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Features of integrin subunit β4 expression depending on clinical and morphological parameters of breast cancer

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ABSTRACT

Aim. To study the features of the expression of the integrin subunit β4 in primary tumor tissue depending on the clinical and morphological parameters of breast cancer.

Materials and methods. We examined biopsy samples from 49 patients with T1–4N0–3M0 breast cancer; the median age was 51.0 [44.0; 60.0] years. Patients did not receive neoadjuvant therapy. Surgical intervention involved resection of the mammary gland with axillary lymph node dissection or radical mastectomy. The expression of markers of estrogen receptor, progesterone receptor, c-erB-2 (Her2/neu), Ki67, CD104 (integrin subunit β4) was assessed using immunohistochemistry. Statistical processing of the results was carried out using the Statisctica 10.0 software package.

Results. In the group of patients with stage N3, cases with positive cytoplasmic/membrane colocalization of integrin subunit β4 expression were more frequently detected (45%), compared with observations where no such expression was found (8%; $p = 0.002$).

Conclusion. Positive cytoplasmic/membrane colocalization of integrin subunit β4 expression is associated with the prevalence of lymphatic metastasis, which corresponds to Stage N3.

Keywords: breast cancer, primary tumor, integrin subunit β4, metastases

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Особенности экспрессии субъединицы интегрина β4 в зависимости от клинико-морфологических параметров рака молочной железы

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РЕЗЮМЕ

Цель исследования – изучить особенности экспрессии субъединицы интегрина β4 в ткани первичной опухоли в зависимости от клинико-морфологических параметров рака молочной железы.

Материалы и методы. Изучался биопсийный материал от 49 больных раком молочной железы T1–4N0–3M0, средний возраст составил 51,0 [44,0; 60,0] год. Неоадъювантной терапии больные не получали. Оперативное вмешательство выполнялось в объеме резекции молочной железы с подмышечной лимфаденэктомией или радикальной мастэктомии. Экспрессия маркеров Estrogen receptor, Progesteron receptor, c-erB-2 (Her2/neu), Ki67, CD104 (субъединица интегрина β4) оценивалась иммуногистохимическим методом. Статистическая обработка результатов проводилась с применением пакета программ Statistica 10.0.

Результаты. В группе больных с N3 чаще (45%) обнаруживались случаи с позитивной цитоплазматической/мембранной колокализации экспрессии субъединицы интегрина β4 в сравнении с наблюдениями, когда подобной экспрессии не было (8%; $p = 0{,}002$).

Заключение. Позитивная цитоплазматическая/мембранная колокализация экспрессии субъединицы интегрина β4 ассоциирована с распространенностью лимфогенного метастазирования, соответствующей критерию N3.

Ключевые слова: рак молочной железы, первичная опухоль, субъединица интегрина β4, метастазы

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все лица подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 8952 от 24.01.2022).

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INTRODUCTION

Breast cancer is the number one cancer in patients with malignant neoplasms. It is also the leading cause of death among women, accounting for 16.2% [1]. Most often, mortality from malignant neoplasms is due to metastasis. The study of metastasis mechanisms is one of the key areas of modern oncology. For metastasis, the nature of intercellular and parenchymal-stromal interaction is important, which are largely mediated by integrins.

In this regard, studying the integrin profile of tumor cells seems promising. Integrins are transmembrane receptors that are macromolecules

consisting of two subunits – alpha and beta. Each subunit in turn has three parts: free extracellular N-terminal domain, a transmembrane segment, and intracellular tails.

In addition, there is evidence that the expression of some integrins can provide selectivity for distant metastasis. Thus, metastatic lung damage has been observed with the expression of integrin α6β4, and distant metastasis to the liver and brain – with the expression of integrin αvβ5 [2, 3]. Among the various integrins, much attention is paid to integrin β4 [4, 5]. This integrin is part of the heterodimer α6β4, which fixes epithelial cells to basement membranes. There is evidence linking the expression of α6β4 to metastasis and the invasion of lung cancer stem cells into the brain [2, 6].

The ability of integrin α6β4 to prevent the development of apoptosis (anoikis) of tumor cells that have detached from the basement membrane has been described in the literature [7, 8]. The expression of integrin α6β4 and laminin ligand underlies the matrix-independent existence of tumor cells. It is believed that expression of integrin α6β4 autocrinely activates laminin synthesis, then the integrin binds to the ligand, and a cascade of events is triggered, including increased cell proliferative activity, invasive growth, and metastasis [9–11]. Such cell subpopulations have the most pronounced resistance to anoikis and are most capable of becoming seed cells initiating regional and distant metastases.

