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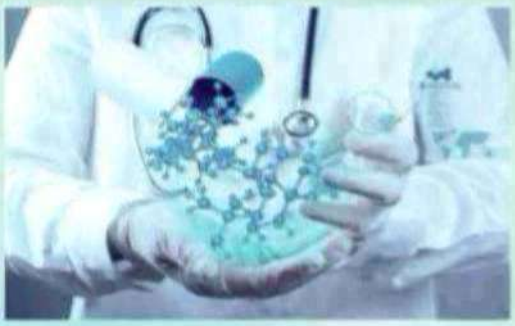

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TUMOR MICROENVIRONMENT AS A LOCAL IMMUNOLOGICAL CIRCUIT OF BREAST CANCER PROGRESSION

Mukhitdinova Lailo Shukhratovna https://orcid.org/0009-0007-5284-6939

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Resume***

The material summarizes current ideas about the cellular and molecular components of the tumor microenvironment in breast cancer, including CD8+ T lymphocytes, Treg, TAMs, CAFs, MDSCs, dendritic cells, cytokines, chemokines, exosomes and extracellular matrix. It has been shown that the clinical value of immune infiltration is determined not so much by its density as by the functional state and spatial organization of cells. Particular attention is paid to the mechanisms of immune evasion, the PD-1/PD-L1 axis, the formation of an immunosuppressive microenvironment in TNBC, the role of TGF- β, IL-10, CCL2, CXCL13 and other signaling interactions, as well as the prospects for using spatial and molecular technologies to predict the course of the disease and the effectiveness of immunotherapy.

Keywords: tumor microenvironment; immune infiltration; TILs; immunotherapy.

ОПУХОЛЕВОЕ МИКРООКРУЖЕНИЕ КАК ЛОКАЛЬНЫЙ ИММУНОЛОГИЧЕСКИЙ КОНТУР ПРОГРЕССИРОВАНИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

Мухитдинова Лайло Шухратовна

Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Резюме***

В материале обобщены современные представления о клеточных и молекулярных компонентах опухолевого микроокружения при раке молочной железы, включая CD8+ Т-лимфоциты, Treg, TAMs, CAFs, MDSCs, дендритные клетки, цитокины, хемокины, экзосомы и внеклеточный матрикс. Показано, что клиническое значение иммунной инфильтрации определяется не столько её плотностью, сколько функциональным состоянием и пространственной организацией клеток. Особое внимание уделено механизмам иммунного уклонения, оси PD-1/PD-L1, формированию иммуносупрессивного микроокружения при TNBC, роли TGF-β, IL-10, CCL2, CXCL13 и другим сигнальным взаимодействиям, а также перспективам использования пространственных и молекулярных технологий для прогнозирования течения заболевания и эффективности иммунотерапии.

Ключевые слова: опухолевое микроокружение; иммунная инфильтрация; TILs; иммунотерапия.

SUT BEZI SARATONI RIVOJLANUVINING MAHALLIY IMMUNOLOGIK KONTURI SIFATIDA O'SMA MIKROKURASI

Muhitdinova Laylo Shuxratovna

Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O'zbekiston, Buxoro sh. A. Navoiy kochasi 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Rezyume***

Materialda ko'krak bezi saratonida o'sma mikro-aylanishining hujayra va molekulyar komponentlari, jumladan CD8+ T-limfotsitlar, Treg, TAMs, CAFs, MDSCs, dendrit hujayralari, sitokinlar, xemokinlar, ekzosomalar va hujayradan tashqari matrix haqidagi zamonaviy tushunchalar umumlashtirilgan. Ko'rsatilishicha, immun infiltratsiyasining klinik ahamiyati uning zichligi bilan emas, balki hujayralarning funksional holati va fazoviy tashkil etilishi bilan belgilanadi. Immun bo'shashish mexanizmlariga, PD-1/PD-L1 o'qiga, TNBCda immunosupressiv mikroatrof muhitni shakllantirishga, TGF- β, IL-10, CCL2, CXCL13 va boshqa signal o'zaro ta'siriga, shuningdek, kasallikning kechishini prognozlash uchun fazoviy va molekulyar texnologiyalardan foydalanish istiqbollariga alohida e'tibor qaratildi immunoterapiya samaradorligi.

Kalit so'zlar: o'simta mikro-aylanishi; immun infiltratsiyasi; TILs; immunoterapiya.

