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ASSOCIATIONS OF TUMOR-ASSOCIATED MACROPHAGE INFILTRATION WITH CYTOKINE EXTRACELLULAR MATRIX SIGNATURES IN BREAST CANCER MICROENVIRONMENT

Background: Tumor-associated macrophages (TAMs) are among the main regulators of the immune microenvironment of breast cancer (BC). Still, their relationships with cytokine signals and the state of the extracellular matrix (ECM) remain poorly characterized. **The study aimed** to evaluate associations of the degree of infiltration with $CD68^+$ and $CD163^+$ macrophages (Mφ) with the status of pro-inflammatory and immunosuppressive cytokines, as well as with the expression of the key ECM proteins in BC tissue. **Materials and Methods.** Postoperative material from 67 patients with stage I—II BC was studied. TAMs infiltration and the expression of SPP1, COX-2, SERPINE2, COL1A1, and COL3A1 were assessed immunohistochemically. The serum IL-6 and IL-10 levels were determined by the ELISA. *IL6*, *IL10,* and *TNF* mRNA expressions were assessed by qRT-PCR. **Results**. The high levels of IL-6 in the serum of patients ($p = 0.0159$) and *IL10* mRNA in BC tissue ($p = 0.0316$) were associated with an increase in the number of $CD68^+$ TAMs. The pronounced infiltration of $CD163^+$ TAMs correlated with an increase in the systemic level of IL-10 ($p = 0.0357$), IL-6 ($p = 0.0286$), and local *TNF* expression ($p = 0.001$). The increased SPP1 expression was accompanied by an increase in $CD163^+$ TAMs ($p = 0.008$) against the background of a decrease in the $CD68^+$ Mφ population in BC tissue ($p = 0.0271$). The high levels of COX-2 were also directly correlated with the degree of M2-like Mφ infiltration ($p = 0.0357$). At the same time, COL1A1 expression was associated with increased infiltration of both TAM phenotypes, while high COL3A1 expression was associated with a decrease in $CD68^+$ Mφ in tumor tissue. The bioinformatic analysis confirmed the obtained results and also allowed us to highlight the features of the tumor microenvironment composition, which depended on the degree of TAM infiltration in BC tissue of different molecular subtypes. **Conclusions**. The results demonstrated the existence of a single regulatory axis, "TAMs — cytokines — ECM", which determined the development of the immunosuppressive and invasive BC microenvironment. The predominance of $CD163^+$ Mφ against the background of increased levels of IL-10, SPP1, and COX-2 was associated with a high degree of BC malignancy.

Keywords: breast cancer, tumor-associated macrophages, CD68, CD163, cytokines, immunosuppression.

Breast cancer (BC) remains one of the most common malignancies worldwide and the leading cause of cancer-related mortality among women. Despite the significant advances in therapeutic strategies, tumor heterogeneity, and dynamic alterations within the tumor microenvironment (TME) continue

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to limit the effectiveness of anticancer treatment. Consequently, there is an increasing emphasis on the development of personalized therapeutic approaches in BC, particularly through the identification and validation of novel TME-associated biomarkers [1—3].

Among the predominant cellular components of the TME in solid tumors, tumor-associated macrophages (TAMs) play a central role. A key feature of TAMs is their functional plasticity, driven by local microenvironmental cues, which enables polarization into two main phenotypes: the pro-inflammatory, antitumorigenic M1 subtype and the immunosuppressive M2-like subtype, which promotes malignant progression [4]. Our previous findings have demonstrated that the high levels of TAMs infiltration, particularly by $CD163^+$ M2-like macrophages (Mφ), are associated with the enhanced metastatic potential, reduced therapeutic efficacy, and poor survival outcomes in BC patients [5].

Cytokines, particularly IL-6, IL-10, and TNF-α, play a pivotal role in regulating TAMs' functional activity. IL-6 is recognized as a critical mediator of chronic inflammation that can promote tumor growth through the activation of the JAK/STAT3 signaling pathway [6, 7]. In contrast, IL-10 facilitates the acquisition of the immunosuppressive M2-like Mφ phenotype and suppresses antitumor immune responses [8]. TNF-α exhibits a dual functionality, possessing both pro-inflammatory and pro-oncogenic properties, with its biological effects largely determined by the local TME context. Importantly, TNF-α contributes to the extracellular matrix (ECM) remodeling and angiogenesis in BC [9].

The tumor matrisome also acts as a key regulator of immune cell infiltration within the TME. Our previous studies demonstrated that the mast cell recruitment to the BC site is modulated by ECM proteins, including osteopontin (secreted phosphoprotein 1, SPP1) and fibrillar collagens [10, 11]. According to the literature, SPP1, secreted by TAMs and tumor cells, promotes their polarization toward the M2 functional state and enhances the invasive potential of transformed cells [12]. Another ECM component, SERPINE2, is involved in proteolytic remodeling of the tumor matrix and establishment of metastatic niches [13]. It has also been reported that TAM infiltration levels are directly associated with the morphometric parameters of collagen fibril organization within the tumor stroma [14]; however, the specific contribution of individual collagen types to this interaction remains unclear.

