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REVIEW

The role of tumor stem cells and the immune microenvironment in the pathogenesis of lung cancer: mechanisms of interaction and research prospects

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ABSTRACT

Despite significant advances in the treatment of malignant neoplasms, the issue of therapy resistance mediated by cancer stem cells (CSCs) necessitates the development of new treatment strategies. Studying the role of CSCs and the immune microenvironment in the pathogenesis of cancer, particularly non-small cell lung cancer (NSCLC), is a pressing issue in modern oncology. This paper is based on an extensive analysis of recent research and aims to study the mechanisms underlying the development of NSCLC.

The origin of CSCs, their markers, and the main signaling pathways involved in regulating their activity are considered. Special attention is paid to the influence of CSCs on the progression of lung cancer and the mechanisms underlying their therapy-mediated resistance. Various approaches to treating lung cancer targeting CSCs, focusing on targeted therapy aimed at specific molecular targets, are highlighted.

The important role of the tumor immune microenvironment in the pathogenesis of lung cancer and its impact on CSCs is emphasized. Mechanisms of immune response regulation in tumors and the potential use of immunotherapy to improve lung cancer treatment outcomes are discussed. The article also reviews modern diagnostic and treatment methods, including molecular-genetic and immunohistochemical approaches.

This paper work represents a review of current knowledge on the mechanisms of lung cancer development and is significant for understanding tumor biology and developing new treatment methods. The need for an interdisciplinary approach and comprehensive use of modern diagnostic and therapeutic methods to improve the prognosis and survival rates of NSCLC patients is emphasized. Special attention is given to the prospects of using combined therapeutic approaches, including targeted drugs and immunotherapy, aimed at suppressing CSC activity and modifying the tumor microenvironment.

In conclusion, a deep understanding of the molecular mechanisms regulating CSC activity and their interaction with the tumor microenvironment opens new opportunities for developing effective treatment strategies. This review underscores the need for further research in this area to ensure more successful treatment and improved quality of life for lung cancer patients.

Keywords: cancer stem cells, immune microenvironment, lung cancer, non-small cell lung cancer, therapy resistance, targeted therapy, immunotherapy

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ОБЗОР

Роль опухолевых стволовых клеток и иммунного микроокружения в патогенезе рака легкого: механизмы взаимодействия и перспективы исследований

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РЕЗЮМЕ

Несмотря на значительные успехи в лечении злокачественных новообразований, проблема резистентности к терапии, опосредованной опухолевыми стволовыми клетками (ОСК), диктует необходимость разработки новых стратегий лечения. Изучение роли ОСК и иммунного микроокружения в патогенезе рака, особенно немелкоклеточного рака легкого (НМРЛ), является актуальным вопросом современной онкологии. Настоящая работа основана на обширном анализе последних исследований и направлена на изучение механизмов, лежащих в основе развития НМРЛ. Рассматривается происхождение ОСК, их маркеры и основные сигнальные пути, участвующие в регуляции активности данного пула клеток. Особое внимание уделяется влиянию ОСК на прогрессирование рака легкого и механизмам, обусловливающим устойчивость к терапии. Освещаются различные подходы к лечению рака легкого, ориентированные на ОСК, с акцентом на таргетную терапию, направленную на специфические молекулярные мишени.

Отмечается важная роль иммунного микроокружения опухоли в патогенезе рака легкого и его влияния на ОСК. Обсуждаются механизмы регуляции иммунных реакций в опухоли и потенциал использования иммунотерапии для улучшения результатов лечения рака легкого. В статье также рассматриваются современные методы диагностики и лечения, включающие молекулярно-генетические и иммуногистохимические подходы.

Работа представляет собой обзор современных знаний о механизмах развития рака легкого и имеет важное значение для понимания биологии опухолей и разработки новых методов лечения. Подчеркивается необходимость междисциплинарного подхода и комплексного использования современных диагностических и терапевтических методов для улучшения прогнозов и выживаемости пациентов с НМРЛ. Особое внимание уделено перспективам использования комбинированных терапевтических подходов, включающих таргетные препараты и иммунотерапию, направленные на подавление активности ОСК и модификацию опухолевого микроокружения.

