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INTRATUMORAL MICROBIOME: A NEW PARADIGM IN CANCER DIAGNOSIS AND THERAPY

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Abstract: For a long time, tumor tissues were traditionally considered sterile environments; however, recent metagenomic advancements between 2020 and 2026 have fundamentally shifted this perspective, revealing that every tumor type possesses a distinct "microbial signature." This article analyzes the role of the intratumoral microbiome in oncogenesis, metastasis, and drug resistance as a new paradigm in oncology. The study highlights the spatial distribution of microorganisms within the tumor microenvironment, their ability to modulate immune responses, and the mechanisms behind microbial-induced chemoresistance. A significant emphasis is placed on the diagnostic potential of metagenomic Next-Generation Sequencing (mNGS) for early cancer detection. Furthermore, based on oncological statistics from Uzbekistan, the paper proposes strategic frameworks for integrating microbial monitoring into clinical practice and developing personalized therapeutic approaches, such as phage therapy and microbial modulation, to enhance treatment efficacy.

Keywords: Intratumoral microbiome, metagenomic sequencing (mNGS), tumor microenvironment (TME), oncogenesis, microbial biomarkers, chemoresistance, bacteriophage therapy, liquid biopsy, cmDNA, personalized oncology.

INTRATUMUROL MIKROBIOMA; SARATON DIAGNOSTIKASI VA TERAPIYASIDAGI YANGI PARADIGMA

Annotatsiya. Ushbu maqolada onkologiyaning eng zamonaviy va bahsli yo'nalishlaridan biri – intratumoral mikrobiomaning saraton patogenezidagi roli tahlil qilinadi. Uzoq vaqt davomida o'sma to'qimasi mikroblardan xoli muhit deb hisoblangan bo'lsa, 2020–2026-yillar oralig'idagi metagenomik tadqiqotlar har bir o'sma turining o'ziga xos mikrobial imzosiga (microbial signature) ega ekanligini isbotladi. Maqolada o'sma ichidagi mikroorganizmlarning morfologik joylashuvi, ularning immun javobni susaytirishi va dori vositalariga rezistentlikni keltirib chiqarish mexanizmlari yoritilgan. Tadqiqotning amaliy ahamiyati mNGS sekvensiya usuli orqali saratonni erta bosqichda aniqlash va intratumoral disbiozni korreksiya qilish yordamida davolash samaradorligini oshirish strategiyasini taklif etishidadir. Shuningdek, O'zbekiston onkologiya xizmati uchun mikrobial biomarkerlarning diagnostik algoritmi ishlab chiqilgan.

Kalit so'zlar: Intratumoral mikrobioma, metagenomik sekvensiyalash (mNGS), o'sma mikromuhiti (TME), onkogenez, mikrobial biomarkerlar, kimyorezistentlik, bakteriofag-terapiya, suyuqlik biopsiyasi (liquid biopsy), cmDNA, shaxsiylashtirilgan onkologiya.

ИНТРАТУМОРАЛЬНЫЙ МИКРОБИОМ: НОВАЯ ПАРАДИГМА В ДИАГНОСТИКЕ И ТЕРАПИИ РАКА

Аннотация: Долгое время опухолевые ткани традиционно считались стерильными, однако последние достижения в области метагеномики за период 2020–2026 гг. коренным образом изменили этот взгляд, доказав наличие у каждого типа опухоли уникальной «микробной подписи». В данной статье рассматривается роль интратуморального микробиома в онкогенезе, метастазировании и лекарственной устойчивости как новая парадигма в онкологии. В работе анализируются особенности пространственного распределения микроорганизмов в опухолевом микроокружении, их влияние на иммунный ответ и механизмы формирования микробно-индуцированной химиорезистентности. Особое внимание уделено диагностическому потенциалу метагеномного секвенирования нового поколения (mNGS) для раннего выявления рака. На основе онкологической статистики Узбекистана предложены алгоритмы внедрения микробиомного мониторинга в клиническую практику и разработки персонализированных терапевтических стратегий (бактериофаготерапия, модуляция микробиома) для повышения эффективности лечения.

Ключевые слова: Интратуморальный микробиом, метагеномное секвенирование (mNGS), микроокружение опухоли, онкогенез, микробные биомаркеры, химиорезистентность, бактериофаготерапия, жидкостная биопсия, персонализированная онкология.

