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Ye. LUKIANOVA [1], O. MUSHII [1], M. KROTEVYCH [2], T. ZADVORNYI [1, *]

[1] R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine, Kyiv, Ukraine

[2] State Nonprofit Enterprise "National Cancer Institute", Kyiv, Ukraine

* Correspondence: Email: tito132007@ukr.net

PD-L1 EXPRESSION IN RECEPTOR-NEGATIVE BREAST CANCER TISSUE

Background. The high heterogeneity and pathogenetic diversity of breast cancer (BCa) indicate the need for further study of tumor cell biology in order to identify molecular biological markers associated with the aggressiveness of tumors with a negative receptor status. Among many factors that may be involved in the initiation and progression of this form of cancer, the study of the immune components of tumor microenvironment, in particular PD-L1, is considered promising. **Aim**. To investigate the relationship between PD-L1 expression in tumor tissue and clinical and pathological characteristics of BCa, taking into account the status of steroid hormone receptors. **Materials and Methods**. In tumor tissue of 116 patients with stage I—II BCa, the mRNA levels of *CD274* gene were determined using the real-time quantitative polymerase chain reaction. The expression of PD-L1 was studied by the immunohistochemical method. **Results**. The tissue of receptor-negative BCa was characterized by a significant decrease in the *CD274* mRNA level against the background of the increased PD-L1 expression compared to neoplasms positive for the expression of steroid hormone receptors. An inverse correlation was found between PD-L1 at the protein level and the age of patients with receptor-negative BCa ($r = -0.613$, $p = 0.00003$). We showed that a characteristic feature of receptor-negative BCa in menopausal patients is the increased expression of PD-L1 both at the protein and mRNA levels ($p = 0.005$ and $p = 0.046$, respectively). The correlation of PD-L1 expression with metastatic lesions in regional lymph nodes ($p = 0.050$), tumor differentiation grade ($p = 0.001$), and the patient survival rate was revealed. **Conclusions**. The obtained data indicated the expediency of using PD-L1 expression indicators for in-depth characterization of the tumor microenvironment of receptor-negative BCa, which will allow for the personalized correction of therapy regimens contributing to the improvement of the patients' quality of life.

Keywords: steroid hormone receptors, breast cancer, PD-L1.

According to the recent statistical data, breast cancer (BCa) occupies a leading position in terms of morbidity and mortality in the structure of oncological diseases both in Ukraine and in the world [1]. The accumulated clinical experience allows us to conclude that the variability of the BCa course is due not only to clinical and morphological prognostic factors but also to the peculiarities of the molecular profile of neoplasms, which requires different approaches to diagnosis and therapy [2].

In particular, it is known that triple-negative BCa is characterized by the absence of classical

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targets for effective therapy [3]. Along with this, it was established that BCa negative for the expression of steroid hormone receptors (SHR) is characterized by a more widely represented immune component in the composition of the tumor microenvironment and a high expression of immune checkpoint molecules [4]. Accordingly, the latest therapeutic approaches, including immune checkpoint inhibition, are most often used in the treatment of patients with BCa of basal and HER2/neu-positive molecular subtypes [5].

It is known that the PD1/PD-L1 signaling cascade is regulated by SHR (primarily estrogen receptor (ER) and progesterone receptor (PR)) [6, 7]. Along with this, there are reports that the predictive value of PD-L1 in BCa is due to a violation of the functional activity of SHR.

Today, the question of the value of PD-L1 in predicting the BCa course remains debatable. There are controversial findings of several studies indicating that PD-L1 levels are associated with the status of the regional lymph node metastasis and lymphovascular invasion, the size of neoplasms and their histological subtypes, as well as survival rates of patients with BCa [8].

Accordingly, the aim of the work was to investigate the relationship between PD-L1 expression indicators in tumor tissue and the clinical characteristics of BCa, taking into account the SHR status.

Materials and Methods

The study was conducted on the post-operative material of 116 patients with stage I—II BCa who were treated at the National Cancer Institute of the Ministry of Health of Ukraine, Kyiv Clinical Oncology Center, and Kyiv Regional Oncology Dispensary in 2015—2023 and gave informed consent for the use of their clinical data for scientific purposes. Before surgery, all patients received neither radiation treatment nor chemotherapy and were examined using conventional clinical and laboratory methods according to the standards of diagnosis and treatment of cancer patients of the Ministry of Health of Ukraine. The tissue samples were encoded and depersonalized.

