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VALIDATION OF A PANEL OF BIOMARKERS ASSOCIATED WITH AGGRESSIVE PHENOTYPE OF ENDOMETRIOID CARCINOMA OF ENDOMETRIUM

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Aim: **To evaluate the prognostic significance of a panel of biomarkers for the identification of a highly malignant molecular subtype of endometrioid carcinoma of the endometrium (ECE).** ***Materials and Methods*****: The expression of a number of markers (CD24, CD44, E2F1, FOXP3, Her2/neu, $p21^{WAF1/CIP1}$, p53, β-catenin, vimentin, E-cadherin, c-Myc, cyclins D1 and E1) was determined by the immunohistochemical method in the samples of resected tumors of 127 patients with ECE of I–II stage. The Kullback method and the PanelomiX web tool were used to assess the informativeness and identify the aggressive subtype of ECE. The associative relationships of the studied markers were determined using the STRING v11 database.** ***Results*****: The study of the prognostic significance of a number of biomarkers in ECE has revealed the informativeness, high specificity and sensitivity (> 95%) of the $p53^{+}FOXP3^{-}c\text{-}Myc^{+}$ phenotype, which is associated with a more aggressive tumor process. Bioinformatics analysis confirmed the correlative relationships between p53, FOXP3 and c-Myc, which are significant prognostic markers associated with cancer progression in ECE patients.** ***Conclusions*****: The identified molecular phenotype of ECE ($p53^{+}FOXP3^{-}c\text{-}Myc^{+}$) has differential and prognostic significance and objectively reflects a highly malignant subtype of this form of cancer.**

Key Words**: endometrioid endometrial carcinoma, aggressive phenotype, biomarker panels.**

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Endometrial cancer (EC) is the most common among oncogynecological diseases of women in European countries [1]. According to the National Cancer Registry of Ukraine, in the last decade, there has been a trend towards an increase in the EC incidence, in particular in people under the age of 40, which has a negative impact on the demographic indicators of the country's working population [2].

It should be noted that the successful treatment of patients with malignant neoplasms can be ensured by two components: an in-depth clinical examination and determination of the molecular and biological characteristics of tumors, which allow predicting the aggressiveness of the cancer and become the basis for adequate therapy. Such a strategy of the treatment process could contribute to increasing the survival rate of cancer patients [3–5].

The biological heterogeneity of EC, in particular, such a morphological form as endometrioid carcinoma of the endometrium (ECE) argues for the feasibility of determining a molecular subtype of tumors associated with a high potential for malignancy. That is, the problem of identifying molecular EC subtypes, which reflect the biology of the tumor and determine the variability of the clinical course of this form of cancer, remains relevant [6–9].

The use of probabilistic and statistical methods (multivariate regression analysis, the method of clustering and classification trees, Bayesian approaches, ROC analysis, etc.) in the analysis of a panel of biomarkers allows for a more objective assessment of the nature of the neoplastic process, minimizes false-negative and false-positive results [10–15]. This approach ensures high accuracy of identification of prognostically significant molecular subtypes of tumors of various genesis.

However, despite the progress in establishing the features of the pathogenesis of many forms of cancer, objective predictors of ECE malignancy that have clinical significance have not still been determined [16, 17]. Correct methods of identification of individual biomarkers have not been developed and their panels, allowing us to establish with high accuracy clinically significant molecular EC subtypes, have not been formed [18–27].

To date, according to the data of the complex genomic and transcriptomic analysis of gene expression in ECE cells, 4 groups of neoplasms have been classified, which are characterized by certain molecular and biological features and are associated with the overall survival of patients with EC. The researchers emphasize the feasibility of developing a clear algorithm for their determination for implementation in pathomorphological laboratories [28, 29]. Therefore, the study of the expression of a number of biomarkers and the validation of their panels for the identification of an aggressive molecular subtype of ECE is an urgent problem.

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Abbreviations used: EC – endometrial cancer; ECE – endometrioid carcinoma of the endometrium; PC – prognostic coefficient; Se – sensitivity; Sp – specificity.

The present study was aimed at the evaluation the prognostic significance of a panel of biomarkers for the identification of a highly malignant molecular subtype of ECE.