Despite a substantial number of studies devoted to the roles of individual cellular components of the TME, cytokines, or elements of the ECM, their combined contribution to the formation of an aggressive BC phenotype remains largely uncharacterized. The lack of comprehensive data on the features of infiltration by different Mφ subtypes, their regulation by local and systemic cytokine profile alterations, as well as the qualitative and quantitative characteristics of tumor ECM in patients with BC, currently limits the ability to identify prognostic biomarkers and effective therapeutic targets.

The aim of this study was to evaluate the associations of $CD68^+$ and $CD163^+$ Mφ infiltration with the status of pro-inflammatory and immunosuppressive cytokines, as well as with the expression of key ECM proteins in BC tissue.

Materials and Methods

The study was conducted on the postoperative material of 67 patients with stage I—II BC. The patients were treated at the Municipal Non-Profit Enterprise "Kyiv City Oncology Center" within 2019—2022. The Institutional Review Board and Research Ethics Committee of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine approved the work. It was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. All patients were examined using generally accepted clinical and laboratory methods by the Standards of Diagnosis and Treatment of Oncological Patients, approved by Order of the Ministry of Health of Ukraine No. 396, adopted on 30/06/2015 (registration number GS 2015—396). No patients received neoadjuvant treatment. All donors of tumor material provided Informed Consent of Agreement to conduct scientific research. The stage of the tumor process was determined according to the International TNM Classification (Brierley 2017) [15]. The clinicopathological characteristics of patients are presented in Table 1.

Immunohistochemistry. The expression of CD68 (clone KP-1, Master Diagnostica, Spain, RTU), CD163 (clone OTI2G12, Abcam, USA, dilution 1:150), COX-2 (clone SP21, Master Diagnostica,

Spain, RTU), SERPINE2 (clone 1E11F12, Proteintech, USA, dilution 1:200), SPP1 (clone 7C5H12, Invitrogen, USA, dilution 1:300), COL1A1 (clone 1B2, MyBioSource, USA, dilution 1:350), and COL3A1 (clone 5G2, MyBioSource, USA, dilution 1:300) was assessed using an immunohistochemical approach. For the evaluation of Mφ infiltration within intra- and peri-tumoral regions, the numbers of $CD68^+$ cells (total Mφ population) and $CD163^+$ cells (M2-like Mφ) were counted in twenty fields of view. The results were expressed as the number of positive cells per mm^2.

The expression levels of SPP1, COL1A1, COL3A1, and COX-2 were quantified according to the optical density of the stained stromal areas using the IHC Profiler plugin in the ImageJ software [16]. SERPINE2 expression was evaluated using the H-score method [17].

Enzyme-linked immunosorbent assay (ELISA). Serum concentrations of IL-6 and IL-10 were measured using the commercial Human IL-6 ELISA Kit and Human IL-10 ELISA Kit (Elabscience, USA) according to the manufacturer's instructions. Blood serum was obtained by centrifugation for 20 min at 1500 rpm, and the samples were stored at –20 °C without repeated freeze–thaw cycles.

Optical density was measured at 450 nm using a Synergy™ HT microplate reader (BioTek, USA). The cytokine concentrations were calculated based on standard calibration curves.

Real-time PCR. Total RNA from breast tumor tissue was extracted using the RNeasy FFPE Kit (QIAGEN, Germany) following the manufacturer's protocol. RNA concentration and purity were determined using a NanoDrop 2000c spectrophotometer (Thermo Scientific, USA). Complementary DNA (cDNA) was synthesized from 100 ng of total RNA using the LunaScript® RT SuperMix Kit (New England Biolabs, USA). Quantitative real-time PCR (qRT-PCR) was performed to evaluate mRNA expression of *IL6*, *IL10*, and *TNF* using a QuantStudio 5 Dx Real-Time PCR System (Thermo Scientific, USA) and Maxima SYBR Green/ROX qPCR Master Mix (2X) (Thermo Fisher Scientific, USA). β-Actin (*ACTB*) served as an endogenous reference gene. Each reaction was performed in triplicate. Relative gene expression levels were calculated using the ΔCt method.

Bioinformatic analysis. Associations between immune cell infiltration in the TME and mRNA expression of the investigated genes were assessed using the TIMER 3.0 (Tumor Immune Estimation Resource) online platform. This resource provides a standardized immune infiltration analysis based on TCGA transcriptomic data with adjustment for tumor purity.