Relevance

The tumor microenvironment in breast cancer is a dynamic immunobiological system that determines the nature of the anti-tumor immune response, invasion, metastasis, and the effectiveness of drug therapy. Modern data show that not only the quantitative indicators of TILs, CD8+, and FOXP3+ cells are of prognostic importance, but also their functional state, spatial organization, and interaction with CAFs, TAMs, extracellular matrix, cytokines, and PD-1/PD-L1 immune control points. A comprehensive study of the tumor's immune landscape using spatial transcriptomy, single-cell analysis, and circulating molecular markers is particularly relevant, which creates prerequisites for more accurate prognosis stratification and personalized immunotherapy.

The tumor microenvironment in breast cancer can no longer be considered a passive background for the growth of malignant cells, as it participates in the formation of immune supervision, immune shutdown, inflammation, angiogenesis, metastasis, and drug resistance; at the same time, the local immune circuit has its own architecture, where not only the presence of TILs, CD8+, or FOXP3+ cells is important, but also their functional state, spatial distribution, and interaction with fibroblasts, macrophages, and extracellular matrix; furthermore, focusing on spatial transcriptomy, exosome PD-L1, and circulating tumor DNA as a tool for dynamic adaptation of immunotherapy is promising [8]. However, such an approach is still closer to a research platform than a simple prognostic scale, and therefore attempts to evaluate the subtle spatial organization of the microenvironment remain the focus of the ongoing research [5]. In such an environment, the loss of E-cadherine/CDH1 in tumor cells prevented the differentiation of inflammatory cancer-related FAP+ fibroblasts in myofibroblastic CAFs, leading to the accumulation of iCAFs that attracted TILs to the tumor center and changed their spatial organization, but at the same time, CDH1-inactivating cells contributed to immune escape by disrupting the retention and activation of ITGAE-expression of CD8+ T-lymphocytes' resident memory, meaning high TIL content does not always automatically mean a favorable prognosis, especially if the local architecture of the infiltrate is disrupted, whereas cell-tumor interaction in TNBC was discovered experimentally by N. Song et al. [7] from the Beckman Research Institute (Duarte, USA) through a series of in vivo CRISPRs, the authors identified the tumor ITGB1 as an important regulator of the development of triple-negative breast cancer with increased infiltration of CD4+ and CD8+ T-cells and led to a more pronounced antitumor effect, describing the previously unknown functional domain ITGB1, the blocking of which by an antibody disrupted the progression of TNBC, and the scheme of cellular cross-communication in the microenvironment of breast cancer was generalized by M. Sharma et al. [11] from GLA University (Mathura, India) after considering CAFs, TAMs, Tregs, MDSCs, cancer-related adipocytes, extracellular matrix, cytokines, chemokines, exosomes, and hypoxia as interconnected elements of tumor progression, metastasis, immunity deviation, and therapy resistance, noting that CAFs can secrete TGF-β and HGF, TAMs more often shift toward the M2-like phenotype and produce VEGF and IL-10, while extracellular vesicles derived from tumors change cell phenotypes and form metastatic niches [4, 6, 10].

In the tumor contour itself, immune control points occupy a special place, as it is they that link morphologically visible infiltration with the functional state of the antitumor response, while the PD-1/PD-L1 axis allows tumors to weaken T-cell activity, but simultaneously becomes a therapeutic target; that is, in this case, a paradox arises when the presence of PD-L1 may indicate both the immune activity

of the microenvironment and the established mechanism of immune evasion, which requires careful interpretation in connection with TILs, CD8+, FOXP3+ and the clinical outcome, as reported by Y. Shin et al. in their publication. [15, 20] from Sejong University (Seoul, Republic of Korea), systematizing data on PD-1/PD-L1 pathway inhibition in breast cancer, and the problem of immunotherapy resistance was examined in detail by Z. Zhou and Q. Zhou [14, 19] from Jiangsu University (Zhengjiang, China), presenting TNBC as a subtype with high invasiveness, frequent metastasis, and poor prognosis, but with relatively higher immunogenicity compared to other subtypes, while neoadjuvant immunotherapy for HR+ breast cancer was analyzed by Z. Tang et al. [12, 16] from Hua-Zhong University of Science and Technology (Wuhan, China), noting that HR+ tumors are traditionally classified as immunologically "cold" variants due to low PD-L1 expression, lower TILs levels, and low mutational burden, but at the same time, within the HR+ group, there are immunologically enriched subsets where a combination of genetic and TME traits can increase sensitivity to a combination of immune checkpoint inhibitors. However, LIMCH1 is highly expressed in breast cancer, is associated with poor prognosis and immunosuppressive status, and functional experiments have demonstrated that it activates the MAPK pathway, increases PD-L1, suppresses CD4+ and CD8+ T-cell infiltration, and forms an immunosuppressive microenvironment, while its high expression was also associated with a low response rate to anti-PD-1 therapy [10, 17].