Real-time reverse transcription polymerase chain reaction (RT-PCR) method. The study of the *CD274* gene (gene product — PD-L1) expression in BCa tissue was performed according to the protocol described in detail in a previous study [9]. RT-PCR was performed on the hardware detection system Quant Studio DX5 Real-Time PCR System using a commercial kit for RT-PCR Maxima SYBR Green/ROX qPCR Master Mix (2X) Assay (Thermo Fisher Scientific, USA) according to the manufacturer's protocol. Sequences of primers for reverse transcription were determined using the resource https://www.origene.com and synthesized by Metabion (Germany). Primer sequences for *CD274* were as follows:

forward 5'- TGCCGACTACAAGCGAATTACTG-3'
reverse 3'- CTGCTTGTCCAGATGACTTCGG-5'

The *ACTB* gene was used as an endogenous control. Fold change (fold difference) between the expressions of the studied miRNA was calculated according to the formula $2^{-\Delta Ct}$ (hereinafter — a.u.) [10].

Immunohistochemistry study. ER, PR, Ki-67, and PD-L1 expressions were studied on paraffin sections (5—7 μm) of the postoperative BCa samples. ER (clone 1D5, dilution 1:100, DakoCytomation, Denmark), PR (clone PgR636, dilution 1:100, DakoCytomation, Denmark), HER2/neu (clone e2400, dilution 1:100, Thermo Scientific, USA), Ki-67 (clone MIB1, dilution 1:100, DakoCytomation, Denmark), and PD-L1 (clone 9B5F4, dilution 1:350, MyBioSource, Canada) were used as primary antibodies.

The Master Polymer Plus Detection System (Peroxidase) reagent kit (Incl. DAB Chromogen) (Master diagnostica, Spain) was used to visualize the reaction results following the manufacturer's recommendations, and the sections were stained with Meyer's hematoxylin (Thermo Scientific Richard-Allan, USA).

The analysis of the immunohistochemical data was performed by the method of counting immunopositive cells using an AxioScope A1 light microscope (Carl Zeiss, Germany) with a magnification of ×400. Expression was evaluated using the H-Score method [11, 12].

Bioinformatical study. The study of overall and relapse-free survival rates of patients with BCa depending on the level of expression of the *CD274* gene was carried out using the Kaplan — Meier Plotter online resource (https://kmplot.com/analysis/index.php?p=service).

Statistical data processing. Processing of the obtained data was performed using the software package GraphPad Prism v. 10.00 (GraphPad Software Inc., USA). Quantitative comparison of two independent groups was performed using the Mann — Whitney U-test. The data are presented as M ± m, where M is the arithmetic mean, and m is the standard error of the mean. The difference was considered significant at $p < 0.05$.

Results

The clinicopathological characteristics of both ER+, PR+ and ER–, PR– BCa cases under study are given in Table 1. Most of the patients were in menopause and had stage II BCa. In both groups of patients, infiltrative ductal adenocarcinoma of a moderate differentiation grade prevailed. A high level of Ki-67 expression was recorded in receptor-negative tumors.

When examining the expression of PD-L1 at the mRNA level, we established that the tumor tissue of receptor-positive BCa was characterized by 8.85 times ($p = 0.038$) higher mRNA levels of the *CD274* gene compared to the samples of receptor-negative neoplasms (Fig. 1, *a*). The analysis of the topology of PD-L1 expression at the protein level allowed us to establish that it was localized both on the surface and in the cytoplasm of BCa cells (Fig. 2). The highest level of PD-L1 expression was recorded in BCa tissue negative for SHR expression (H-Score 232.9 ± 8.48) compared to SHR-positive tumors (H-Score 193.5 ± 12.86) ($p = 0.021$) (Fig. 1, *b*).

An inverse correlation between the level of this protein and the age of patients with receptor-negative BCa (r = –0.613, $p = 0.00003$) (Fig. 3, *b*) was found. An increase in the expression of PD-L1 at the level of protein and mRNA (by 1.35 and 7.72 times, respectively) was also recorded in the tumor tissue of SHR-negative BCa patients who were in menopause compared to similar indicators of women with preserved menstrual status ($p = 0.005$ and $p = 0.046$, respectively) (Fig. 4, *a*, Table 2). We found that a characteristic feature of SHR-positive BCa in patients with metastases in the regional lymph nodes was a 20% ($p = 0.050$) higher expression of PD-L1 at the protein level compared to patients without lymph node involvement (Fig. 4, *d*).

