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EXPRESSION OF HEPATOCYTE GROWTH FACTOR AND C-MET RECEPTOR IN STROMAL FIBROBLASTS AND TUMOR CELLS OF ENDOMETRIAL CARCINOMA

Background. HGF/c-Met is one of the main signaling pathways that ensure communication between epithelial cells and components of the tumor microenvironment determining the invasive and metastatic potential of many cancers. However, the significance of HGF and c-Met in endometrial carcinoma (ECa) progression remains unclear. **Aim.** To evaluate copy number variations as well as expression of the c-Met receptor and its ligand HGF in endometrial carcinomas considering the clinical and morphological characteristics of ECa. **Materials and Methods.** The study was conducted on ECa samples of 57 patients, among which 32 had lymph nodes and/or distant metastasis. The copy number of *c-MET* gene was estimated by qPCR. The expression of HGF and c-Met in tissue samples was determined by the immunohistochemical method. **Results.** Amplification of *c-MET* gene was detected in 10.5% of the ECa cases. The expression of HGF in tumor cells was associated with the tumor differentiation grade and was higher in poorly differentiated ECa ($p = 0.041$). The number of HGF$^+$ fibroblasts in the stromal component was increased in the ECa cases with metastasis compared to the cases without metastasis ($p = 0.032$). The content of stromal c-Met$^+$ fibroblasts was higher in deeply invasive carcinomas of patients with metastases than in tumors with invasion of <1/2 myometrium ($p = 0.035$). **Conclusion.** Increased expression of HGF and c-Met in stromal fibroblasts of endometrial carcinomas is associated with metastasis in patients with ECa and deep invasion of the tumor into the myometrium that can contribute to the aggressive course of the disease.

Keywords: HGF, c-Met, stromal fibroblasts, tumor cells, endometrial carcinoma.

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Endometrial cancer (ECa) is a leading cancer of the female reproductive system in Ukraine and worldwide. In 2020, over 400,000 new cases of ECa were reported worldwide [1]. The treatment of ECa patients remains an ongoing clinical challenge due to the variability of the disease and difficulties in determining the molecular subtypes of endometrial carcinomas with an aggressive phenotype [2—4]. Identifying molecular and biological features of tumor cells that have a prognostic value remains a focus of ECa research. Based on the tumor-host interaction paradigm, detecting biological signs associated with tumor progression not only in tumor cells but also in the cells of tumor microenvironment cells is important.

It is now widely accepted that cancer development is accompanied by significant changes in the tumor microenvironment, affecting both the stromal cells and the components of the extracellular matrix [5]. In the initial stages of malignancy, the microenvironment components play an anti-tumor role by ensuring tissue homeostasis in the epithelium and promoting the elimination of tumor cells. However, over time, stromal cells acquire tumorigenic properties as a result of interaction with tumor cells, which can stimulate tumor development [6—8]. The influence of stromal cells on tumor cells is mediated via the secretion of cytokines and growth factors, resulting in pathological paracrine signaling. Factors secreted by stromal cells are considered potential prognostic markers and therapeutic targets.

The hepatocyte growth factor (HGF) is a multifunctional cytokine involved in the regulation of cell division, motility, migration, and invasion [9, 10]. It is a natural ligand for the tyrosine-protein kinase receptor — mesenchymal–epithelial transition factor (c-Met). Normally, HGF is secreted mainly by stromal cells, but, as it has been established, tumor cells can also acquire the ability to produce this cytokine and, by binding c-Met on their surface, provide an autocrine regulation loop [11]. HGF/c-MET signaling mediates the morphogenesis and regeneration of various tissues and organs; in particular, it plays an important role in the restoration of the endometrium during the menstrual cycle [12, 13].