Discussions

The cellular composition of the local immune response determines not only the presence of infiltration but also its functional sign, where CD8+ T-cells are more often associated with effector antitumor potential, FOXP3+ Treg-cells are associated with immunoregulatory and immunosuppressive components, and macrophages associated with tumors can maintain both an inflammatory and tumor-promoting scenario; therefore, for prognosis, it is not the individual cell type that is important, but the balance between effector, regulatory, and myeloid elements, which, for example, in the work of L. Ren et al. [11, 13] from the State Key Laboratory of Bioactive Substances and Functions of Natural Medicines (Beijing, China) identified IFI30 as a critical infiltration regulator, where macrophages associated with breast cancer tumors, IFI30, were enhanced by enhancing H3K27 in modification and contributed to progression and metastasis in an immune-dependent manner, while mechanistically IFI30 activated the ATF3-CCL5 axis, recruited TAMs, induced M2-like polarization, and increased PD-L1 in macrophages. Furthermore, the interaction of Treg cells and DC-regulating macrophages in the lymphoid niche was examined by S. Wang et al. [3, 8] from the Second Shandong Medical University (Weifan, China), who using scRNA-seq, transcriptomic datasets, TNBC cell lines, and mouse models proved that radiation therapy reduces ISLR expression, disrupting MIF/CD74 signaling and weakening the Treg-mregDC lymphoid niche, but with ISLR suppression, IL-10 and TGF-β secretion decreases against the background of increased CD8+ T-cell infiltration and increased PD-1 blockade efficiency; however, similar to the phenomenon of CD8+ T-cell depletion during breast cancer lumination based on TCGA, GTEx, and HPA, as well as SLC12A8, which is elevated in tumor tissues and cell lines, is associated with poor prognosis and a decrease in functionally active CD8+ T-cell infiltration, which from a pathogenetic perspective is associated with the mechanical activation of SLC12A8 TLR signaling pathways in CD8+ T-cells, increasing PD-1 and causing their function [9, 16] gives a subtle characteristic of CD8 effector T-cells in TNBC, and accordingly, the RNA mono-cell sequences and analyzes transcripts to evaluate the immune landscapes of TNBC, with CD8 T-cells being predominantly enriched in "hot" tumors and correlating with better remission and overall survival, resulting in CXCL13 being identified as a key regulator of the immune-active microenvironment favorable for ICI effectiveness, and additionally, an AI model was developed to recognize CD8 T-cells with AUC=0.823 in the training cohort and AUC=0.805 in the validation cohort, emphasizing the value not just of CD8+ density, but of the activated effector state of CD8 cells. Macrophages associated with tumors are central participants in the progression of TNBC, forming an immunosuppressive microenvironment; under the influence of IL-10 and TGF-β, they shift toward M2-like phenotypes, support tumor growth, angiogenesis, metastasis, and evade immunity. Issues regarding TAM depletion strategies, reprogramming into M1-like groups, and blocking the CD47-SIRPα phagocytosis control point are also discussed separately, and for our topic, this links local cellular indicators with systemic cytokines IL-10 and TGF-β, thereby summarizing the role of TAMs in TNBC by T. Wu and Y. Liao

[10, 17] from Guangdong Medical University (Zhangjiang, China). Meanwhile, the regulatory link of the T-cell response was revealed in the publication by M. Boutet et al. [4, 5] from the Department of Microbiology and Immunology, Albert Einstein Medical College (New York, USA), where they identified function loss mutations in MLL3/KMT2C in an aggressive breast cancer model that stabilized HIF1α by increasing CCL2 secretion by tumor cells and strengthening the recruitment of CCR2+ regulatory T-cells; furthermore, Treg cell depletion slowed down the onset and progression of the tumor, and in human tumors, Treg infiltration correlated with the presence of MLL3 mutations, while HIF1α supported the differentiation of infiltrating Treg tumors in ICOS GITR effectors that secrete TGF-β and IL-10, thereby concluding a direct link between the FOXP3+/Treg component and immunosuppressive cytokines and the progression of the oncological process.