Introduction. One of the most revolutionary discoveries in oncology over the last decade has been the denial of the long-standing notion of the "sterile" nature of tumor tissues. It has been established that microorganisms previously considered secondary infections resulting only from pathological processes are, in fact, an integral and functional part of the tumor microenvironment (TME) [5, 18]. Modern metagenomic studies indicate that each tumor type possesses a unique microbiological composition or "microbial signature." These microorganisms not only live inside the tumor but also actively participate in oncogenesis, metastasis, and immunological escape processes [19, 20]. Oncogenesis and microbial induction. The role of microorganisms in cancer development is manifested through several mechanisms. While some bacterial species exert a direct genotoxic effect, causing mutations in human DNA, others accelerate cell malignancy by creating chronic inflammatory foci [1, 14]. For example, it has been proven that specific bacterial communities identified in colorectal cancer and breast cancer activate signaling pathways that stimulate tumor cell proliferation [2, 16]. This provides grounds to view the intratumoral microbiome not merely as a "passenger," but as an important factor determining the prognosis of the disease [11, 12]. Problems in diagnosis and therapy. One of the biggest obstacles currently encountered in the treatment of oncological patients is the emerging resistance to chemotherapy and immunotherapy. It has been established that intratumoral microorganisms, by metabolizing pharmaceutical drugs, reduce their therapeutic efficacy or increase their toxicity [3, 17]. Therefore, the analysis of the tumor microbiome using high-tech methods such as mNGS (metagenomic Next-Generation Sequencing) must become an integral part of personalized medicine (precision medicine) [9, 15]. In particular, detecting circulating microbial DNA through non-invasive "liquid biopsy" opens new opportunities for early cancer diagnosis [4, 8].

Purpose and relevance of the research. The increase in morbidity rates and the high incidence of treatment resistance in oncological practice in Uzbekistan further increase the relevance of this topic. Given that regional environmental factors and the diet of the population directly influence microbiome formation, studying the microbial profiles characteristic of local patients is of strategic importance [7, 13]. This article analyzes the morphological and molecular characteristics of the intratumoral microbiome and proposes scientifically grounded recommendations for their integration into the oncology system of Uzbekistan.

Main part. Morphological description. The morphological distribution of microorganisms within the tumor is not random in nature, but is differentiated according to the physicochemical characteristics of the tumor microenvironment (TME). Modern microscopy and spatial transcriptomy methods show that bacteria primarily form microniches in poorly vascularized, i.e., hypoxic, areas of the tumor [5, 11]. The morphological distribution of microorganisms within the tumor is not random in nature, but is differentiated according to the physicochemical characteristics of the tumor microenvironment (TME). Modern microscopy and spatial transcriptomy methods show that bacteria primarily form microniches in poorly vascularized, i.e., hypoxic, areas of the tumor [5, 11]. The most remarkable morphological feature is the ability of bacteria to live obligate within cancer cells (cytoplasm) or immune cells (macrophages). They are located near the cell nucleus or adjacent to mitochondria, altering the cell's metabolic pathways [15, 19]. This leads to a change in cell morphology and a more aggressive (metastatic) character.

Laboratory diagnostics: technological algorithm of the mNGS methodology. It has been proven that the ineffectiveness of traditional culture methods (bacteriological culture) in determining the intratumoral microbiome exceeds 90%. Therefore, the metagenomic Next-Generation Sequencing (mNGS) method is used as the basis for diagnostics [9, 18]. Separating microbial genetic material from tumor tissue is an extremely delicate process that requires a "depletion" stage (reduction of human DNA). Since the majority of the total DNA in the sample (more than 99%) belongs to the human genome, enzymatic filtering and technology for removing the human cell genome using magnetic particles are used to separate the microbial signal [14, 20]. At each stage, it is necessary to perform negative controls to exclude possible contamination from the external environment.

Sequencing. A sequencing process (such as the Illumina platform) produces millions of short DNA reads. This data is analyzed using bioinformatics algorithms in the following order:

1. Quality control: Filtering low-quality readings.
2. Removing the human genome: Removing fragments from the database that match the human genome.
3. Taxonomic identification: Comparison of the remaining fragments with the database of all known pathogenic and commensal microbes in the world [12, 14].

