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A STUDY OF TRANSFERRIN AND FERRITIN EXPRESSION IN TUMOR CELLS OF PATIENTS WITH BREAST CANCER

Summary. ***Aim****: to study and to evaluate the clinical significance of the expression of iron-containing proteins ferritin and transferrin in tumor cells of patients with breast cancer (BC).* ***Object and methods****: the study included 143 patients with BC stage II–III.* ***Methods****: clinical, morphological and immunohistochemical, statistical.* ***Results****: it was shown that BC is characterized by intertumor heterogeneity of expression of transferrin and ferritin. The high degree of differentiation of BC correlates with the lack of expression of transferrin and ferritin. Positive expression of these proteins in the cells of primary tumors correlated with the development of metastases in regional lymphatic nodes. Correlation dependences between parameters of expression of transferrin and ferritin in tumor cells and overall survival in patients with BC have been determined.* ***Conclusions****: the expression of transferrin and ferritin may be individual predictive markers of clinical course and survival in patients with BC and one more molecular target for the development of new anticancer agents.*

INTRODUCTION

Ferritin (FER) and transferrin (TRFER) belong to the iron-containing proteins involved in many physiological and pathological processes. According to the data of literature, iron-containing proteins play the main role in control of iron homeostasis in organism as well as in such biological processes as development of tissues, functional activity of cells, angiogenesis, proliferation and regulation of cellular cycle, etc. [1–4]. Expression of genes involved in iron metabolism, including genes of TRFER, FER and ferroportin, is regulated by iron regulatory proteins 1/2 (IRP1/2) on the posttranscriptional level [5, 6]. Interest in study of the role of iron-containing proteins in cancer patients is conditioned by their role in regulation of iron metabolism in the presence of malignant neoplasm in organism [7, 8]. In series of studies, connections between changes in level of iron-containing proteins and progression of tumor, as well as increased DNA synthesis in tumor cells (TC), expression of angiogenic factors (VEGF), reaction of cells to the oxidative stress, have been showed [9–11].

According to the results of numerous studies, FER is a cytoplasmic protein playing key role in intracellular iron homeostasis. At the same time, it can locate in cell nuclei, including tumor nuclei. This protein has many functions, particularly protection of cells from oxidative stress, regulatory role in transcription processes, and preservation of iron in bioactive and non-toxic forms [12–14]. Synthesis of intracellular FER is controlled on transcriptional and translational levels by two ways — iron-dependent and iron-independent [14]. FER is also known as proinflammatory mediator, expression of which can by induced by cytokines; however, it can induce expression of both proinflammatory and antiinflammatory cytokines and be immunosuppressant [15].

Another one iron-containing protein TRFER, which main function consists in transfer and delivery of iron to the cells, belongs to the markers of malignant tumor phenotype, since it is associated with proliferation of cells. It has been clearly demonstrated by example of cancer and neuroendocrine carcinomas of pancreatic gland: the highest expression of TRFER was in proliferating cells of both primary tumors and metastases [16]. Number of TRFER receptors (TfR1 and TfR2-alpha) in proliferating cells of hepatoma compared with cells in dormancy increases up to 300 and 200%, respectively [17]. Using comparative immunohistochemical (IHC) studies of expression of markers in tumor and normal cells, it has been showed that level and distribution of TRFER receptor in tumors of other genesis (colorectal cancer) changes depending on stage of tumor process and tumor differentiation grade: high expression of TRFER receptors in cells of highly differentiated forms of cancer at stages A and B by Dukes and lack/low expression in cells of low differentiated carcinomas with metastases at stage C or D [18]. Biological role of TRFER at tumor growth is confirmed also in study, in which was stated that TRFER receptors can have different regulatory properties and differentially be expressed in proliferating cells compared with those being in dormancy [19]. Although interest in iron-containing proteins and their role in TC homeostasis significantly increased in recent years, number of studies on FER and TRFER in TC of mammary gland is insufficient.

