinase-inactive Met; PI3K: phosphatidylinositol 3-kinase; COX-2: cyclooxygenase-2

Key Words: HGF, endometrial carcinoma, TNF-alpha, TIMP-2, Review

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