Correlation analysis was performed in the "Gene" module, where the relationship between the expression of a selected gene and estimated macrophage infiltration was calculated. Spearman's rank correlation coefficient (default setting in TIMER 3.0) was used, and correlation coeffi-

Table 1. **Clinical characteristics of BC patients**

Characteristics	Number of patients	
	N	%
Total number of patients	67	100
Average age, years	58.36 ± 1.66	
Age fluctuation, years	28—89	
Reproductive status		
Menstrual cycle preserved	21	31.3
Menopause	46	68.7
Clinical stage		
I	22	32.8
II	45	67.2
Tumor size (category T)		
T1	27	40.3
T2	40	59.7
Lymph node involvement (category N)		
N0	44	65.7
N1-3	23	34.3
Histological type		
Infiltrative ductal adenocarcinoma	49	73.1
Infiltrative lobular adenocarcinoma	18	26.9
Tumor differentiation grade		
G1 (high)	3	4.5
G2 (moderate)	56	83.6
G3 (low)	8	11.9
Molecular subtype		
Luminal A	30	44.8
Luminal B	20	29.9
Triple-negative (Basal-like)	8	13.4
HER2/neu-positive	9	11.9

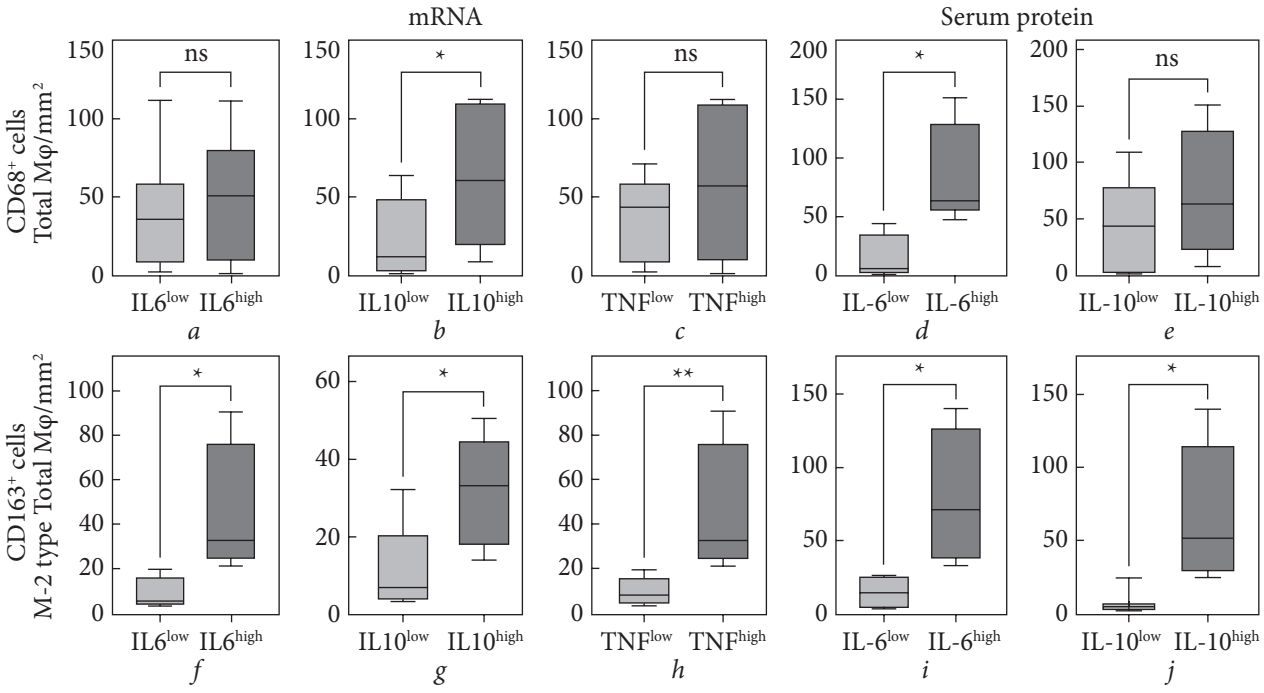

Fig. 1. Relationship between the degree of $CD68^+$ and $CD163^+$ TAM infiltration in BC tissue and indicators of mRNA expression and levels of circulating cytokines. * $p < 0.05$; ** $p < 0.001$

cients along with *p*-values were obtained directly from the database interface.

The graphical outputs were exported using built-in visualization tools. The analysis was conducted for both the overall BC cohort and individual molecular subtypes according to the TCGA classification.

Statistical analysis. All statistical analyses were performed using GraphPad Prism software, version 10.00 (GraphPad Software Inc., USA). The patients were divided by the median expression into two comparison groups: low and high expression levels. Comparisons between two independent groups were conducted using the non-parametric Mann — Whitney U-test. The quantitative data were presented as the mean ± standard error of the mean (M ± m). Box-and-whisker plots were used to visualize the distribution of the values across the study groups. In these plots, the central line within the box represented the median; the lower and upper edges of the box corresponded to the first and third quartiles, respectively. The whiskers extending from the box indicated the minimum and maximum values observed in either group.