When HGF interacts with c-Met, a number of intracellular signaling pathways are activated, including PI3K/Akt, STAT3, SRC/FAK, and MAPK/ERK [10]. c-Met-mediated deregulation of these cascades is a characteristic feature in a number of aggressive forms of malignant neoplasms. In tumor cells, non-canonical HGF-independent activation caused by a number of factors, such as hypoxia, molecular disturbances in the structure of the *c-MET* gene, and downregulation of suppressor miRNAs, can be observed along with the canonical activation of c-Met by its ligand HGF. The association of aberrant functioning of the HGF/c-Met pathway with an unfavorable prognosis has been shown in a number of cancers, including lung, gastric, breast, pancreatic, head and neck, cervical, colorectal, renal cell, and hepatocellular cancers [9, 10]. Deregulation of the HGF/c-Met pathway leads to stimulation of proliferation, angiogenesis, inhibition of apoptosis, metabolic reprogramming, and epithelial–mesenchymal transition. One of the most significant consequences of impairing this pathway is the activation of invasion and metastasis [14].

The most common molecular changes of HGF and c-Met in various cancer types include their overexpression, amplification (gene copy number gain) of the *c-MET* gene, and aberrant paracrine and autocrine secretion of HGF [9]. Information on disturbances in HGF/c-Met signaling in endometrial carcinomas and their relationship with ECa aggressiveness is scarce. The study of Felix et al. [15] did not reveal a relationship between the expression of HGF or c-Met and the prognosis of ECa, however, it found that the co-expression of HGF and fibroblast growth factor (bFGF) in tumor cells is correlated with the risk of recurrence. In other studies, it was shown that HGF and c-Met are markers of unfavorable prog-

nosis in patients with ECa [16, 17]. Considering the prognostic perspective of these markers, it is important to study in-depth the features of functioning and disorders of HGF/c-Met signaling in ECa.

The aim of the study was to evaluate the copy number as well as expression of the c-MET receptor and its ligand HGF in ECa considering the clinical and morphological characteristics of tumors and the presence of metastases.

Materials and Methods

The study was conducted on ECa samples of 57 patients, among which 32 had metastatic lesions in lymph nodes and/or distant organs (average age 58.3 ± 4.2 years). All patients were informed about the study and provided written consent for participation. Morphological analysis was performed on histological samples stained with hematoxylin and eosin. The histological type of all examined tumors was diagnosed as endometrioid endometrial carcinoma of high (grade 1, G1), moderate (grade 2, G2), and low (grade 3, G3) differentiation grades.

The study was carried out in line with fundamental ethical principles — complete confidentiality of information about participants' personal data and the amount of treatment provided; the results were used only for research purposes. The research program was approved by the Commission on Bioethics of the RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, the NAS of Ukraine, and the work was agreed with the local ethics committee with a conclusion on compliance with moral and ethical standards of the European Convention on Bioethics (1997), as well as the current legislation of Ukraine.

Analysis of *c-MET* gene copy number was performed by quantitative PCR using the *HBB* gene as a reference control. Genomic DNA was isolated from tumor tissue and blood using the innuPREP mini reagent kit (Analytik Jena). The number of *c-MET* copies was determined in DNA samples obtained from tumor tissue, relative to conditionally normal DNA, isolated from the blood of the same patient. The nucleotide sequence of the primers was as follows:

c-MET:
Forward 5'-AACTGGTGTATGCAGATTGC-3';
Reverse 5'-AGCAAGAGTCCCCATCCTA-3';
HBB:
Forward 5'-TAGCAACCTCAAACAGACAC-3';
Reverse 5'-ATCCTGAGACTTCCACACTG-3'.

PCR was performed in a volume of 20 μl using SYBR Green MasterMix M02 reagents (UkrGenTech), to which 0.3 mM of each primer and 100 ng of DNA were added. The reaction mixture was heated to 95 °C for 12 min, after which 40 cycles of amplification were performed as follows: denaturation at 95 °C for 15 s, annealing at 60 °C for 30 s, and elongation at 72 °C for 30 s. PCR results were calculated according to the formula $2^{-\Delta\Delta Ct}$ [18]. The amplification was considered as present if the obtained value of the number of copies of the gene in the tumor relative to the blood was above 1.5.