Our previous *in vitro* studies have showed that the most essential disorders of homeostasis of endogenous iron and increased level of FER and TRFER expression are detected in TC of human mammary gland of the most aggressive mesenchymal phenotype and in cells

with phenotype of treatment resistance to the antitumor drugs of different mechanism of action [20, 21]. Also, we have determined connection between FER level in blood serum and tumor tissue and sensitivity to neoadjuvant therapy in patients with breast cancer (BC) [22, 23]. However, to date there is no consensus of opinion concerning significance of presence of these proteins for prognosis of clinical course and survival of BC patients.

Aim of the study was to investigate the expression of iron-containing proteins FER and TRFER in TC of BC patients and to evaluate their clinical significance.

OBJECT AND METHODS

Retrospective analysis of the results of examination, treatment and survival of 143 BC patients of II–III stage, who have been receiving inpatient treatment on the basis of Lugansk Regional Clinical Oncology Dispensary during 2005–2010, has been carried out. Stage of tumor process was determined according with the International clinical classification of tumors (TNM, 6th edition, 2002). Histological type of removed tumors was verified at morphological study of histological sections (staining with hematoxylin and eosin) according with the WHO International histological classification (2001). All patients underwent adjuvant polychemotherapy (PCT) according with the standards of treatment approved in Ukraine by FAC or AC schemes with 21 day interval, number of PCT courses — 4–6. Postsurgical radiotherapy (RT) was carried out on gamma-therapeutic equipment «TERAGAM» (single focal dose 2 Gy, total focal dose 40 Gy) on the area of postsurgical scar, inguinal, parasternal and supraclavicular areas.

For IHC study of FER and TRFER expression in TC, standard streptavidin-biotin-peroxidase method was applied. As primary were used antibodies specific to FER and TRFER (Abcam, USA). For visualization of the results of reaction, reagent kit EnVision System, LSAB2 (Dako, Denmark) were used according with manufacturer's recommendations; histological sections were stained with Mayer hematoxylin. Evaluation of the results was carried out using optic microscopy at magnification ×200. For evaluation of FER and TRFER expression, semi-quantitative method was applied. In each histological specimen, expression of markers in 1000 TC was analyzed determining quantity of positive and negative cells in percentage and calculating level of expression of marker (high, moderate, strong). Strong positive expression of marker was considered quantity of positive TC > 10% and strong/moderate expression of markers [24].

Statistical processing of the results of study was carried out using methods of variation statistics with use of program STATISTICA 6.0. For evaluation of significance of differences in expression of studied markers and other clinical-pathological parameters, χ^2 was used. Evaluation of survival was carried out by Kaplan — Meier method taking date of the beginning of treatment as reference point. Multivariate analysis was performed using Cox regression model and log-rank test. Correlation analysis was carried out by calculation of Spearman correlation. Critical level of statistical significance was 0.05.

RESULTS AND DISCUSSION

General clinical characteristic of BC patients of II–III stage is given in Table 1. Age of patients varied from 25 to 76, mean age — 50.3 ± 4.3. The highest (27.1%) number of patients was in age interval 51–60. Most (61.5%) patients were in menopause. Part of BC patients of II stage has constituted 44.0%, III — 56.0%. Number of women with BC of IIa and IIb stages was almost equal and constituted 21.0 and 23.0%, respectively. Among patients with III stage T3a (33.1%) was prevailed; stage T3b was detected in 22.9% of patients. In 22.4% of patients, no metastases in lymph nodes (LN) were detected, in 77.6% metastatic involvement of LN was diagnosed. Complex examination of patients (radiological, ultrasound, laboratory), which was carried out before treatment, has not detected remote metastases. Morphological study of surgical material has showed that infiltrating duct cancer occurred more often (77.6%), than lobular cancer (22.4%); moderate tumor differentiation grade was determined in 42.6% of patients.

Total number of tumors with positive TRFER and FER expression was the same in both groups and constituted 75 (52.4%) and 74 (51.4%), respectively. Hereafter, TRFER and FER expression has been analyzed depending on such clinical features, as stage of disease, histological type of tumor and its differentiation grade, presence/lack of metastases of cancer in regional LN, overall survival (OS) of patients. No significant differences in frequency of positive (+) tumors depending on stage and histological structure of BC was detected. In particular, TRFER+ tumors were detected in 37 (58.7%) patients with II stage and in 38 (60.3%) — with III stage; FER+ — in 33 (52.3%) and 41 (51.2%) patients correspondingly. TRFER+ were 57 (51.3%) samples of infiltrating duct cancer and 18 (56.25%) — infiltrating lobular cancer; FER+ — 58 (52.2%) and 16 (50%), respectively.