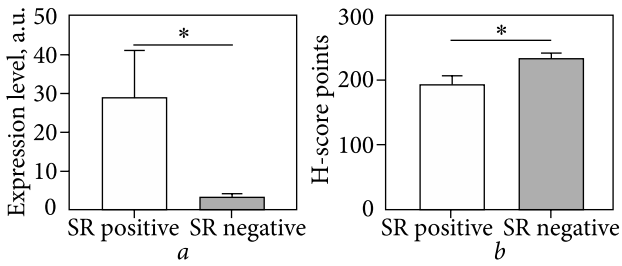

Fig. 1. Expression of PD-L1 at the level of mRNA (*a*) and protein (*b*) in BCa tissue with different SHR statuses

Table 1. **Clinicopathological characteristics of the BCa cases**

Characteristics	ER+, PR+		ER–, PR–	
	Number of patients			
	n	%	n	%
Total number of patients	67	100	49	100
Average age, years	54.2 ± 11.5		55.6 ± 7.2	
Age fluctuation, years	24—81		27—84	
Reproductive status				
The menstrual cycle is preserved	33	49.2	23	53.1
Menopause	34	50.8	26	46.9
Stage				
I	18	26.9	22	44.9
II	49	73.1	27	45.1
Tumor size (T category)				
T1	33	49.2	21	57.1
T2	34	50.8	28	42.9
Lymph node involvement (N category)				
N0	42	62.7	28	57.1
N1	25	37.3	21	42.9
Histological type				
Infiltrative ductal adenocarcinoma	44	65.7	31	63.3
Infiltrative lobular adenocarcinoma	23	34.3	18	34.7
Tumor differentiation grade				
G1	21	31.3	14	28.6
G2	34	50.8	20	40.8
G3	12	17.9	15	30.6
Proliferative activity				
Ki-67 low	47	70.1	18	34.7
Ki-67 high	20	29.9	31	63.3