В заключение, глубокое понимание молекулярных механизмов, регулирующих деятельность ОСК, и их взаимодействие с микроокружением опухоли открывает новые возможности для разработки эффективных стратегий лечения. Данный обзор подчеркивает необходимость дальнейших исследований в этой области, чтобы обеспечить более успешное лечение и повышение качества жизни пациентов с раком легкого.

Ключевые слова: опухолевые стволовые клетки, иммунное микроокружение, рак легкого, немелкоклеточный рак легкого, резистентность к терапии, таргетная терапия, иммунотерапия

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INTRODUCTION

Lung cancer is one of the main problems of modern oncology, and it is hoped that progress in treatment can be achieved by improving our understanding of the molecular basis and biology of the tumor, especially at the level of cells that initiate the tumor process. The most common type of lung cancer is its non–small cell variants (NSCLC), which account for about 90 % of lung cancers, the rest are small cell lung cancer (SCLC). NSCLC includes three histological subtypes: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. In most patients with NSCLC, the diagnosis is made at a late stage, when various treatment methods are ineffective [1].

In 2015, a new classification of lung tumors was proposed by the World Health Organization [2], which includes appropriate histopathological and immunohistochemical data, which can be obtained not only from surgical material, but also from biopsies and cytological material [1, 2]. This is especially important due to the fact that about 70 % of patients with lung cancer are in the late stages of the disease, when the process is considered inoperable [1, 2]. For resectable lung tumors, it is important to diagnose tumors *in situ* and minimally invasive operations, in which the probability of recurrence-free survival after complete resection is 100 % [2].

However, in most cases, clinicians are dealing with locally advanced NSCLC, the recurrence and generalization of which, even after the successful surgical stage of treatment, is the main cause of death. These processes, as well as the development of chemo- and radioresistance, according to modern concepts, are not least associated with the presence of stem cells (CSC) in the tumor, a minor subpopulation that ensures their preservation and survival. Since CSC biomarkers can be used for diagnosis, targeted therapy and prediction of the course of the disease, assessing the significance of known ones and searching for new ones seems relevant. Potential markers for NSCLC include surface markers (CD44, CD133, EpCAM, ABCG2), as well as intracellular markers (ALDH, SOX2). The literature discusses not only their diagnostic and prognostic significance in NSCLC, but also the most informative methods of determination, including molecular genetic and immunohistochemical [3, 4], as well as the possibility of using them as targets for therapy [5, 6]. Currently, the noticeable increase in the number of publications on CSC research indicates the relevance of this topic in the scientific community. The valuable scientific data provided by the literature on the mechanisms of oncogenesis and the prospects for the treatment of lung cancer based on them determine the need for a more in-depth scientific analysis of the role of CSC in the pathogenesis of NSCLC. The modern literature provides numerous data on the biology of CSC, their role in the progression of NSCLC, and the development of its resistance to various treatment methods [5, 6].

The purpose of the review is to analyze the current level of scientific knowledge about the role of CSC in NSCLC and the clinical use of these data. The main focus is on identifying the key mechanisms of these cells' involvement in oncogenesis, their interaction with the immune microenvironment of the tumor, as well as developing treatment strategies aimed at CSC in NSCLC. The data obtained as a result of the review, in our opinion, can serve as a foundation for further research and development of promising treatments for NSCLC.

CSC in NSCLC: origin, markers, signaling pathways, role in progression

According to modern concepts, cancer stem cells (CSC) arise from normal tissue-specific stem cells of the original tissues; their main function is to maintain and regulate the processes of growth, development and repair of tissues in the body. CSC are capable of self-renewal, differentiation [7] and proliferation [8] and cause such adverse properties as: chemoresistance, recurrence and metastasis [7]. As a rule, a high number of CSC is associated with aggressive tumor growth and unfavorable clinical outcomes [8], although CSC themselves have low proliferative activity. Reviews of CSC note their common characteristics for various malignant tumors involved in the development of resistance to therapy and are devoted to the development of new therapeutic strategies [7–10].