Results

At the first stage of the study, we evaluated the association of Mφ infiltration and cytokine levels in BC tissue with patients' blood serum. We found that in BC patients with high serum IL-6 concentrations, the level of $CD68^+$ Mφ infiltration in tumor tissue was 11.14-fold higher ($p = 0.0159$) compared to the patients with low levels of this cytokine (Fig. 1). A 5.13-fold increase in $CD68^+$ TAM infiltration ($p = 0.0316$) was observed in the tumors characterized by high *IL10* mRNA expression. In addition, a statistically significant increase in $CD163^+$ TAM infiltration (5.97-fold ($p = 0.0286$), 4.86-fold ($p = 0.0317$), and 4.12-fold ($p = 0.001$), respectively) was recorded in BC samples with high *IL6*, *IL10*, and *TNF* mRNA expression levels (Fig. 1).

It was established that a high content of M2-like Mφ in BC tissue is associated with an increase in circulating and tumor-associated cytokines in BC patients. In particular, in patients with elevated serum IL-10 and IL-6 concentrations, the level of tumor-associated $CD163^+$ Mφ infiltration was 12.01-fold ($p = 0.0357$) and 5.11-fold ($p = 0.0286$) higher, respectively, compared to patients with low levels of these cytokines (Fig. 1).

Subsequently, we analyzed the relationship of Mφ infiltration with the expression levels of stromal proteins in tumor tissue. It was demonstrated that high SPP1 expression in BC tissue was associated with significantly lower (2.06-fold, $p = 0.0271$) levels of $CD68^+$ TAMs compared to the tumors characterized

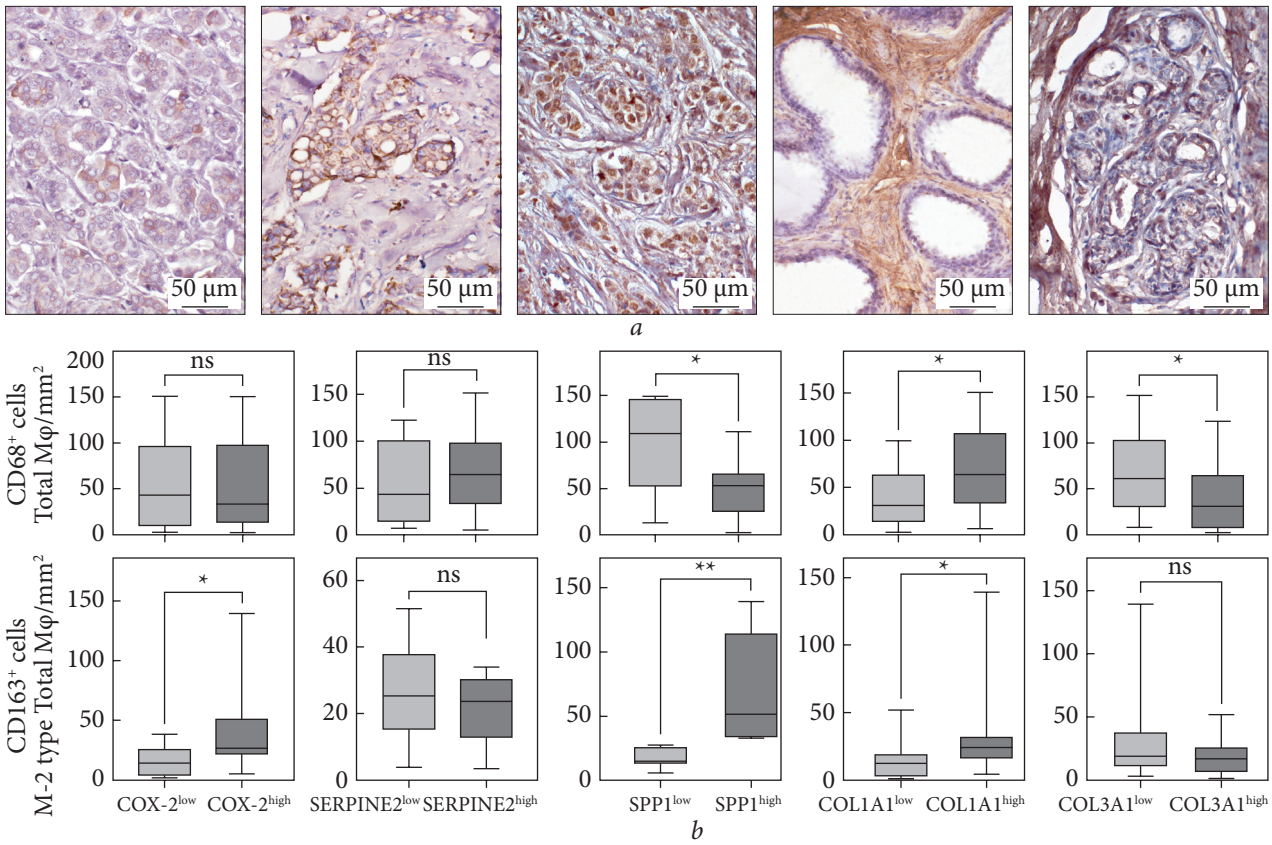

Fig. 2. ECM protein expression patterns and corresponding to of TAM infiltration in BC tissues: Immunohistochemical staining of ECM proteins in BC samples, chromogen — 3,3′-diaminobenzidine; counterstained with Meyer's hematoxylin (*a*); TAM infiltration levels in BC samples grouped according to ECM protein expression (*b*). * $p < 0.05$; ** $p < 0.001$