In group of patients with high and moderate BC differentiation grade, number of tumors with positive expression of TRFER and FER was lesser, than in patients with low differentiation grade ($p < 0.05$) (Table 2). Number of tumors with positive expression of both markers turned out to be significantly higher ($p < 0.05$) in BC patients with metastases in LN (Table 3).

Results of correlation analysis are given in Table 4. No correlation between TRFER and FER expression and stage of BC and histological type of tumor has been determined. Also, it has been determined that TRFER/FER negative expression correlates with high differentiation grade of tumors, and positive TRFER/FER expression in primary tumor — with development of metastases in regional LN. No significant correlations between TRFER and FER expression in samples of one tumor were detected ($r = 0.10$; $p > 0.05$) that points out at different ways of regulation of these proteins, which are quite complicated in TC, finally not determined and need further study [25].

Table 1

General clinical characteristic of BC patients

Index	Number of patients	
	n	%
Total number of patients	143	100
Menstrual cycle		
Preserved	55	38.5
Menopause	88	61.5
BC stage by TNM (category T)		
II (T2) including T2a T2b	63 48 15	44.0 21.0 23.0
III (T3) including T3a T3b	80 62 18	56.0 33.1 22.9
Metastases in regional LN (category N)		
N0	32	22.4
N1–3	111	77.6
Remote metastases (category M)		
M0	143	100.0
BC morphology		
Infiltrating duct cancer	111	77.6
Infiltrating lobular cancer	32	22.4
BC differentiation grade		
High	40	28.0
Moderate	61	42.6
Low	42	29.4
Methods of treatment		
Mastectomy by Madden + PCT	51	35.7
Mastectomy by Madden + PCT + RT	57	39.9
Mastectomy by Madden + RT	35	24.4

Table 2

Distribution of tumors by TRFER and FER expression depending on BC differentiation grade

Differentiation grade	Number of tumors with positive expression of TRFER		Number of tumors with negative expression of TRFER		Number of tumors with positive expression of FER		Number of tumors with negative expression of FER	
	n	%	n	%	n	%	n	%
High (n = 40/100.0%)	19	47.5	21	52.5	16	40.0	24	60.0
Moderate (n = 61/100.0%)	21	34.4	40	65.6	24	39.3	37	40.7
Low (n = 42/100.0%)	35	83.3	17	16.7	34	80.1	7	9.9
Total (n = 143/100.0%)	75	52.4	68	47.6	74	51.4	69	48.6

Using Kaplan — Meier method, 5-year OS of patients depending on TRFER and FER expression has been calculated. As data in Fig. 1 and 2 show, survival of BC patients was higher at lack of TRFER and FER expression in remote tumors. Cox regression analysis conducted for determination of connections between TRFER and FER expression and OS rates of patients has showed that these proteins may be used as subsidiary predictive markers of BC prognosis (for TRFER $\beta = -0.44$; $p < 0.05$; for FER $\beta = -0.29$; $p < 0.05$).

When analyzing obtained results and summarizing conducted study, one should mention that molecular and clinical aspects of changes in iron homeostasis in organism of patients and TC and their diagnostic value are characterized by complexity of signal pathways of expression of markers, which are connected

Table 3

Distribution of tumors by TRFER and FER expression depending on presence of BC metastases in regional LN

Category N	Number of tumors with positive expression of TRFER		Number of tumors with negative expression of TRFER		Number of tumors with positive expression of FER		Number of tumors with negative expression of FER	
	n	%	n	%	n	%	n	%
N0 (n = 32/100.0%)	9	28.1	23	71.9	11	34.4	21	65.6
N1–3 (n = 111/100.0%)	66	59.5	45	40.5	63	56.8	48	43.2
Total (n = 143/100.0%)	75	52.4	68	47.6	74	51.4	69	48.6

Table 4

Correlation of expression of studied molecular markers with clinical and morphological features of BC