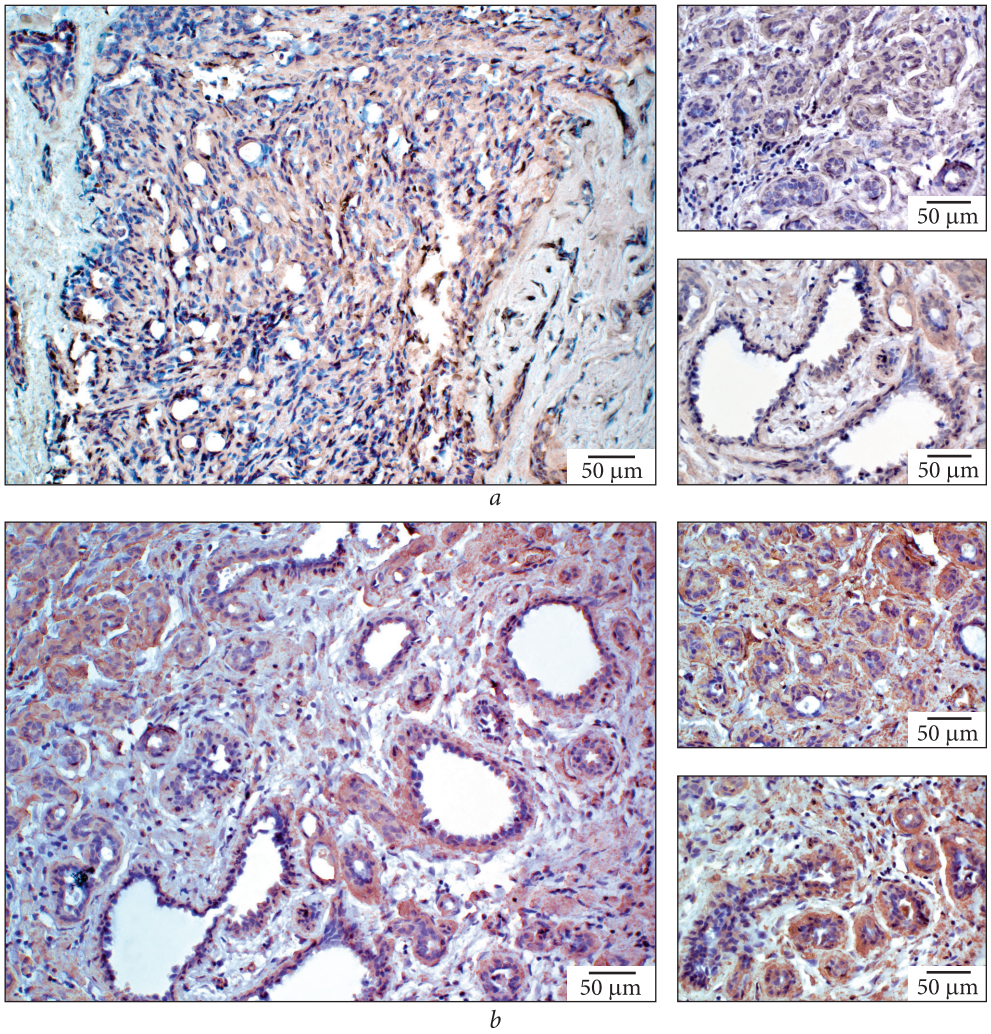

Fig. 2. PD-L1 protein expression in BCa tissue with different SHR statuses: *a*) ER+ PR+; *b*) ER- PR-. Immunohistochemical staining with chromogen 3,3'-diaminobenzidine tetrahydrochloride. Counterstaining with hematoxylin, ×400

Table 2. ***CD274*** **mRNA expression level in BCa tissues with different SHR statuses, a.u.**

Characteristic		ER+ PR+	ER- PR-
Reproductive status	The menstrual cycle is preserved	2.877 ± 0.19	**87.11 ± 34.82**
	Menopause	31.97 ± 15.47	**11.24 ± 4.68**
Stage	I	11.15 ± 8.08	11.15 ± 8.08
	II	21.48 ± 13.18	82.58 ± 78.37
T	T1	3.77 ± 1.04	9.26 ± 6.99
	T2	24.76 ± 15.10	81.47 ± 79.52
N	N0	4.71 ± 0.27	59.82 ± 51.72
	N1	41.02 ± 18.29	3.90 ± 0.62
Histological type	Ductal adenocarcinoma	34.92 ± 21.61	72.31 ± 61.48
	Lobular adenocarcinoma	12.63 ± 8.17	7.32 ± 6.46
Tumor grade	G1—2	87.78 ± 76.85	21.73 ± 18.37
	G3	4.21 ± 1.02	23.55 ± 9.91
Proliferative activity	Ki-67 low	35.36 ± 21.39	10.31 ± 5.59
	Ki-67 high	9.47 ± 6.55	107.5 ± 105.10

Note: Significant difference ($p < 0.05$) is highlighted in bold.

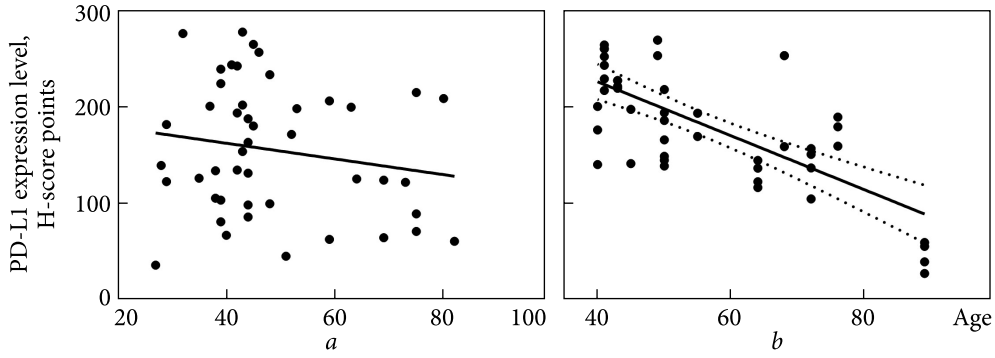

Fig. 3. Relationship of PD-L1 expression at the protein level in SHR+ (*a*) and SHR– (*b*) BCa tissue with the age of patients