by a low expression of this matricellular protein (Fig. 2). At the same time, in the tumors with high SPP1 expression in tumor stroma, a 2.17-fold increase ($p = 0.008$) in the level of CD163$^+$ M2-like Mφ infiltration was observed compared to tumors with low SPP1 expression. In addition, a high COX-2 expression in BC tissue was associated with a 1.85-fold ($p = 0.0357$) increase in CD163$^+$ TAM abundance.

We found that BC tissue with high COL1A1 expression is characterized by an increased number of CD68$^+$ and CD163$^+$ Mφ by 2.05-fold ($p = 0.043$) and 1.99-fold ($p = 0.049$), respectively, compared to tumors with a low expression of this collagen type. However, the opposite trend was observed for COL3A1: BC tissue: a high expression of this collagen type demonstrated a 1.98-fold decrease in the level of CD68$^+$ Mφ infiltration.

It was established that a decrease in the IL-6 levels in the blood serum of BC patients, as well as a reduction in COX-2 expression in tumor tissue, is associated with an increased level of CD163$^+$ M2-like Mφ infiltration, which was accompanied by a lower CD68$^+$/CD163$^+$ ratio (Table 2).

Table 2. **Association of CD68$^+$/CD163$^+$ TAM ratio with circulating and tumor-associated cytokine levels and expression profiles of ECM proteins**

Marker	CD68$^+$/CD163$^+$ ratio	
	Low	High
Circulating cytokine levels		
IL-6	**4.379 ± 1.653**	**1.282 ± 0.155**
IL-10	4.810 ± 2.064	1.510 ± 0.246
Tumor-associated marker levels		
IL6	1.789 ± 0.423	3.966 ± 2.234
IL10	3.287 ± 1.498	1.309 ± 0.567
TNF	3.454 ± 1.455	1.148 ± 0.079
COX-2	**4.035 ± 1.172**	**1.403 ± 0.133**
SERPINE2	3.846 ± 1.458	2.249 ± 0.446
SPP1	3.550 ± 0.606	1.508 ± 0.242
COL1A1	2.279 ± 0.477	2.941 ± 0.853
COL3A1	2.465 ± 0.541	2.777 ± 0.789

Note: A significant difference between the groups ($p < 0.05$) is highlighted in bold.