MATERIALS AND METHODS

We have studied the samples of surgical material of 127 patients with ECE stage I–II (age range of 59.3 ± 3.2 years), who were not prescribed special treatment before surgery. All patients were treated in the Department of Oncology and Gynecology of the National Cancer Institute of the Ministry of Health of Ukraine. All patients gave informed consent for the use of their surgical material for scientific purposes. The study was conducted in compliance with national bioethical norms and the provisions of the Declaration of Helsinki.

Tumors associated with a high degree of morphological malignancy included low differentiated ECE with deep invasion of the myometrium (G3 tumors with invasion > 1/2 of the myometrium), tumors with a low malignancy included moderately differentiated ECE without deep invasion in the myometrium (G2 tumors with invasion < 1/2 myometrium).

The expression of biomarkers (CD24, CD44, E2F1, FOXP3, Her2/neu, $p21^{WAF1/CIP1}$, p53, β-catenin, vimentin, E-cadherin, c-Myc, cyclins D1 and E1) was assessed by immunohistochemical method. The expression of the marker lower than the median value (< Me) was considered low (–), and higher than the median value (> Me) — high (+).

To assess the significance of the expression of certain biomarkers and determine the their optimal combination for identifying objectively an aggressive molecular ECE subtype (G3 tumors with invasion of > $^1/_2$ of the myometrium), we used the web-method "PanelomiX" (Swiss Institute of Bioinformatics, Switzerland), which allows testing different combinations of markers according to the Iterative Combination of Biomarkers and Thresholds method. Reliability and efficiency of biomarker panels were analyzed using cross-validation and ROC analysis. The panel of biomarkers was defined under the condition of minimizing false negative (Sp — specificity) and false positive results (Se — sensitivity).

Kullback method was used for assessing the informativeness of the studies markers. The stability of the biological system based on the expression indices of the studied biomarkers associated with the aggressive phenotype of ECE was determined by the redundancy coefficient (R, %) [30]. Its increase testifies to a pronounced heterogeneity in the morphofunctional characteristics of the cells of a malignant neoplasm.

The associations of the investigated proteins was analyzed using the STRING v11 database (http://www.string-db.org) that integrates information about the interaction of proteins in structural complexes contained in the KEGG, Reactome databases, UniProt, Pfam, SMART, InterPro, etc. (obtained as a result of experimental and clinical studies) into a single network (interactome) and allows estimating the probability of their possible association.

RESULTS AND DISCUSSION

When screening the expression of biomolecular markers in endometrial tumor cells (p53; FOXP3; $p21^{WAF1/CIP1}$; E2F1; cyclin E; D; Her2-neu; c-Myc; E-cadherin; β-catenin; vimentin; CD44; CD24) we have determined a molecular ECE phenotype $p53^+FOXP3^-c\text{-}Myc^+$, which correlates with a low differentiation grade and deep invasion of the tumor into the myometrium. Our data showed that in ECEs, which are associated with a more aggressive course of the tumor process, the expression of p53, c-Myc, cyclin E, E2F1 was almost twice as high, and the expression of FOXP3 was reduced compared to these indices in moderately differentiated ECE with invasion < $^1/_2$ myometrium (Table 1). At the same time, the expression of other studied markers did not differ significantly between ECEs with high and low grades of morphological malignancy [31]. This allows us to determine the most aggressive subtype of this form of cancer, which is a fundamental basis for predictive assessment of the personalized EC prognosis [31].

The data obtained suggest that such biomarkers could be included into the diagnostic panel for determining the molecular subtype of EC with more aggressive behavior.