Protein expression was determined in the samples of 55 endometrial carcinomas by the immunohistochemical method using polyclonal antibodies against HGF (PA5-83494, Invitrogen, Sweden) and monoclonal antibodies against c-Met (EP1454Y, Bio SB, USA). Expression analysis was performed separately in epithelial cells of endometrial carcinomas and in fibroblasts of the surrounding stroma. The results of the immunohistochemical reaction were evaluated by counting the number of stained cells, expressed as a percentage (labeling index, LI, %). Marker expression was considered positive when staining was observed in more than 5% of tumor cells [19].

All statistical analyses were performed with the Statistica 8.0 software package (StatSoft, Inc., USA). The analysis of differences between groups of patients was carried out using nonparametric Mann — Whitney U-test and Fisher's exact test.

To identify the relationship between the data, Spearman's rank correlation coefficient (r) was calculated. A *p*-value less than 0.05 was considered statistically significant.

Results

Determination of the *c-MET* gene copy number showed that its amplification was observed in 10.5% of the investigated ECa cases (Fig. 1). The majority of endometrial carcinomas with *c-MET* amplification (66.7%) were characterized by a low differentiation grade (Table 1). In addition, among cases with *c-MET* amplification, tumors with deep invasion into the myometrium predominated (83.3%). In 50.0% of such ECa cases, the presence of metastases in lymph nodes and/or distant organs was revealed. No significant difference in clinical and morphological indices was found between the groups of patients with and without *c-MET* amplification, which may indicate the randomness of this phenomenon in ECa.

Positive expression of HGF and c-Met in the epithelial component of carcinomas was determined in 49.1 and 45.5% of cases, respectively, in the stromal component — in 40.0% and 34.5% of cases, respectively (Fig. 2). The average level of HGF expression in epithelial cells of carcinomas was 18.5 ± 3.3%, in the stromal fibroblasts — 14.8 ± 3.6%. The values for the c-Met expression were 17.5 ± 3.3 and 18.5 ± 3.8%, respectively.

Correlation analysis revealed a significant positive relationship between the expression of HGF in tumor cells and the number of HGF^+ fibroblasts in the stroma ($r = 0.56$; $p < 0.05$). A similar dependence was observed for the c-Met marker ($r = 0.52$; $p < 0.05$). In addition, we found a positive correlation between the expression of HGF in tumor cells and the number of $c\text{-}Met^+$ stroma fibroblasts in G1 and G2 carcinomas ($r = 0.57$; $p < 0.05$).

Based on the obtained data of the expression of these markers in tumor cells, the following phenotypes of ECa were defined: $HGF^+c\text{-}Met^+$, $HGF^-c\text{-}Met^+$, $HGF^+c\text{-}Met^-$, and $HGF^-c\text{-}Met^-$. When analyzing the expression of HGF and c-Met in tumor cells and the number of fibroblasts positive by these markers, it was found that among the investigated ECa cases, a combined expression pattern was most often detected, in particular, the tumor cells had the $HGF^+c\text{-}Met^+$ phenotype, and the expression of HGF was observed in fibroblasts (Table 2). The vast majority of carcinomas with a combined expression pattern were of low differentiation grade (80%) and had deep invasion into the myometrium (70%). In addition, metastases were found in most patients with such tumors. The autocrine pattern (the absence of HGF expression in stromal component along with the $HGF^+c\text{-}Met^+$ phenotype of tumor cells) was observed twice less frequent than the combined pattern, and the majority of these tumors had deep invasion into the myometrium. The paracrine expression pattern (i.e. the presence of HGF expression in stromal fibroblasts while the tumor cells had the $HGF^-c\text{-}Met^+$ phenotype) was the least common. In all patients with this pattern, deeply invasive tumors and metastases were observed. It is worth noting that

Table 1. **Analysis of the *c-MET* gene copy number taking into account the clinical and morphological characteristics of patients**

Characteristics	*c-MET* copy number, n (%)		*P* (Fisher's exact test)
	Without amplification	With amplification	
Differentiation grade			
G1-G2	20 (39.2)	2 (33.3)	0.5748
G3	31 (60.8)	4 (66.7)	
Depth of invasion			
<1/2	15 (29.4)	1 (16.7)	0.4543
>1/2	36 (70.6)	5 (83.3)	
Metastases			
Absent	29 (56.9)	3 (50.0)	0.5390
Present	22 (43.1)	3 (50.0)	