Correlation pairs		Correlation coefficient	Evaluation of correlation
TRFER expression	Stage of disease	0.09	No correlation between TRFER/FER expression and stage of disease
FER expression		−0.02	
TRFER expression	Histological type of BC	0.06	No correlation between TRFER/FER expression and histological type of tumor
FER expression		0.07	
TRFER expression	Differentiation grade of BC	−0.39*	Negative TRFER/FER expression correlates with high differentiation grade of tumor
FER expression		−0.33*	
TRFER expression	Metastases in regional LN	0.48*	Positive TRFER/FER expression in primary tumor correlates with development of metastases in regional LN
FER expression		0.31*	

*Level of significance of correlation coefficient $p < 0.05$.

with iron metabolism [25]. Significance of disorders of iron homeostasis for occurrence and progression of cancer diseases, including BC, is confirmed by data of numerous epidemiological and experimental studies [1, 26–28]. Mechanisms of these disorders to date are not fully studied. There are data showing synergism of disorders of iron and estrogen metabolism at occurrence of BC. In general, characteristic feature of TC is increased expression of proteins-importers and decrease of level of proteins-exporters of iron [28]. During the process of carcinogenesis, excess of iron contributes to the formation of active oxygen forms, which cause DNA damages. At the same time, estrogen can be additional substrate of these reactions due to attachment of hydroxyl group and formation of catechol estrogen [28–30]. Compensatory protective mechanism, which contributes to the neutralization of free radicals and protection of DNA from damages caused by excess of iron, is increasing of FER level in TC. Disorders of estrogen metabolism on the background of excess of iron also cause stimulation of TRFER synthesis in TC of mammary gland. It is confirmed by obtained by us data and results of previous studies [22], which are the evidence of presence of increased level of FER and TRFER expression in more than 50% of studied tumors of mammary gland.

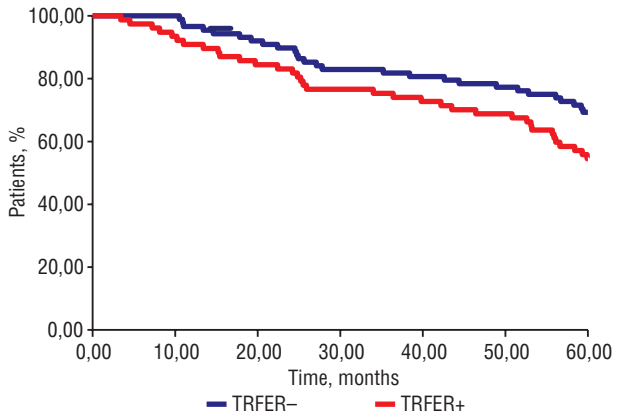

Fig. 1. OS of BC patients calculated by Kaplan — Meier method depending on TRFER expression in TC

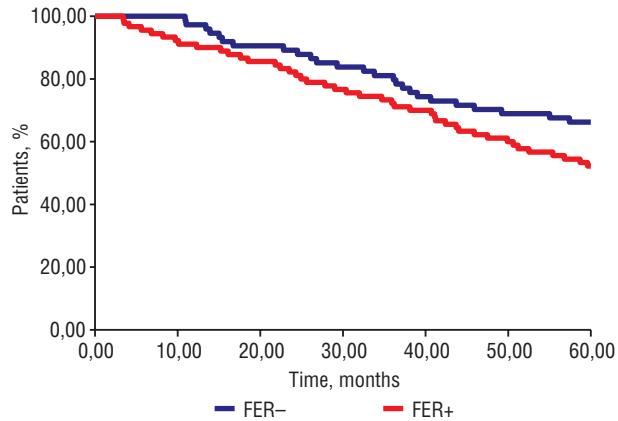

Fig. 2. OS of BC patients calculated by Kaplan — Meier method depending on FER expression in TC

Lack of correlation between level of TRFER and FER expression in TC of examined patients and stage and morphological structure of BC, probably, is connected with presence of additional factors of regulation of studied proteins on the level of other systems of iron metabolism in organism. Data obtained concerning high level of TRFER and FER expression in tumors of low differentiation grade is confirmation of participation of these malignant proteins in proliferation, growth and formation of stage of BC malignancy. This is evidenced by the results of our previous *in vitro* studies concerning increase of expression of iron-containing proteins already in the early stages of malignant transformation of cells of mammary gland and intensification of evidence of these disorders in the process of acquisition by them of more aggressive mesenchymal phenotype [20, 31].