Taking into account the above, the issue of assessing the level of informativeness of the expression indices of the investigated biomarkers in relation to the identification of molecular ECE subtypes associated with the unfavorable course of the disease in patients remains open. When the significance of biomarker expression for recognizing the tumors with more aggressive behavior was assessed by Kullback method taking into account the Me expression values, the expression of p53, FOXP3, c-Myc exceeded significantly the minimum threshold value of the informativeness coefficient (I = 0.5) proving their high informativeness. The differential prognostic significance of the following combination of markers and their expression levels (p53 and c-Myc — high, FOXP3 — low) allows iden-

Table 1. Expression of biomolecular markers in ECEs of various grades

Clinical and morphological parameters	Cyclin E1	E2F1	FOXP3	p53	c-Myc
G2 < $^1/_2$	9.9 ± 0.6	7.7 ± 0.9	18.1 ± 2.1	14.7 ± 3.2	6.2 ± 2.7
G3 > $^1/_2$	16.7 ± 2.0*	11.2 ± 1.0*	9.7 ± 0.8*	55.3 ± 3.5*	13.1 ± 2.8*

Notes: *$p < 0.05$ compared to G2 tumors with < $^1/_2$ myometrial invasion.

Table 2. Informativeness of biomarkers for the assessment of the aggressive ECE subtype

Biomarker	Informativeness coefficient (I)	Prognostic coefficient (PC)
$p53^{low}$	4.46	– 6.48
$p53^{high}$	5.91	+ 8.57
$FOXP3^{low}$	4.48	+ 7.87
$FOXP3^{high}$	2.52	– 4.44
$c\text{-}Myc^{low}$	1.01	– 2.30
$c\text{-}Myc^{high}$	1.08	+ 2.91

Notes: Indices of biomarker expression: high (⩾ Me); low (< Me). PC indicators "+" correspond to G3-tumors with invasion $>{}^1/_2$ myometrium, PC indicators "-" correspond to G2-tumors with invasion $<{}^1/_2$ myometrium.

tifying aggressive forms of ECE (Table 2). Therefore, the obtained results allowed us to associate the expression values of biomarkers in G3 tumors with invasion of $> {}^1/_2$ myometrium with a high potential of ECE malignancy.

Screening of a number of combinations of marker expression, the significance of which was assessed by optimization of Se, Sp in the range of 0.50–1.00, made it possible to determine the threshold values of their expression for the classification of tumors with various degrees of malignancy. Thus, a three-component complex (p53 > 44.75%; FOXP3 < 14.0%; c-Myc > 10.0%) was identified with maximum probability (Se = 0.98; Sp = 1.00) for determining a more aggressive ECE subtype.

When analyzing possible variants of phenotypes with low/high expression of p53, FOXP3, c-Myc proteins depending on their threshold values it was established that in the group of G2 neoplasms with invasion $< {}^1/_2$ myometrium, the $p53^-FOXP3^+c\text{-}Myc^-$ phenotype prevailed (76%) and the $p53^+FOXP3^-c\text{-}Myc^+$ and $p53^-FOXP3^-c\text{-}Myc^-$ phenotypes were observed in 6% of cases. In this group $p53^+FOXP3^+c\text{-}Myc^+$, $p53^+FOXP3^+c\text{-}Myc^-$, $p53^+FOXP3^-c\text{-}Myc^-$ and $p53^-FOXP3^-c\text{-}Myc^+$ phenotypes were not determined. On the contrary, in the group of low differentiated tumors with invasion $> {}^1/_2$ myometrium, the $p53^+FOXP3^-c\text{-}Myc^+$ phenotype was observed in 46% cases, and the $p53^-FOXP3^+c\text{-}Myc^-$ phenotype in 5% of cases. Phenotypes such as $p53^+FOXP3^+c\text{-}Myc^+$, $p53^-FOXP3^+c\text{-}Myc^+$ and $p53^-FOXP3^-c\text{-}Myc^+$ were absent (Table 3).

Taking into account the polymorphism of the identified variants of the phenotypes, in order to assess the stability of the biological system, an analysis of its redundancy was carried out. A higher value of the redundancy coefficient of 72.2% was established in G3 tumors with invasion of the myometrium $> {}^1/_2$ compared to neoplasms of a moderate differentiation grade with low invasion of the myometrium (57.8%). The obtained data reflect a higher stability and orderliness of the biological system in moderately differentiated tumors with invasion of the myometrium $< {}^1/_2$, compared to the group of G3 tumors with invasion $> {}^1/_2$, which is disorganized and more heterogeneous. The latter may determine the high morphofunctional plasticity of tumor cells, which causes the manifestation of ECE of a more malignant molecular subtype.