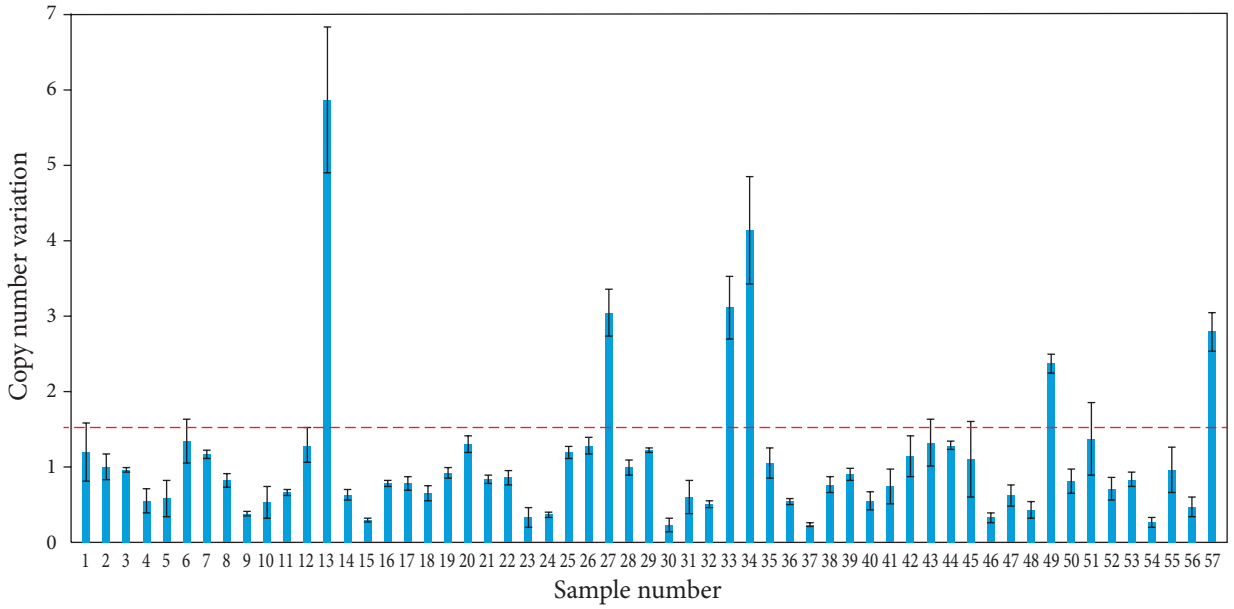

Fig. 1. *c-MET* gene copy number in endometrial carcinoma samples

Table 2. **Expression patterns of HGF and c-Met in tumor cells and fibroblasts**

Expression of HGF in fibroblasts	Variants of phenotypes by the expression of HGF and c-Met in tumor cells, n (%)			
	$HGF^+c\text{-}Met^+$	$HGF^+c\text{-}Met^-$	$HGF^-c\text{-}Met^+$	$HGF^-c\text{-}Met^-$
HGF^+	10 (18.2) *	7 (12.7)	3 (5.5) ***	2 (3.6)
HGF^-	5 (9.0) **	4 (7.3)	10 (18.2)	14 (25.5)

Note: * combined expression pattern; ** autocrine expression pattern; *** paracrine expression pattern.

Table 3. **Features of HGF and c-Met expression depending on the clinical and morphological characteristics of ECa cases**

Characteristics	Marker expression (LI, %), mean ± SE			
	HGF		c-Met	
	Tumor cells	Stromal fibroblasts	Tumor cells	Stromal fibroblasts
Differentiation grade				
G1 and G2	8.3 ± 2.6	10.5 ± 6.1	16.0 ± 4.8	15.8 ± 5.3
G3	25.1 ± 4.9 *	17.4 ± 4.6	16.8 ± 4.1	20.5 ± 5.4
Depth of invasion				
<1/2	21.9 ± 7.2	6.1 ± 3.5	15.6 ± 6.1	5.7 ± 3.3
>1/2	17.4 ± 3.8	18.2 ± 4.8	18.3 ± 3.9	23.6 ± 5.0
Metastases				
Absent	18.6 ± 5.1	2.8 ± 1.3	20.5 ± 4.9	14.2 ± 4.9
Present	18.7 ± 4.6	24.4 ± 6.0 **	15.2 ± 4.4	21.9 ± 5.7

Note: *$p = 0.041$ compared to G1 and G2 carcinomas; ** $p = 0.032$ compared to the group of patients without metastases (Mann — Whitney U-test).