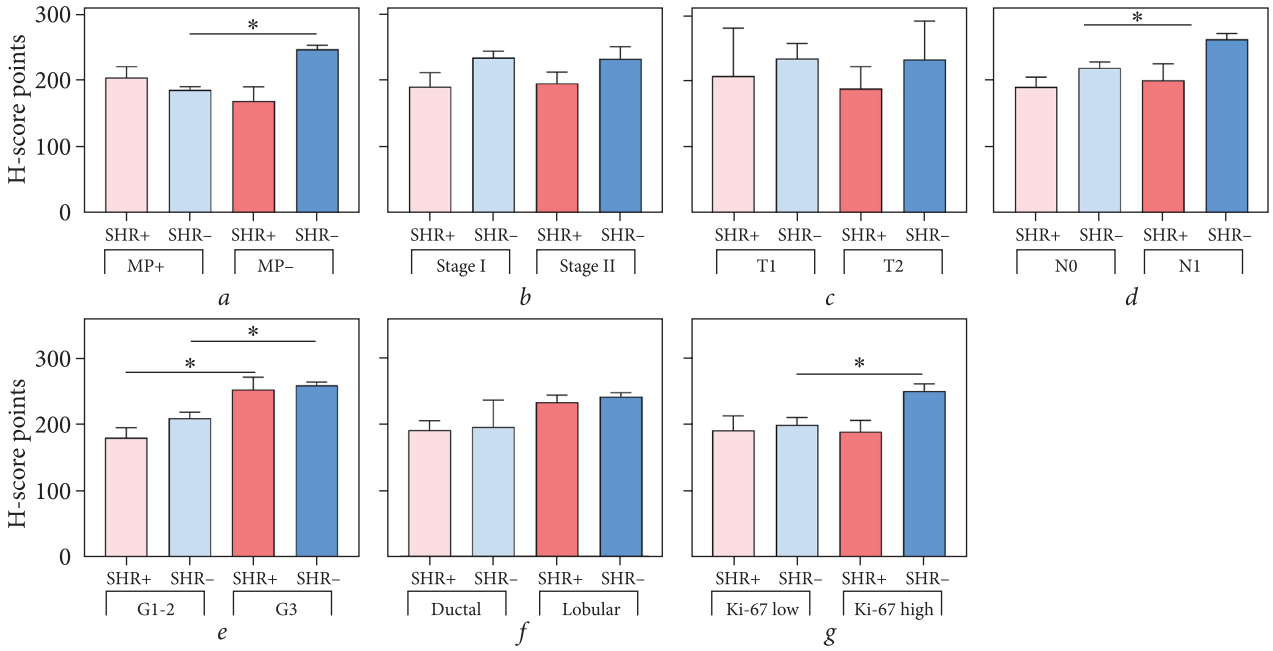

Fig. 4. Features of PD-L1 expression at the protein level in BCa tumor tissue with different SHR statuses depending on menopausal status (*a*), tumor stage (*b*), tumor size (*c*), lymph node involvement (*d*), differentiation (*e*), histological type (*f*), and proliferative activity (*g*). *$p < 0.05$

A significant increase in PD-L1 indicators was recorded in the tissue of both receptor-positive ($p = 0.032$) and receptor-negative ($p = 0.001$) poorly differentiated BCa compared to neoplasms with a moderate and high differentiation grade (Fig. 4, *e*).

Certain differences were found when analyzing the dependence of PD-L1 expression on the proliferative activity of BCa. We found that the expression of this protein was 25.3% higher ($p = 0.032$) in the tissue of receptor-negative BCa with high Ki-67 expression (Fig. 4, *g*).

A bioinformatic analysis of the 10-year survival of patients with BCa with different SHR statuses depending on the expression of PD-L1 at the level of mRNA and protein in the tumor tissue demonstrated that the overall and relapse-free survival of patients with receptor-negative BCa was 15% ($p = 0.049$) and 30% ($p = 9.7e^{-5}$) lower in the case of low expression of *CD274* in tumor tissue (Fig. 5).

Similar data were obtained in the study of the survival of patients with BCa depending on the PD-L1 expression at the protein level in the tumor tissue (Fig. 6). A significant increase in overall survival (by 54%, $p = 0.0032$) was recorded in patients whose tumor tissue was characterized by low levels of PD-L1 expression. The frequency of recurrence of the disease in the group of patients with receptor-negative BCa and high expression of PD-L1 in the tumor tissue was 55% higher ($p = 0.0041$) compared to the patients with a low level of PD-L1. The low expres-