On the basis of multicenter studies within the framework of the project "The Cancer Genome Atlas Research" with the use of complex genomic and transcriptomic analysis, 4 molecular subtypes of ECE were identified: "POLE-ultramutated"; "MSI-hypermutated"; "Copy number low" and "Copy number high", which are characterized by different malignancy degree correlating with the 5-year survival rate of patients. The most unfavorable course of the disease was observed in 25% of patients with endometrioid G3-tumors, which by their morphological features were similar to serous neoplasms ("serous-like" subtype). Such tumors were characterized by amplification of *c-MYC, ERBB2 (HER-2/neu), CCNE1, FGFR3, SOX17* genes and *TP53* mutation [28, 31–36].

In the bioinformatic analysis of complex algorithms for protein interactions [37, 38], the power of the relationship between the components of the identified molecular subtype associated with the progression of the tumor process in the endometrium was determined. The probability of the existence of an assumed relationship between *TP53, FOXP3* and *c-Myc* genes was established: *TP5* ↔ *c-Myc* (score = 0.923); *TP53* ↔ *FOXP3* (score = 0.576); *FOXP3* ↔ *c-Myc* (score = 0.569) (Figure).

Therefore, based on the morpho-functional characteristics of the endometrium and the results of the information-probability analysis, the heterogeneity and complexity of the ECE biological system has been proven. This argues for the feasibility of further research of this form of cancer aimed at assessing the cause-and-effect relationship between the biological features of tumor cells and components of tumor microenvironment in the progression of the neoplastic process.

The applied complex of morphological, bioinformatics and information-probabilistic methods made it possible to confirm the high informativeness of the determined $p53^+FOXP3^-c\text{-}Myc^+$ phenotype in the detection of an aggressive mo-

Table 3. Variants of phenotypes including three biomarkers (p53, FOXP3, c-Myc) depending on the threshold values of their expression

Clinical and pathological characteristics of ECE	Number of tumors,%							
	$p53^+FOXP3^+c\text{-}Myc^+$	$p53^+FOXP3^+c\text{-}Myc^-$	$p53^+FOXP3^-c\text{-}Myc^+$	$p53^+FOXP3^-c\text{-}Myc^-$	$p53^-FOXP3^+c\text{-}Myc^+$	$p53^-FOXP3^+c\text{-}Myc^-$	$p53^-FOXP3^-c\text{-}Myc^+$	$p53^-FOXP3^-c\text{-}Myc^-$
G2 $< {}^1/_2$	0	0	6.0	0	12.0	76.0	0	6.0
G2 $> {}^1/_2$	0	0	11.0	11.0	11.0	33.1	11.7	22.2
G3 $< {}^1/_2$	16.7	33.3	0	0	0	33.3	16.7	0
G3 $> {}^1/_2$	0	3.9	46.0	27.0	0	5.0	0	18.1