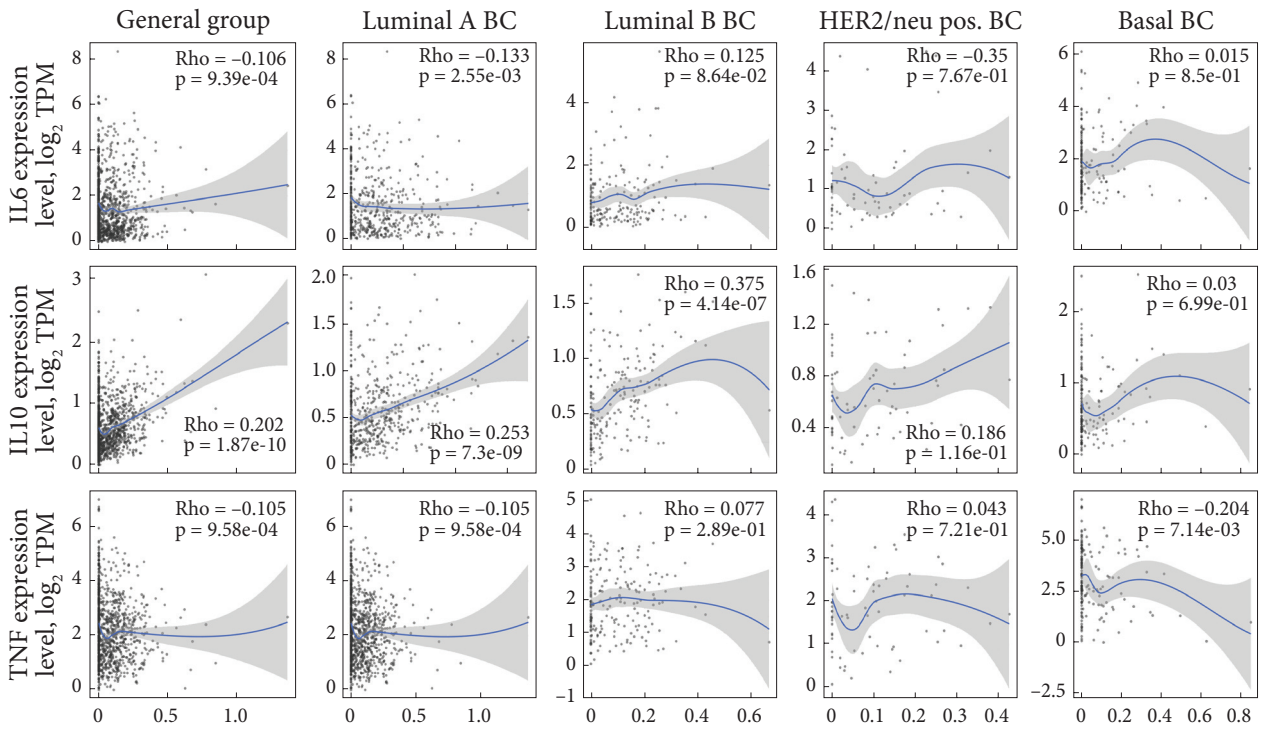

Fig. 3. Correlation analysis between TAMs infiltration levels and cytokine gene expression in BC tissue according to the TIMER 3.0 database (https://compbio.cn/timer3)

Considering the results of our previous study indicating that the mechanisms regulating TAM infiltration into BC tissue may differ in tumors of different molecular subtypes [5], we performed a bioinformatic analysis of the correlations between TAM infiltration levels and the expression of cytokine- and ECM-related genes in BC tissue (Fig. 3), using the TIMER 3.0 database. The analysis demonstrated that Mφ infiltration positively correlated with *IL10* gene expression and negatively correlated with the expression of *IL6* and *TNF*, both in the overall patient cohort and groups stratified by molecular subtypes of BC. At the same time, strong positive correlations were observed between TAM infiltration and *SPP1*, *COL1A1*, and *COL3A1* gene expression across all molecular BC subtypes (Fig. 4). In addition, a weak negative correlation was identified between TAM infiltration and *COX2* gene expression, and a weak positive association was observed with *SERPINE2* expression. Of particular interest, the strongest correlations were found between TAM infiltration and *SPP1* expression in HER2/neu-positive tumors ($\rho = 0.61$), as well as between TAM infiltration and *SERPINE2* mRNA expression in the luminal B subtype ($\rho = 0.436$).

Summarizing the presented results, it can be noted that Mφ infiltration of tumor tissue is associated with both the systemic and local cytokine profiles in patients with BC. In particular, an increase in the total number of $CD68^+$ TAMs at the tumor site is associated with the activation of pro-inflammatory cytokine signaling, whereas an increase in the proportion of $CD163^+$ M2-like Mφ is accompanied by more pronounced systemic and transcriptional shifts toward anti-inflammatory mechanisms. In addition, it should be noted that the infiltration of $CD163^+$ M2-like Mφ into tumor tissue is associated with higher expression levels of SPP1, COX-2, COL1A1, and COL3A1 in the BC stroma (Fig. 5).

Discussion

The obtained results confirm the key role of TAMs in shaping both immunosuppressive and pro-inflammatory TME in BC. The significant increase in $CD68^+$ Mφ infiltration, along with high serum IL-6 levels and elevated *IL10* mRNA expression in tumor tissue, indicates the activation of cytokine-mediated mechanisms that promote tumor growth. It is known that IL-6 stimulates tumor cell proliferation and survival through the activation of the JAK/STAT3 signaling pathway and contributes to the TME remodeling [6, 18, 19], which is consistent with our findings.