Inducing epithelial-mesenchymal transition transcription factors (EMF-FT), including SNAIL and SLUG, and induced by signaling pathways such as TGFß, Wnt and Notch, tumor cells begin to show

distinctive signs of CSC: oncogenicity, invasiveness and resistance to basic treatments [11]. Other common signaling pathways involved in CSC include Hedgehog (Hh), PI3K/Akt/mTOR, and NF-κβ [12]. Although many of these pathways are also observed in normal cells and non-stem cancer cells [13], their altered activity, along with certain membrane markers and transcription factors, is a distinctive feature of CSC. Some of these characteristics, such as the high expression of CD44+, CD133+, ATP-binding cassette transporters (ABC), epithelial cell adhesion molecules (EpCAM), aldehyde dehydrogenase 1 (ALDH1), and transcription factors Oct4 and Sox2, are common to CSC in many forms of cancer [11]. Recognition of such similarities may reveal new therapeutic possibilities for influencing common markers or pathways, and thus contribute to the development of effective treatments targeting CSC.

Identification of the origin of tumor stem cells (CSC) in the lungs is a difficult task, since the epithelium of the trachea and bronchioles is at rest and has low proliferative activity [11]. The most common hypothesis states that CSC arise from normal tissue-specific stem cells. Squamous cell lung cancer originates from the basal cells of the proximal respiratory tract (trachea and bronchi) [12]. Clara cells in squamous cell lung cancer are also able to exhibit stem properties, and adenocarcinoma is associated with normal stem cells from the junction of bronchoalveolar ducts [12].

Although the available knowledge about the functions of lung CSC is limited, a number of CSC markers belonging to differentiation clusters (CD) have been proposed. Many studies have confirmed the presence of the following molecules on lung CSC: CD133, CD44, CD90, EpCAM, CXCR4 [14, 15]. However, it should be noted that impaired expression of these markers is characteristic not only of NSCLC, but also of many types of cancers.

EpCAM is a transmembrane glycoprotein expressed in most human carcinomas; high expression is noted in rapidly proliferating tumors of epithelial origin [12].

CD133 is a marker widely used to identify stem cells in both tumor and normal tissues. The CD133 transcription process is regulated by five promoters, and the 5P5 promoter plays a crucial role in CD133 expression in the CSC [16]. Some studies have characterized CD133+ cells in NSCLC [11, 15]. For example, Eramo et al. The presence of CD133 in NSCLC was detected in a small amount of less than 1 % [16]. CD133+ cells were able to form tumor spheroids *in vitro* in about 30 % of cases when grown in a serum-free medium; CD133+ cells derived from tumor spheroids are capable of inducing tumors with histological signs similar to those of the original tumor when inoculated to immunodeficient mice [16]. Moreover, CD133+ cells show resistance to chemotherapy due to the expression of high levels of ATP-binding G2 [17].

CD44 (P-glycoprotein 1), a transmembrane type I glycoprotein, belongs to the family of cell adhesion molecules, is a receptor for hyaluronic acid, when interacting with which cell detachment, metastasis and invasion can occur. CD44 is responsible for various functions such as cell differentiation, survival, migration, proliferation. Studies have demonstrated that CD44 plays a crucial role in ensuring self-renewal and resistance to apoptosis of CSC [11, 18]. Mutations in the key regulator of apoptosis, the p53 gene, may be associated with high CD44 expression in pancreatic cancer [19]. CD44+ adenocarcinoma and squamous cell lung cancer cells demonstrate the ability to form spheroid bodies *in vitro* [20] and lead to tumor formation *in vivo* when administered to mice with immunodeficiency [14, 21].