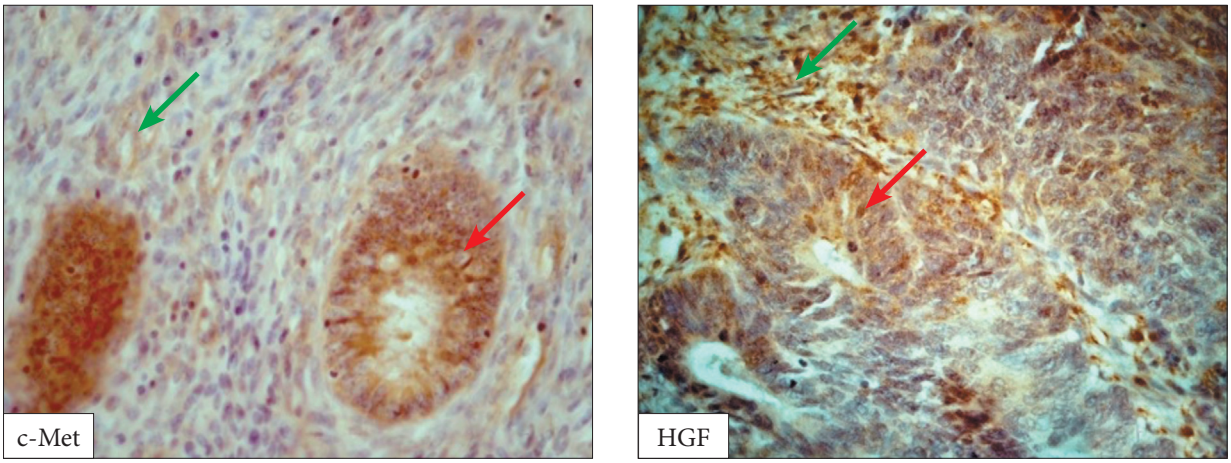

Fig. 2. Staining for c-Met (A) and HGF (B) proteins in tumor cells (red arrow) and stromal fibroblasts (green arrow) of ECa. Immunohistochemical method, additional staining with Mayer's hematoxylin, ×400

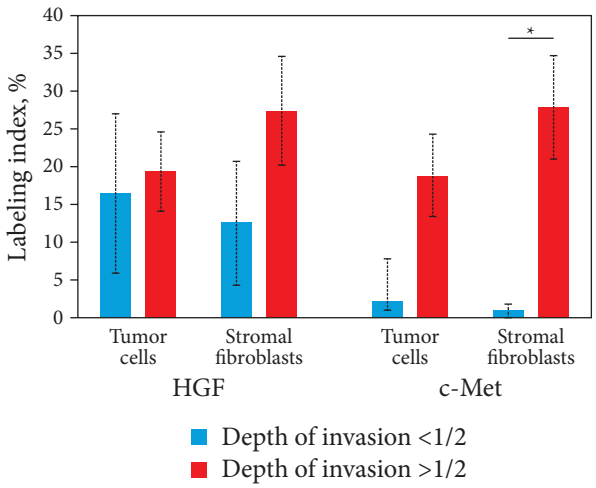

Fig. 3. Expression of HGF and c-Met in ECa patients with metastases depending on the depth of tumor invasion into the myometrium. *p = 0.035 compared to stromal fibroblasts of deeply invasive carcinomas

among carcinomas with positive expression of c-Met in tumor cells, 10 (18.2%) cases were identified where HGF expression was not determined either in stroma components or in tumor cells.