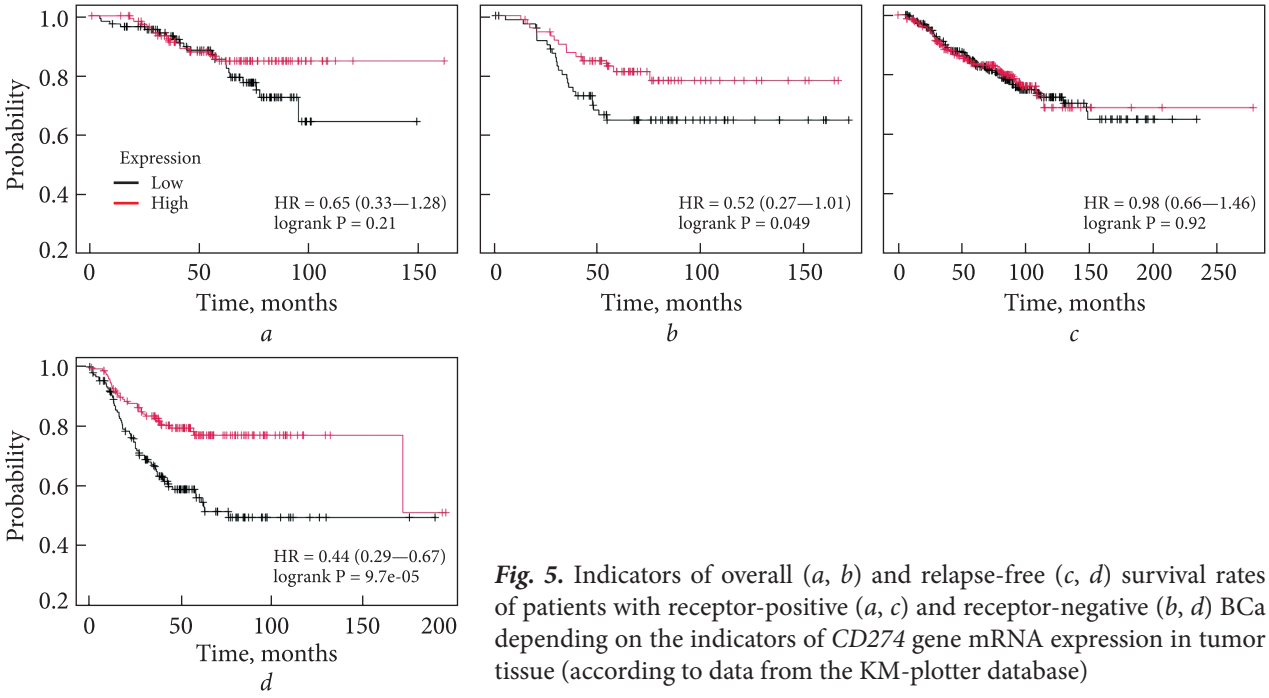

Fig. 5. Indicators of overall (*a*, *b*) and relapse-free (*c*, *d*) survival rates of patients with receptor-positive (*a*, *c*) and receptor-negative (*b*, *d*) BCa depending on the indicators of *CD274* gene mRNA expression in tumor tissue (according to data from the KM-plotter database)