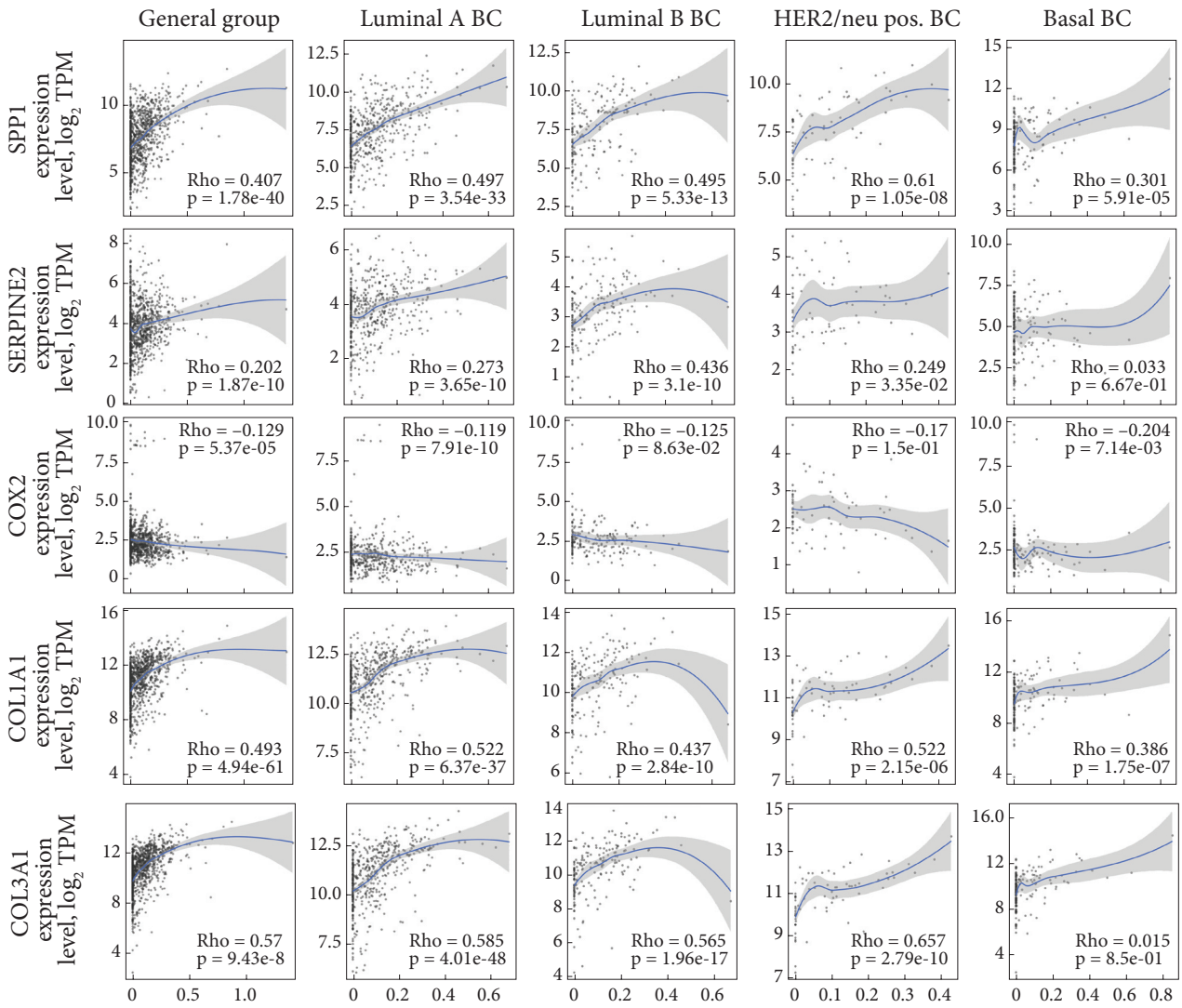

Fig. 4. Correlation analysis between TAM infiltration levels and ECM-related gene expression in BC tissue according to the TIMER 3.0 database (https://compbio.cn/timer3)

Luminal A	Luminal B	HER2/neu-positive	Basal-like
IL6 ↓	IL10 ↑	SPP1 ↓	TNF ↓
IL10 ↑	SPP1 ↑	SERPINE2 ↑	SPP1 ↑
TNF ↓	SERPINE2 ↑	COL1A1 ↑	COX2 ↓
SPP1 ↑	COX2 ↓	COL3A1 ↑	COL1A1 ↑
SERPINE2 ↑	COL1A1 ↑		COL3A1 ↑
COL1A1 ↑	COL3A1 ↑		
COL3A1 ↑			

Fig. 5. Composition of the BC microenvironment across different molecular subtypes associated with a high degree of TAM infiltration

The pronounced infiltration of CD163$^+$ TAMs in BC tissue, along with elevated IL-10 levels, both in blood serum and in BC tissue, suggests the enhancement of immunosuppressive processes within the tumor site. M2-like TAMs are considered the main source of IL-10, and their high counts are associated with the suppression of antitumor immune responses and unfavorable clinical outcomes [20]. Moreover, the increased TNF expression in tumor tissue may indicate the involvement of CD163$^+$ TAMs in chronic inflammation and ECM remodeling, creating conditions favorable for enhanced invasiveness and metastasis of BC [9].

The obtained data indicate the involvement of ECM proteins in shaping an immunosuppressive TME dominated by M2-like Mφ. Indeed, ele-

vated SPP1 expression was accompanied by an increase in CD163$^+$ M2-like Mφ alongside a reduction in the total CD68$^+$ TAM population. This is consistent with reports demonstrating that SPP1 promotes M2 polarization and contributes to immunosuppressive remodeling of the TME in BC [21, 22].

Moreover, it was established that an M2-like Mφ-enriched TME is characterized by the activation of the COX-2-dependent inflammatory cascade. In our study, the increased CD163$^+$ TAM infiltration was associated with elevated COX-2 levels in tumor tissue, which is in line with the findings showing that COX-2 in TAMs enhances ECM remodeling as well as the invasive and migratory activity of BC cells via activation of the PI3K/Akt signaling pathway [23].