The spatial organization of immune infiltration becomes a separate level of analysis, because the same cell density can have different clinical significance depending on whether they are located in the stroma, in tumor islets, in the immune exclusion zone, or in a metastatic niche, and this is especially important for prediction, as the tumor can be infiltrated but functionally closed for an effective cytotoxic response; accordingly, modern studies are increasingly using single-celled, spatial transcriptomy, and computational signatures, among which, for example, N. Su et al. [8, 10] from Xiamen University (Xiamen, China) showed that inhibiting NEDD4 in TNBC can reprogram the tumor's immune microenvironment through the β-TrCP/YAP/ECM axis, and high expression of NEDD4 manifested as a correlation with a very poor prognosis and reduced CD8+ T-cell infiltration; however, as a result of depletion, NEDD4 enhanced CD8+ T-cells through indirect cytotoxicity, stabilized β-TrCP, led to YAP degradation, and altered the immunosuppressive extracellular matrix, increasing the penetration of CD8+ cells into the tumor; i.e., the use of the XMU-MP-10 small molecule in mouse models inhibited TNBC growth. The intra-tumor heterogeneous-stable relationship between heterogeneity and prognosis and immune infiltration in breast cancer was developed by Chinese scientists [2, 8], which is considered very important in solving one of the main problems of local analysis, as a small fragment of the tumor may not reflect the entire immune landscape. However, among the variants of such a reaction, there may be quite unexpected immune remodeling reactions, one of which was described by Y. Jiang et al. in their publication. [7, 8], who conducted research on the impact of peripheral nerve damage on macrophages with tumors in breast cancer, thereby showing that peripheral nerve damage can restructure TAMs and increase immunity deviation; however, as the authors themselves assert, this direction is not standard for clinical oncology, but it expands the understanding of factors capable of changing the local immune landscape, i.e., sometimes not only the tumor cell and not only the lymphocyte, but also the surrounding tissue neuroimmune environment may be important; moreover, the local immune profile of the metastatic focus may differ from the original tumor microenvironment and have its own prognostic load. [10, 12] concluded that there may be differences in the prognostic criteria of cancer cells involved in the formation of immune metastasis landscapes in the brain, which, as a predictor measured in a primary biopsy, should be evaluated as an early risk marker rather than a complete description of future metastatic niches.

Conclusion

The spatial organization of immune infiltration represents an increasingly important dimension in the assessment of the tumor immune microenvironment in breast cancer. The clinical and prognostic significance of immune-cell density cannot be interpreted independently of their anatomical distribution within the tumor, including their localization in the stroma, tumor islets, immune-exclusion zones, and metastatic niches. Therefore, tumors with comparable levels of immune infiltration may demonstrate substantially different biological behavior and responses to therapy.

Current evidence indicates that the tumor immune microenvironment is a dynamic and spatially heterogeneous system shaped not only by malignant cells and immune populations but also by the extracellular matrix, stromal components, vascular structures, and neuroimmune interactions. Molecular studies, including investigations of the NEDD4–β-TrCP/YAP/ECM axis, demonstrate that modulation of tumor-associated pathways may alter extracellular matrix properties and facilitate the recruitment and functional activity of cytotoxic CD8+ T cells. These findings support the concept that therapeutic targeting of tumor–immune interactions may convert an immunologically excluded tumor into a more permissive microenvironment for antitumor immunity.

The marked intratumoral heterogeneity of immune infiltration also represents an important limitation of conventional biopsy-based assessment. A single tissue fragment may not adequately reflect the overall immune landscape of a heterogeneous primary tumor and may therefore have limited predictive value for subsequent metastatic behavior. Furthermore, immune profiles in metastatic sites, particularly in the brain, may differ substantially from those of the primary tumor, indicating that immune-related biomarkers obtained from primary biopsies should be interpreted as indicators of risk rather than definitive descriptions of future metastatic niches.

Emerging evidence concerning neuroimmune interactions further expands the understanding of factors regulating the tumor microenvironment. Peripheral nerve injury and alterations in the local neural environment may influence tumor-associated macrophages and modify the balance between immunosuppressive and antitumor immune responses. Although these mechanisms remain insufficiently characterized for routine clinical application, they highlight the importance of considering the tumor microenvironment as an integrated multicellular and tissue-level ecosystem.

Consequently, the future development of prognostic and predictive biomarkers in breast cancer should move beyond simple quantification of immune-cell populations toward multidimensional characterization of their spatial distribution, functional state, molecular interactions, and tissue context. Integration of single-cell transcriptomics, spatial transcriptomics, multiplex imaging, digital pathology, and computational immune signatures may provide a more accurate representation of tumor–immune interactions and improve patient stratification. Such approaches may ultimately facilitate the identification of patients most likely to benefit from immunomodulatory and combination therapies and contribute to the development of personalized strategies for preventing and treating metastatic disease.

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