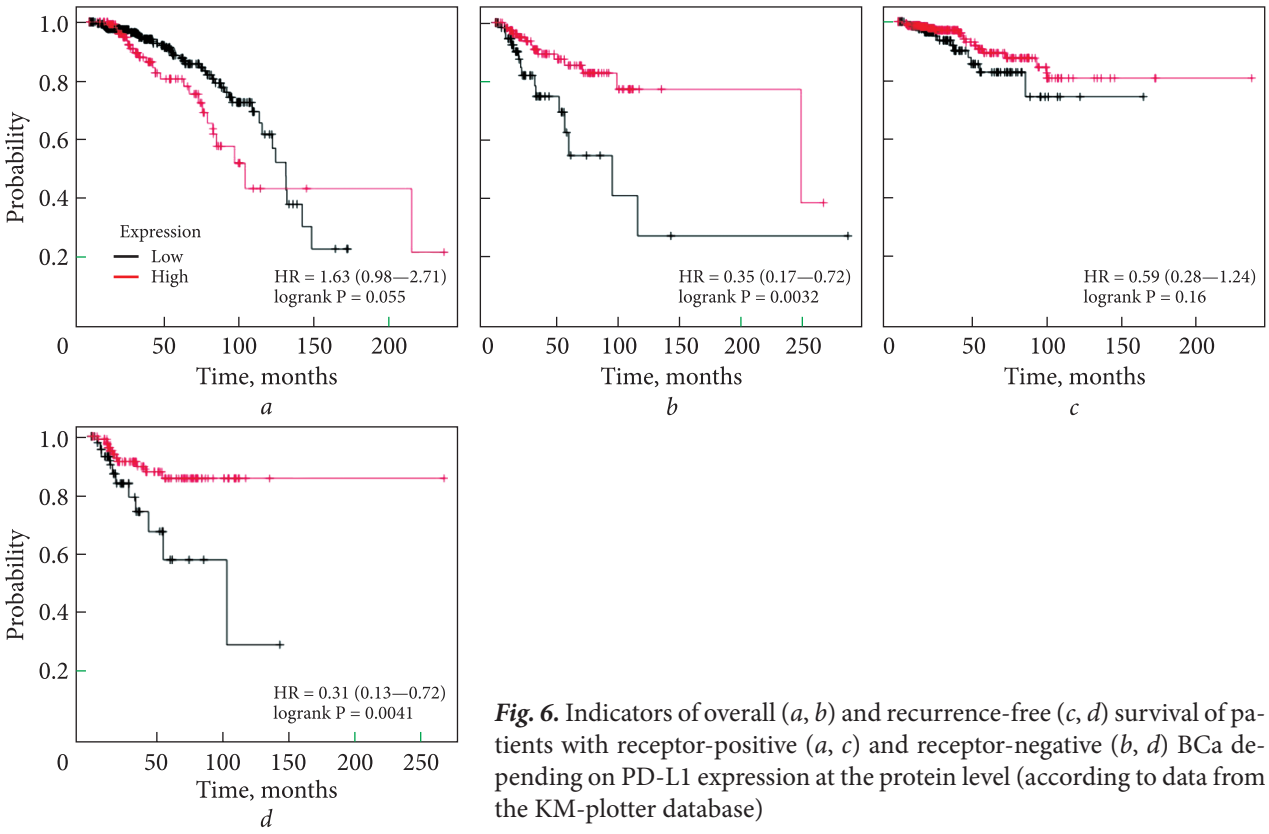

Fig. 6. Indicators of overall (*a*, *b*) and recurrence-free (*c*, *d*) survival of patients with receptor-positive (*a*, *c*) and receptor-negative (*b*, *d*) BCa depending on PD-L1 expression at the protein level (according to data from the KM-plotter database)

sion of PD-L1 in the tissue of receptor-positive BCa was associated with a 20% ($p = 0.055$) decrease in the overall 10-year survival of the patients.

Thus, the tissue of receptor-negative BCa is characterized by a significant decrease in *CD274* mRNA levels against the background of increased PD-L1 expression. An inverse correlation between PD-L1 at the protein level and the age of patients with receptor-negative BCa was revealed. It was shown that a characteristic feature of receptor-negative BCa in menopausal patients is an increased expression of PD-L1 at both the protein and mRNA

levels. The relation of PD-L1 expression of receptor-negative BCa to metastases in regional lymph nodes, tumor differentiation grade, and the survival rates of patients has been revealed.

Discussion

The obtained results demonstrate an important prognostic role of PD-L1 in receptor-negative BCa tumors. According to our data, patients with elevated expression of PD-L1 at the protein level and the absence of ER and PR expression in BCa tissue have a higher frequency of metastasis to lymph nodes, increased proliferative activity, and low tumor differentiation grade. Similar conclusions were obtained in the works of other authors, where it was noted that the high expression of PD-L1 correlated with the BCa aggressiveness and the presence of metastases in the lymph nodes [13, 14]. A knockout of the *CD274* gene in receptor-negative BCa cells was accompanied by a decrease in their proliferative activity, adhesion, and invasiveness as well as a weakening of the functioning of key signaling cascades involved in the formation of an aggressive BCa phenotype [15].

The results of our study are consistent with those of other authors demonstrating that receptor-negative breast tumors are characterized by a higher level of PD-L1 expression compared to receptor-positive tumors [14]. It is known that receptor-negative BCa more often acquires an aggressive phenotype, which may be associated with an increased ability to immune evasion due to PD-L1 activation. Such results indicate the importance of PD-L1 as a potential marker of the immune component of the tumor microenvironment of receptor-negative BCa and reinforce the relevance of using immune checkpoint inhibitors for the treatment of this group of patients.

The decrease in the level of mRNA against the background of an increased level of protein can be explained by the post-transcriptional mechanisms of PD-L1 expression regulation. For example, in the report of Yi et al. [16], it has been demonstrated that DNA methylation can reduce the level of PD-L1 mRNA, while the stability of the PD-L1 protein itself is preserved. In addition, some protein modifications, in particular phosphorylation and glycosylation, can contribute to the accumulation of PD-L1 on the cell membrane, which can increase its total level in tumor cells and affect their immune status [17].

Particular attention should be paid to the features of the PD-L1 expression regulation depending on the SHR status of breast neoplasms. Shuai et al. [6] showed that ER reduces PD-1/PD-L1 expression and infiltration of CD8+ T cells by inhibiting IL-17 signal transduction, which leads to inhibition of the T cell receptor signaling cascade. These data are confirmed by several other studies that show an inverse relationship between PD-L1 expression levels and ER activity in BCa cells, and also describe in detail the direct mechanism of this interaction at the molecular level [18].