An additional aspect to highlight is the role of the collagen matrix as a physical barrier that simultaneously may serve as a structural guide for the directed migration of cells within the TME [24]. Available studies indicate that the increased collagen density and excessive ECM deposition are associated with enhanced TAMs infiltration [25, 26]. However, the role of individual collagen types in shaping the immune profile of the TME has been insufficiently investigated. Our findings demonstrate that the elevated stromal expression of type I collagen in BC tissue is positively associated with TAM abundance, whereas the infiltration inversely correlates with COL3A1 expression levels. The evaluation of the CD68$^+$/CD163$^+$ TAM ratio confirmed the role of M2-like macrophages in TME remodeling: lower values of this index were associated with reduced serum IL-6 levels and decreased COX-2 expression in tumor tissue.

The results of this study confirm that TAMs — particularly the CD163$^+$ M2-like phenotype — act as central regulators of the BC TME. The identified associations between TAM infiltration, cytokine profiles, and the expression of key ECM proteins emphasize the existence of an integrated "immune—ECM axis" that determines tumor aggressiveness. The increased IL-10, SPP1, COX-2, and SERPINE2 levels in patients with high abundance of CD163$^+$ TAMs indicate the development of an immunosuppressive and structurally remodeled TME, potentially contributing to tumor invasion, metastasis, and therapy resistance. These findings expand current understanding of the interplay between immune and stromal components of the TME and provide a rationale for future research toward personalized therapeutic strategies.

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АСОЦІАЦІЇ МІЖ ІНФІЛЬТРАЦІЄЮ ПУХЛИНО-АСОЦІЙОВАНИХ МАКРОФАГІВ І ЦИТОКІНОВИМИ ТА ECM-СИГНАТУРАМИ В МІКРООТОЧЕННІ РАКУ МОЛОЧНОЇ ЗАЛОЗИ

Пухлино-асоційовані макрофаги (TAMs) є одними з головних регуляторів імунного мікрооточення раку молочної залози (РМЗ), проте їх взаємозв'язок із цитокіновими сигналами та станом позаклітинного матриксу (ECM) залишається недостатньо охарактеризованим. **Метою** дослідження було оцінити зв'язок ступеня інфільтрації $CD68^+$ та $CD163^+$ макрофагів із статусом прозапальних та імуносупресивних цитокінів, а також експресією ключових білків ECM у тканині РМЗ. **Матеріали та методи.** Досліджено післяопераційний матеріал 67 пацієнток із РМЗ I—II стадій. Імуногістохімічно оцінювали інфільтрацію TAMs та експресію SPP1, COX-2, SERPINE2, COL1A1 і COL3A1. Рівні IL-6 та IL-10 у сироватці визначали методом імуноферментного аналізу; експресію *IL6*, *IL10* і *TNF* мРНК — на основі qRT-PCR. Статистична оцінка здійснювалася за допомогою критерію Манна — Вітні. Додатково проведено кореляційний аналіз даних TCGA з використанням TIMER 3.0. **Результати.** Високі рівні IL-6 у сироватці крові хворих ($p = 0{,}0159$) та *IL10* мРНК у тканині РМЗ ($p = 0{,}0316$) асоціювалися зі зростанням кількості $CD68^+$ TAMs. Виражена інфільтрація $CD163^+$ TAMs корелювала зі збільшенням системного рівня IL-10 ($p = 0{,}0357$), IL-6 ($p = 0{,}0286$) та локальної експресії *TNF* ($p = 0{,}001$). Підвищена експресія SPP1 супроводжувалася збільшенням $CD163^+$ TAMs ($p = 0{,}008$) на фоні зниження $CD68^+$ популяції макрофагів у тканині РМЗ ($p = 0{,}0271$). Високі рівні COX-2 також прямо корелювали зі ступенем M2-орієнтованої інфільтрації ($p = 0{,}0357$), тоді як експресія COL1A1 асоціювалася з підвищенням інфільтрації обох фенотипів TAMs, а високий рівень COL3A1 — зі зменшенням $CD68^+$ клітин у пухлинній тканині. Біоінформатичний аналіз підтвердив отримані результати, а також дозволив виділити особливості композиції TME, що залежать від ступеня інфільтрації TAMs у тканині РМЗ різних молекулярних підтипів. **Висновки.** Результати демонструють існування єдиної регуляторної осі "TAMs — цитокіни — ECM", яка обумовлює розвиток імуносупресивного та інвазивного мікрооточення РМЗ. Переважання $CD163^+$ макрофагів на тлі зростання рівнів IL-10, SPP1, COX-2 асоціюється з високим ступенем злоякісності РМЗ, що може бути перспективною терапевтичною мішенню.

Ключові слова: рак молочної залози, пухлино-асоційовані макрофаги, CD68, CD163, цитокіни, імуносупресія.