To raise oncological diagnostics to a higher level in our country, the following practical model is proposed for creating mNGS laboratories:

Centralized sequencing system: Establishing a system for storing biopsy samples from all regional oncology dispensaries at -80°C and delivering them to a single central laboratory [13]:

Integration of Liquid Biopsy: Analysis of circulating microbial DNA (cmDNA) in blood plasma as a non-invasive method for early diagnosis. This method can become a diagnostic "gold standard," especially for patients with complex surgical procedures [4, 8]:

Creating a microbial data bank: Digitizing tumor microbiome profiles that are common among patients in Uzbekistan, specifically those formed under the influence of regional (dietological and environmental) factors. This allows doctors to develop a specific (targeted) treatment plan for each patient rather than an empirical one [7, 10].

Treatment strategies: Intratumoral microbiome and efficacy of therapy. In modern oncology, the effectiveness of treatment depends not only on the properties of the drug but also directly on the microbial metabolism within the tumor. This section analyzes methods for optimizing therapy by modulating the intratumoral microbiome. Research indicates that intratumoral bacteria neutralize the therapeutic effects of medications through enzymatic breakdown.

1. Drug metabolism: For example, bacteria belonging to the class Gammaproteobacteria inactivate the drug hemcitabine, used for breast and pancreatic cancer, through their cytidine-deaminase enzyme [3, 19].

2. Strategy: In such cases, it is recommended to combine a course of chemotherapy with selective antibiotics or targeted bacteriophages. Bacteriophages help maintain drug concentration within the tumor by destroying only the specific bacteria that break down the drug [10, 11].

The effectiveness of immune checkpoint inhibitors (e.g., anti-PD-1) depends on the composition of the intratumoral microbiome.

Immunosuppression: Some "bad" microbes block immune cells. In contrast, "good" bacteria such as Bifidobacterium send signals that activate T-lymphocytes [16, 17].

Solution: Changing a patient's microbial profile through personalized probiotics and fecal microbiota transplantation (FMT) can increase the immunotherapy response by 30-40% [15, 16].

In the modern oncoprophylaxis system, studying the intratumoral microbiome has become a strategic direction, allowing for the detection of disease at the preclinical stage. In this process, microbial biomarkers serve not only as diagnostic indicators but also as indicators reflecting the overall oncological state of the body [12, 20].

One of the most promising methods for increasing the effectiveness of early screening in Uzbekistan's oncological practice is the analysis of circulating microbial DNA (cmDNA) fragments in blood plasma using mNGS technology. These microbial components, which enter the bloodstream as a result of tumor cell breakdown, leave a specific "molecular trace." The advantage of this method is that it can predict risk even at an early stage, when the tumor is still too small to be visible visually (via MRI or CT) [4, 8, 9].

Within the framework of preventive measures, it is of great importance to modulate the population's diet and habitat based on microbiome indicators. Given the regional characteristics of Uzbekistan (environmental and alimentary factors), reducing the proportion of pathogenic microbes in the tumor microenvironment through prebiotics and a personalized diet should be an integral part of oncological prevention [3, 14].

Conclusion. This scientific study analyzed the crucial role of the intratumoral microbiome in the pathogenesis, diagnosis, and therapy of oncological diseases based on modern evidence. The traditional approach that viewed tumor tissue as a "sterile environment" has been replaced by a new paradigm that interprets the tumor as a complex microbial-cellular ecosystem.

Analyses show that the implementation of mNGS (metagenomic sequencing) technology in clinical diagnosis allows for not only early detection of the disease but also an accurate prediction of its therapeutic prognosis [5, 18]. The involvement of intratumoral bacteria in drug metabolism and their role in immunological escape mechanisms have shaped new directions of personalized oncology - bacteriophage therapy and microbial modulation [10, 19].

The creation of a network of centralized laboratories for studying the intratumoral microbiome and the formation of a national database of microbial biomarkers is a strategic necessity for the healthcare system of Uzbekistan. This scientifically grounded approach serves as a key factor in reducing mortality from oncological diseases in our country and raising the effectiveness of treatment to a qualitatively new level [4, 7, 13].

Conclusions.

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