At the same time, progesterone is also able to inhibit the infiltration of the functionally active immune cells into the tumor microenvironment. During the induction of carcinogenesis in transgenic mice with PR overexpression, a reliable increase in the frequency of development of mammary gland neoplasms with a microenvironment poor in immune cells was revealed, and the signaling cascades involved in the immune response were weakly active against the background of increased expression of immunosuppressor genes [7].

In addition, the relationship between PD-L1 expression levels and the age of patients with receptor-negative breast cancer deserves special attention. Our previous studies prove the relationship between the tumor microenvironment's composition and the functional state depending on the patient's age [19—21]. For comparison, Erraez-Jaramillo et al. [22] showed the existence of an inverse relationship between the levels of PD-L1 and the age of patients, while Cirqueira et al. [23] established an inverse relationship between the expression levels of this protein and the age of patients with BC in the general group.

The results of the bioinformatic analysis showed that a low level of PD-L1 correlates with a more favorable prognosis, which was also confirmed by other studies [24]. In addition, the better prognosis of patients was associated with the TIL-mediated antitumor inflammatory response rather than with tumor immune escape [25].

Therefore, the results of our study confirm the prognostic role of PD-L1 in receptor-negative BCa tumors. We showed that an increased level ofthe PD-L1 protein is associated with greater tumor aggressiveness, increased metastasis to lymph nodes, and high proliferative activity of tumor cells. In addition, our bioinformatic analysis

showed that high PD-L1 levels are associated with a better prognosis, suggesting its potential use as a prognostic marker. Thus, PD-L1 can be considered as an important prognostic marker of receptor-negative BCa. The obtained data indicate the expediency of using PD-L1 expression indicators for in-depth characterization of the tumor microenvironment of receptor-negative BCa, which will allow personalized correction of therapy regimens and contribute to improving the patients' quality of life.

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Є. Лук'янова [1], О. Мушій [1], М. Кротевич [2], Т. Задворний [1]

[1] Інститут експериментальної патології, онкології і радіобіології ім. Р.Є. Кавецького НАН України, Київ, Україна
[2] ДНП «Національний інститут раку», Київ, Україна

ОСОБЛИВОСТІ ЕКСПРЕСІЇ PD-L1 У ТКАНИНІ РЕЦЕПТОР-НЕГАТИВНОГО РАКУ МОЛОЧНОЇ ЗАЛОЗИ

Вступ. Висока гетерогенність та патогенетичне різноманіття раку молочної залози (РМЗ) вказують на необхідність подальшого вивчення біології пухлинної клітини з метою ідентифікації молекулярно-біологічних маркерів, асоційованих з агресивністю новоутворень з негативним рецепторним статусом. Серед багатьох факторів, які можуть бути залучені до ініціації та прогресії цієї форми раку, перспективним вважається дослідження особливостей імунної компоненти пухлинного мікрооточення, зокрема PD-L1. **Мета**: дослідити зв'язок експресії PD-L1 у пухлинній тканині із клініко-патологічними характеристиками РМЗ з урахуванням статусу рецепторів стероїдних гормонів. **Методи**. У дослідженні взяли участь 116 пацієнток з I—II стадією РМЗ, які дали інформовану згоду на проведення наукових досліджень. Рівні мРНК гена *CD274* визначали за допомогою кількісної полімеразної ланцюгової реакції в реальному часі. Експресію PD-L1 вивчали імуногістохімічним методом. **Результати**. Встановлено, що тканина рецептор-негативного РМЗ характеризується достовірним зниженням рівня мРНК гена *CD274* на фоні підвищеної експресії PD-L1 порівняно з новоутвореннями позитивними за експресією рецепторів стероїдних гормонів. Виявлено обернений кореляційний зв'язок між PD-L1 на рівні білка та віком пацієнтів із рецептор-негативним РМЗ (r = –0,613, p = 0,00003). Показано, що характерною ознакою рецептор-негативного РМЗ у пацієнток у менопаузі є підвищена експресія PD-L1 як на рівні білка, так і на рівні мРНК (p = 0,005 та p = 0,046, відповідно). Доведено зв'язок експресії PD-L1 з такими ознаками злоякісності рецептор-негативного РМЗ, як метастатичне ураження регіонарних лімфатичних вузлів (p = 0,050), ступінь диференціювання новоутворень (p = 0,001) та виживаність хворих. **Висновки.** Отримані дані вказують на доцільність використання показників експресії PD-L1 для поглибленої характеристики пухлинного мікрооточення рецептор-негативного РМЗ, що дозволить здійснювати персоналізовану корекцію схем терапії та сприятиме покращенню якості життя хворих.

Ключові слова: рецептори стероїдних гормонів, рак молочної залози, PD-L1.