The aim of this study was to investigate the expression patterns of the integrin subunit β4 in primary tumor tissue depending on the clinical and morphological parameters of breast cancer.

MATERIALS AND METHODS

All stages of the study comply with the legislation of the Russian Federation and regulatory documents of scientific organizations. All individuals signed a voluntary informed consent to participate in the study in accordance with the requirements of the local Ethics Committee of Siberian State Medical University (Protocol No. 8952 of January 24, 2022). We examined biopsy samples of primary tumor tissue from 49 patients with T1–4N0–3M0 breast cancer who received treatment as needed at the Cancer Research Institute of Tomsk National Research Medical Center from 2013 to 2020.

Biopsy samples were collected before patients began to receive therapy. The median age of the patients was 50.0 [44.0; 60.0] years. The patients did not receive neoadjuvant therapy. The surgical intervention involved resection of the mammary gland and axillary lymph node dissection or radical mastectomy. The primary tumor tissue and the removed lymph nodes were examined. The diagnosis was established according to the 2019 WHO classification and the TNM Classification of Malignant Tumors, 8th edition, of the Union for International Cancer Control.

Immunohistochemistry and histologic examination were performed using standard methods. Only cases with invasive ductal carcinoma of the mammary gland were included in the study. The degree of malignancy was determined using the Scarff – Bloom – Richardson histologic grading.

For immunohistochemistry, the following antibodies were used: progesterone receptor (clone PgR636, Dako), estrogen receptor (clone 1D5, Dako), c-erB-2 (Her2/neu) (Polyclonal Rabbit, Dako), Ki67 (clone SP6, Cell Marque), CD104 (integrin subunit β4, clone JM11-06, Invitrogen, dilution 1:200). Molecular subtypes of breast cancer were determined by assessing the expression of receptors to estrogen, progesterone, Ki67, and HER2. Luminal A, luminal B HER2 negative, luminal B HER2 positive, HER2 positive (non-luminal), and basal-like (triple negative) molecular subtypes have been established.

The whole slide image (WSI) method was used to digitize the histologic preparations using the Pannoramic Mirax Midi scanning microscope (Carl Zeiss, Germany). The analysis of the digitized sections was performed using the Panoramic Viewer 1.15.4.43061 software. The cytoplasmic expression and cytoplasmic/membrane colocalization of the expression of the integrin subunit β4 (CD104) were assessed in primary tumor cells (Figure).

The Statistica version 10.0 software package was used for statistical data processing. Due to the non-normal distribution of the studied variables, significant differences in medians between two independent samples were assessed using the non-parametric Mann – Whitney test. The t-test was used to compare the frequency of the detected features. The results were considered statistically significant at $p < 0.05$.

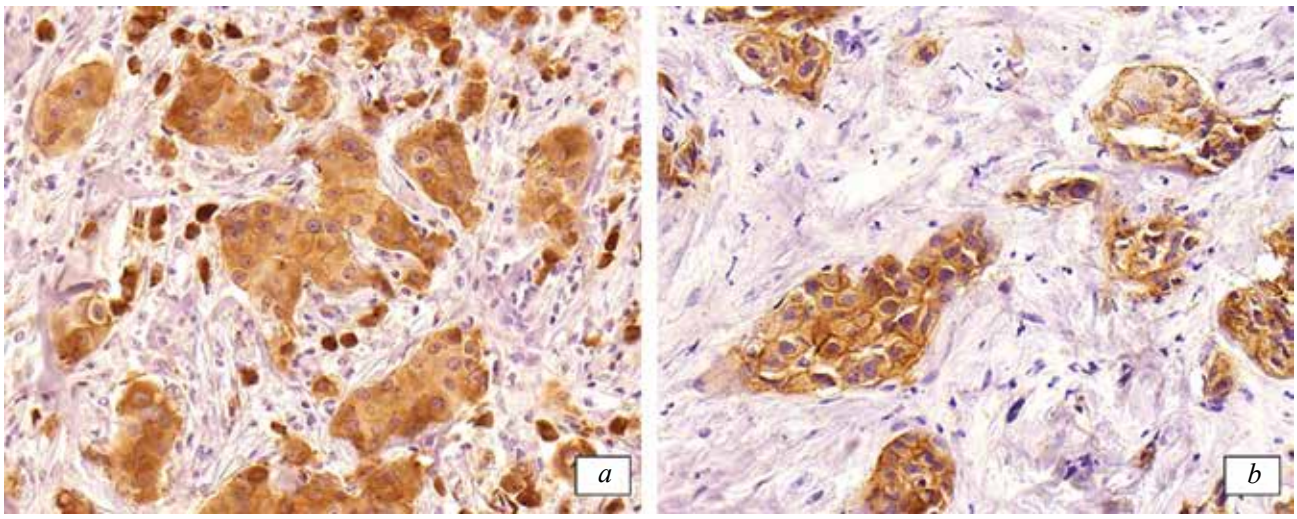

Figure. Expression of the integrin subunit *β*4 (CD104) in the primary tumor: *a* – cytoplasmic expression, *b* – cytoplasmic/membrane colocalization of expression. ×400

RESULTS

A study was conducted to examine the expression patterns of the integrin subunit β4 (CD104) in the cells of invasive ductal carcinoma of the mammary gland depending on various clinical and morphological manifestations of the tumor process.