Determined existence of connections between expression of studied proteins and development of metastases in regional LN and survival of BC patients coincides with data of literature and confirms significance of disorders of iron metabolism for progression and aggressiveness of clinical course of BC, as well as confirms fact of cancer ferrotoxicity [32]. For instance, significant expression of TRFER and FER in TC of BC patients has been determined — 92.2% of tumors were positive, at that expression of marker directly correlated with cancer metastases in LN and malignancy of neoplasms [26]. Expression of TRFER (TfR1) and FER receptors in TC of patients with non-small cell lung carcinoma was determined in 88 and 62% of tumors correspondingly [27], but no correlation between indexes of expression of these markers in cells and their concentration in peripheral blood was determined. Significance of iron-containing proteins in cancer patients has been demonstrated also in other studies [18, 19].

Since iron-containing proteins participate in proliferation of cells and progression of tumors and are connected with some biological features of tumor growth and clinical prognosis, they may be considered molecular targets for antitumor drugs [9, 33]. Possibility of such approach to the treatment of cancer patients has been showed in some experimental studies [34, 35], as well as is has been confirmed by the results of our previous studies, which have showed significant increase of expression of iron-containing proteins in resistant to antitumor drugs cells of BC *in vitro* and TC of BC patients resistant to neoadjuvant chemotherapy [21, 22].

Thus, results of carried out study and data of literature show that iron ions and iron-containing proteins play important role in metabolism of normal and neoplastic cells, can be individual markers of predictive prognosis of survival of BC patients. Data obtained can be the basis for development of new diagnostic criteria and improvement of existing schemes of antitumor treatment taking into account indexes of TRFER and FER in TC of mammary gland.

CONCLUSIONS

1. BC is characterized by intertumor heterogeneity of TRFER and FER expression. Part of tumors with strong positive TRFER and FER expression has constituted 52.4 i 51.4%, respectively.

2. No correlation between TRFER and FER expression, on the one hand, and stage of disease and histological BC type, on the other hand, has been determined.

3. High differentiation grade of BC correlates ($p < 0.05$) with lack of TRFER and FER expression.

4. Positive TRFER and FER expression in cells of primary tumor of mammary gland correlates with development of metastases in regional LN.

5. Prognostic value of TRFER and FER expression in TC of mammary gland for the evaluation of OS of patients has been determined. TRFER and FER expression can be individual predictive marker of survival of BC patients and one more molecular target for the development of new antitumor agents.

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ДОСЛІДЖЕННЯ ЕКСПРЕСІЇ ТРАНСФЕРИНУ ТА ФЕРИТИНУ У ПУХЛИННИХ КЛІТИНАХ ХВОРИХ НА РАК МОЛОЧНОЇ ЗАЛОЗИ

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Резюме. ***Мета:*** *вивчення експресії залізовмісних білків феритину (ФЕР) і трансферину (ТРФЕР) у пухлинних клітинах та оцінка її клінічного значення у хворих на рак молочної залози (РМЗ).* ***Об'єкт і методи:*** *у дослідження включено 143 пацієнток із РМЗ II–III стадії.* ***Методи дослідження:*** *клінічні, морфологічний, імуногістохімічний, статистичний.* ***Результати****: показано, що РМЗ характеризується міжпухлинною гетерогенністю експресії ТРФЕР і ФЕР. Високий ступінь диференціювання РМЗ корелює з відсутністю експресії ТРФЕР і ФЕР. Позитивна експресія цих білків у клітинах первинної пухлини пов'язана з розвитком метастазів у регіонарних лімфатичних вузлах. Встановлено кореляційну залежність між експресією ТРФЕР та ФЕР у пухлинних клітинах і загальною виживаністю хворих на РМЗ.* ***Висновки****: експресія ТРФЕР і ФЕР може бути індивідуальним предиктивним маркером перебігу хвороби та виживаності пацієнток із РМЗ і ще однією молекулярною мішенню для розробки нових протипухлинних агентів.*

Ключові слова: рак молочної залози, трансферин, феритин, прогноз.

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