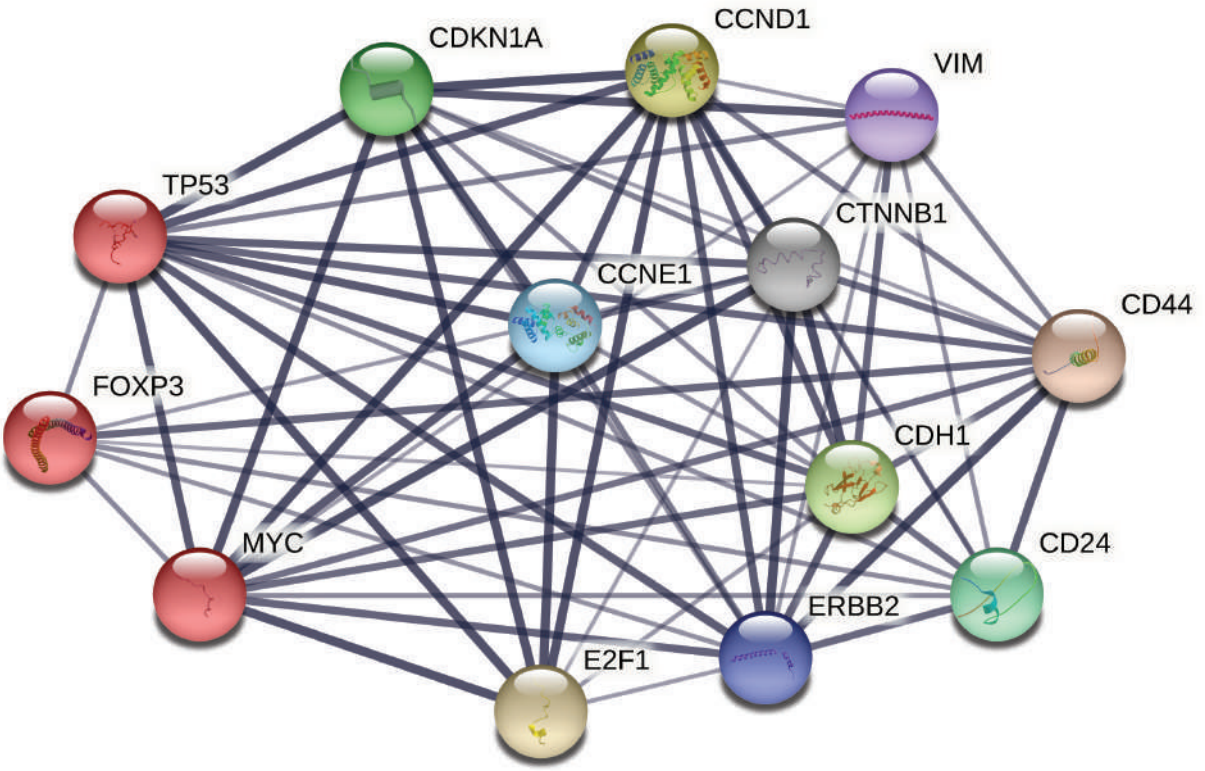

Figure. Analysis of functional associations of proteins encoded by *TP53, FOXP3*, and *c-Myc* genes (marked in red) using STRING web resource

lecular subtype of ECE, which is of great practical value providing rationale for predicting the course of the disease and personalized correction of the therapeutic means.

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ВАЛІДАЦІЯ ПАНЕЛІ БІОМАРКЕРІВ, АСОЦІЙОВАНИХ З АГРЕСИВНИМ ФЕНОТИПОМ ЕНДОМЕТРІОЇДНОЇ КАРЦИНОМИ ЕНДОМЕТРІЮ

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***Мета*:** Оцінка прогностичної значущості панелі біомаркерів для ідентифікації високозлоякісного молекулярного підтипу ендометріоїдної карциноми ендометрію (ЕКЕ). ***Об'єкт і методи*:** зразки операційного матеріалу 127 хворих на ЕКЕ I–II стадії віком 36–72 роки (середній вік — 59,3 ± 3,2 року). Експресію досліджених маркерів визначали імуногістохімічним методом. Для оцінки інформативності та ідентифікації агресивного підтипу ЕКЕ використовували метод Кульбака та вебінструмент PanelomiX. Асоціативні зв'язки досліджених маркерів визначали за допомогою бази даних STRING v11. ***Результати*:** У хворих на ЕКЕ оцінено прогностичну значущість ряду біомаркерів: CD24, CD44, E2F1, FOXP3, Her2/neu, $p21^{WAF1/CIP1}$, p53, β-катеніну, віментину, E-кадгерину, c-Myc, циклінів D1 і E1. З високою специфічністю та чутливістю (> 95 %) встановлено інформативність фенотипу $p53^{+}FOXP3^{-}$c-Myc^{+}, що асоціюється з більш агресивним пухлинним процесом в ендометрії. Біоінформатичним аналізом підтверджено корелятивні зв'язки між p53, FOXP3 і c-Myc, які є значущими прогностичними маркерами, асоційованими з прогресією пухлинного процесу у хворих на ЕКЕ. ***Висновки*:** Доведено, що ідентифікований молекулярний фенотип ЕКЕ — $p53^{+}FOXP3^{-}$c-Myc^{+} має диференційно-прогностичну значущість і об'єктивно відображає високозлоякісний підтип цієї форми раку.

***Ключові слова*:** ендометріоїдна карцинома ендометрію, агресивний фенотип, панелі біомаркерів.