The age of the patients did not differ depending on the presence or absence of positive cytoplasmic expression or cytoplasmic/membrane colocalization of the integrin subunit β4 expression. Positive and negative cytoplasmic expression of the integrin subunit β4 was detected with approximately the same frequency both in the group of patients with preserved menstrual function and in menopause. Positive cytoplasmic/membrane colocalization of integrin subunit β4 expression was detected more frequently (73%) in the group of patients with preserved menstrual function compared to cases without expression of this marker (42%; $p = 0.032$).

The presence of cytoplasmic or cytoplasmic/membrane colocalization of integrin subunit β4 expression was not associated with the characteristics of the primary tumor corresponding to different T criterion values. No significant differences were found in the frequency of cases with negative and positive expression of the studied marker in the groups of patients with T1, T2, T3 and T4 cancer.

The frequency of negative and positive cytoplasmic expression or cytoplasmic/membrane colocalization of integrin subunit β4 expression did not differ according to tumor grade G1, G2, or G3. There were also no differences in the percentage of cases with negative and positive cytoplasmic expression or cytoplasmic/membrane colocalization of integrin subunit β4 expression depending on the molecular subtype of breast cancer.

The prevalence of lymphatic metastasis, characterized by the N criterion, turned out to be associated with the features of expression of the integrin subunit β4 in the cells of invasive ductal breast cancer. Namely, in cases with the presence of metastases in the displaced axillary lymph nodes on the affected side, corresponding to the N1 criterion, positive cytoplasmic/membrane colocalization of the expression of the integrin subunit β4 was detected less frequently compared with cases without such localization of studied marker expression.

In cases with diffuse lymphatic metastasis with metastatic infraclavicular lymphadenopathy on the affected side, or with a combination of the internal mammary lymphadenopathy with metastases to the axillary lymph nodes or with metastases to the supraclavicular lymph nodes on the affected side, corresponding to stage N3, positive cytoplasmic/membrane colocalization of expression of the integrin subunit β4 was detected more often (45%) compared with cases without this type of expression localization (3/38 (8%; $p = 0.002$). The frequency of negative and positive cytoplasmic expression of the integrin subunit β4 did not differ between groups with stage N0, N1, N2, and N3 (Table).

Table

Features of cytoplasmic and cytoplasmic/membrane colocalization of integrin subunit β4 expression depending on the clinical and morphological parameters of invasive ductal carcinoma