In addition to the analysis based on the expression patterns, we investigated the dependence of the expression level for each marker separately considering clinical and pathological parameters. When studying the expression of proteins taking into account the ECa differentiation grade, an increase in the level of HGF was noted in the epithelial and stromal components of low-differentiated tumors (Table 3). Notably, the expression of HGF in tumor cells was approximately three times higher in G3 carcinomas compared to G1 and G2 (p = 0.041). Along with this, there was a trend toward an increase in the number of HGF^+-fibroblasts in tumors invading >1/2 of the myometrium (Table 3). The number of c-Met^+-fibroblasts in deeply invasive tumors changed in a similar manner.

It was found that the expression of HGF in tumor cells of ECa was approximately the same in patients with and without metastases (Table 3). However, a significant increase was observed in the number of HGF^+ fibroblasts in the tumors of patients with metastases compared to those without metastatic lesions (p = 0.032).

Analyzing the features of HGF expression in the group of ECa patients with metastases, we have established that its level in epithelial cells does not depend on the depth of tumor invasion, while the number of HGF^+-fibroblasts increased slightly in carcinomas with the invasion of >1/2 of the myometrium (Fig. 3). It was also shown that in cases with metastases and invasion of >1/2 of the myometrium, an increased expression of c-Met in epithelial cells was ob-

served compared to carcinomas with invasion of <1/2 of the myometrium. Along with this, the number of c-Met$^+$ fibroblasts significantly increased in the stroma of deeply invasive carcinomas ($p = 0.035$).

Discussion

Altered HGF/c-Met signaling is one of the causes of the changes in the properties of the tumor microenvironment from anti- to protumorigenic, which is characteristic for a number of aggressive forms of malignant neoplasms [5—7]. However, the features of the expression of HGF and c-Met in the stromal and epithelial components of the tumor and their relationship with the tumor progression remain poorly studied.

The conducted study made it possible to establish that HGF/c-Met signaling can be involved in the ECa progression because, in particular, it is associated with invasion and metastasis. Based on the obtained data, the increased expression of HGF and c-Met in both tumor and stromal cells could play an important role in these processes. We established that the expression of HGF and c-Met was associated with such indicators of the tumor process as a low differentiation grade, deep invasion of the tumor into the myometrium, and the presence of metastases.

Our data on the association of specific phenotypes (by the expression of HGF and its receptor c-Met in epithelial tumor cells) with the number of HGF$^+$ and c-Met$^+$ fibroblasts may suggest that the combination of paracrine and autocrine regulation of HGF/c-Met signaling (combined expression pattern) is important for the ECa progression. This is consistent with the data of Edakuni et al. [20] who established an association of paracrine and combined expression patterns of HGF and c-Met with the adverse disease course in breast cancer patients. In addition, we determined the correlation of the expression of these markers in stromal fibroblasts of G1 and G2 carcinoma. This suggests that HGF is capable of activating c-Met expression in stromal components through an autocrine loop, as indicated by previous *in vitro* studies [21]. The detection of cases of deeply invasive carcinomas with paracrine and autocrine expression patterns of HGF and c-Met in stromal components may be evidence of the important role of this signaling in determining the invasive properties of ECa by modulating the tumor microenvironment.

It should be noted that amplification of the *c-MET* gene is a rare phenomenon (in our study it was found only in 10.5% of cases). The relationship between the aggressive course of the disease and the amplification of the *c-Met* gene has been shown in various localizations, including NSCLC, breast, gastric, and kidney cancer [9]. It is noted that this amplification is associated with increased expression and constitutive activation of the c-Met receptor [9, 10]. Our findings suggest that there is no association between *c-MET* amplification and clinical and pathological indices of ECa.

The frequency of c-Met overexpression at the mRNA or protein levels in various cancer types may exceed 80% and correlates with the advanced stages of the disease and low survival rates [9]. Similar to c-Met, elevated HGF expression is also associated with a poor prognosis in different malignancies. Data on the expression of HGF and c-Met in ECa are sparse. According to the literature, ECa is characterized by significant variability in the expression of these markers, with the number of positive cases ranging from 15—100% for HGF and 22—87% for c-Met [15—17]. Overexpression of c-Met was also detected in 40% of clear cell endometrial carcinomas and 43% of mucinous endometrial carcinomas [22]. Such a significant range of expression fluctuations may be related to the lack of a standardized system for evaluating the results of immunohistochemical detection of the expression of these proteins [9].

In the study by Bishop et al. [16], it is noted that the expression of HGF was determined not

only in the tumor cells of the endometrium but also in the cells of the stroma although the levels of IHC expression of the marker in each of these cell types were not specified. Notably, the patients with high expression of HGF and c-Met in the ECa had reduced overall survival compared to patients with low expression of these markers in the tumor cells [16]. Felix et al. [15] showed that patients whose tumors expressed HGF and basic fibroblast growth factor (bFGF) had an increased risk of recurrence compared to the cases negative by the expression of both markers. In other tumor types, the expression of HGF and c-Met in tumor cells and stromal components was shown to be associated with cancer progression [20, 21].

In conclusion, our study has revealed the relationship between the expression of HGF and c-Met in tumor cells and stromal fibroblasts with the course of the disease in ECa patients. The detected associations of stromal expression of HGF and c-Met with the presence of metastases may indicate the possibility of considering these proteins as prognostic markers of ECa. The obtained data indicate that the HGF/c-Met pathway is essential for realizing the interaction between tumor cells and cells of the tumor microenvironment to determine the ECa aggressiveness. Understanding the role of HGF/c-Met signaling in determining cancer aggressiveness is the basis for the effective implementation of the principles of personalized medicine in the treatment of patients with ECa.

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ЕКСПРЕСІЯ ФАКТОРА РОСТУ ГЕПАТОЦИТІВ ТА РЕЦЕПТОРА C-MET У СТРОМАЛЬНИХ ФІБРОБЛАСТАХ ТА ПУХЛИННИХ КЛІТИНАХ КАРИНОМИ ЕНДОМЕТРІЮ

HGF/c-Met є одним із основних сигнальних шляхів, які забезпечують зв'язок між епітеліальними клітинами та компонентами мікрооточення пухлини, визначаючи інвазивний та метастатичний потенціал багатьох карцином. Однак, значення HGF і c-Met у прогресії раку ендометрію (РЕ) залишається нез'ясованим. **Мета.** Оцінити зміну копійності, а також експресію рецептора c-Met та його ліганду HGF у карциномах ендометрію з урахуванням клінічних та морфологічних характеристик РЕ. **Матеріали та методи.** Дослідження проведено на зразках РЕ 57 пацієнтів, серед яких 32 мали метастази у лімфовузли та/або віддалені органи. Зміну копійності гена *c-MET* оцінювали за допомогою кПЛР. Експресію HGF і c-Met у зразках пухлинної тканини визначали імуногістохімічним методом. **Результати.** Ампліфікація гена *c-MET* була виявлена в 10.5% випадків РЕ. У більшості карцином встановлено комбінований патерн експресії HGF і c-Met, за яким в пухлинних клітинах спостерігалася коекспресія цих маркерів, а в стромі збільшувався вміст HGF^+ фібробластів. Експресія HGF у пухлинних клітинах асоціювалася зі ступенем диференціації пухлини і була вищою в низькодиференційованих карциномах ($p = 0{,}041$). Кількість HGF^+ фібробластів у стромальному компоненті збільшувалась у випадках РЕ з наявністю метастатичного процесу порівняно з неметастатичними випадками ($p = 0{,}032$). Вміст стромальних $c\text{-}Met^+$ фібробластів був вищим у глибоко інвазивних карциномах пацієнтів з метастазами порівняно до пухлин з інвазією <1/2 міометрія ($p = 0{,}035$). **Висновок.** Підвищена експресія HGF і c-Met у стромальних фібробластах карцином ендометрію пов'язана з метастазами та глибокою інвазією пухлини в міометрій і може сприяти агресивному перебігу захворювання.

Ключові слова: HGF, c-Met, стромальні фібробласти, пухлинні клітини, карцинома ендометрія.