Parameter	Cytoplasmic expression of the integrin subunit β4		Cytoplasmic/membrane colocalization of integrin subunit β4 expression	
	No (n = 28)	Yes (n = 21)	No (n = 38)	Yes (n = 11)
	1	2	3	4
Age, *Me* [Q_1; Q_3]	51.0 [45.0; 60.0]	48.0 [42.0; 56.0] p_{1-2} = 0.464	51.0 [45.0; 61.0]	47.0 [35.0; 56.0] p_{3-4} = 0.143
Menstrual function status, abs. (%)				
Preserved	12/28 (43%)	12/21 (57%) p_{1-2} = 0.166	16/38 (42%)	8/11 (73%) p_{3-4} = 0.032
Menopause	16/28 (57%)	9/21 (43%) p_{1-2} = 0.166	22/38 (58%)	3/11 (27%) p_{3-4} = 0.032
Characteristics of the primary tumor node, abs. (%)				
T1	7/28 (25%)	5/21 (24%) p_{1-2} = 0.468	9/38 (24%)	3/11 (27%) p_{3-4} = 0.419
T2	15/28 (54%)	8/21 (38%) p_{1-2} = 0.133	19/38 (50%)	4/11 (37%) p_{3-4} = 0.223
T3	1/28 (4%)	3/21 (14%) p_{1-2} = 0.104	3/38 (8%)	1/11 (9%) p_{3-4} = 0.458
T4	5/28 (17%)	5/21 (24%) p_{1-2} = 0.272	7/38 (18%)	3/11 (27%) p_{3-4} = 0.256
Cancer Grade, abs. (%)				
G1	1/28 (3,5%)	1/21 (5%) p_{1-2} = 0.359	1/38 (3%)	1/11 (9%) p_{3-4} = 0.195
G2	26/28 (93%)	19/21 (90%) p_{1-2} = 0.353	36/38 (94%)	9/11 (82%) p_{3-4} = 0.107
G3	1/28 (3,5%)	1/21 (5%) p_{1-2} = 0.359	1/38 (3%)	1/11 (9%) p_{3-4} = 0.195
Molecular genetic type, abs. (%)				
Luminal A	6/28 (21%)	3/21 (14%) p_{1-2} = 0.264	8/38 (21%)	1/11 (9%) p_{3-4} = 0.182
Luminal B HER2 negative	15/28 (54%)	9/21 (43%) p_{1-2} = 0.223	20/38 (53%)	4/11 (36%) p_{3-4} = 0.160
Luminal B HER2 positive	3/28 (11%)	4/21 (19%) p_{1-2} = 0.215	4/38 (10,5%)	3/11 (27%) p_{3-4} = 0.150
HER2 overexpression	2/28 (7%)	4/21 (19%) p_{1-2} = 0.102	4/38 (10,5%)	2/11 (18%) p_{3-4} = 0.234
Triple negative	2/28 (7%)	1/21 (5%) p_{1-2} = 0.386	2/38 (5%)	1/11 (9%) p_{3-4} = 0.310
Characteristics of lymphatic metastases, abs. (%)				
N0	13/28 (46.5%)	8/21 (38%) p_{1-2} = 0.288	16/38 (42%)	5/11 (45%) p_{3-4} = 0.429
N1	11/28 (39%)	6/21 (29%) p_{1-2} = 0.233	17/38 (45%)	0/11 (0%) p_{3-4} = 0.003
N2	1/28 (3.5%)	2/21 (10%) p_{1-2} = 0.154	2/38 (5%)	1/11 (10%) p_{3-4} = 0.271
N3	3/28 (11%)	5/21 (23%) p_{1-2} = 0.129	3/38 (8%)	5/11 (45%) p_{3-4} = 0.002

DISCUSSION

A study of the expression patterns of the integrin subunit β4 in invasive breast carcinoma cells revealed a relationship between positive cytoplasmic/membrane colocalization of integrin subunit β4 expression and the prevalence of lymphatic metastasis corresponding to stage N3.

Determining the localization of expression was important. Given that integrins consist of three parts

(free extracellular N-terminal domain, transmembrane segment, and intracellular tails), we decided to differentiate between cytoplasmic expression and cytoplasmic/membrane colocalization of the integrin subunit β4 expression when determining expression. Only membrane/cytoplasmic colocalization of integrin subunit β4 expression was found to be associated with the most advanced lymphatic metastasis corresponding to stage N3.

The study did not reveal significant associations between the frequency of positive cytoplasmic expression and cytoplasmic/membrane colocalization of integrin subunit β4 expression and other clinical and morphological patterns of breast cancer.

The integrin subunit β4, a member of the integrins that recognize laminin, plays the main role in maintaining epithelial differentiation and structure. Under physiological conditions, loss of epithelial cell contact with the basement membrane results in cessation of proliferation and induction of apoptosis, known as anoikis. However, in malignant tumors, cells can adapt to a lack of adhesion, allowing them to avoid anoikis and contributing to their invasiveness and metastatic potential [12]. One of the mechanisms is the synthesis of basement membrane molecules. Such surrogate substitution of the basement membrane bond restores the ability to proliferate and avoids anoikis [13].

As a result, such tumor cells acquire the ability to grow independent of attachment to the stroma. The integrin subunit β4 mediates tumor growth independent of the matrix by activating the Shp2-Src signaling pathway. It is believed that acquisition of matrix-independent growth ability promotes metastatic spread [14, 15]. Apparently, the ability for matrix-independent existence is one of the necessary factors that ensures metastasis. Studying the key processes responsible for the role of integrin subunit β4 in lymphatic metastasis can be useful both for understanding the metastasis mechanisms and for identifying potential targets for targeted therapy.

CONCLUSION

The obtained data indicate the role of integrin subunit β4 expression in the mechanisms of lymphatic metastasis development in breast cancer. Positive cytoplasmic/membrane colocalization of integrin subunit β4 expression is associated with the predominance of lymphatic metastasis corresponding to stage N3 cancer.

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Authors' contribution

Zavyalova M.V., Perelmuter V.M. – conception and design. Alifanov V.V., Andryukhova E. S. – collection and processing of material. Kuznetsov G.A., Zavyalov A.V., Popova V.E., Pismenny D.S. – drafting of the manuscript. Grigorieva E.S., Tashireva L.A. – editing the manuscript.

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