Studies have shown that in lung cancer, CD44 expression in NSCLC cells is higher than in SCLC, and in squamous cell lung cancer its highest level was observed [22]. CD44 regulates several signaling pathways contributing to cancer progression, including Notch, Hedgehog (HH), Wnt, STAT3, Hippo, JNK and RhoGTPase, and It is a co-receptor involved in the signaling pathways of tyrosine kinase receptors [23, 24]. In addition, CD44 is a key mediator of adhesion between endothelial cells, while playing an important role in pathological angiogenesis [25]. CD44 can also promote tumor proliferation and evasion of immunity by stimulating PD-L1 expression on the surface of tumor cells [26]. Cells coexpressing CD44 and ALDH, which is typical for squamous cell lung cancer, always exhibit a high ability for self-renewal, increased migration and tumorigenicity [27].

CD90 is a glycoprotein anchored by glycosylphosphatidylinositol, expressed mainly in leukocytes and participates in cell-matrix and cell-cell interactions.

Although CD90 is known as a marker for various types of CSC, its potential role as a marker for NSCLC has not yet been fully described [11, 28]. It has been reported that CD44 and CD90 coexpressed CSC can be detected in primary pancreatic cancer cell lines [19]. Mutations activating CD90 expression are not described in the literature, however, in a mouse model it has been shown that DNA methylation plays a role in stimulating the expression of this molecule. Serial xenotransplantation of EpCAM+CD90+ NSCLC cells (adenocarcinoma and squamous cell carcinoma) to mice with immunodeficiency revealed rapid growth of these cells during heterotopic grafting [14].

CXCR4 is a chemokine receptor present on the surface of hematopoietic stem cells involved in the formation of premetastatic niches in the bone marrow [29]. The CXCR4/CXCL12 pathway plays a role in tumor metastasis, induction of angiogenesis, and development of resistance to apoptosis. Moreover, CXCR4 is present on circulating tumor cells released from tumors into peripheral blood, which induces their spread to distant CXCL12-positive sites [30]. The expression of CXCR4 is regulated by the nuclear respiratory factor NRF, a mutation in which can lead to higher expression of CXCR4 [31]. CXCR4+ cells isolated from NSCLC lines exhibited the properties of CSC *in vitro*: they formed tumor spheroids, had the ability to self-renew, and demonstrated radiation resistance [32].

Taking into account the described properties of CSC, their determination in tumors, in particular lung tumors, is an urgent scientific and clinical task [11, 33].

Due to the fact that CSC markers can also be expressed on normal stem cells necessary for self-renewal and tissue regeneration, the belonging of stem cells to tumor cells can be determined not only by the expression of membrane markers, transcription factors and signaling pathways, but also by the results of some functional tests, which, despite their certain complexity, They are informative, especially for research purposes, as well as for conducting preclinical trials of potential drugs aimed at CSC. In addition to the mentioned spheroid formation test, organoids obtained from patients with NSCLC can become a tool for such studies, due to their ability to recreate the tissue architecture and maintain genomic changes in primary tumors during long-term *in vitro* growth [34]. The organoid culture method allows CSC to be propagated *in vitro*, reflecting the complexity of tumor formation using tumor tissues. Moreover, the culture of organoids allows for the functional analysis of CSC, including their genetic engineering using CRISPR/Cas9-mediated genome editing [35]. Organoids obtained from the patient can be used to identify signs of CSC resistance to treatment. Most organoid models for cancer research are applicable to adenocarcinomas of different localizations [36]. However, as the understanding of the mechanisms of tumor development expands, organoids may become a more widely used tool [36]. Thus, in combination with other *in vivo* experiments, such as xenotransplantation of CSC, organoid cultures, human CSC have high potential to improve understanding of cancer biology [37].

CSC-mediated resistance to treatment and the possibility of overcoming it

Drug resistance has been described as one of the most serious problems in the treatment of cancer, while the multidrug resistance of CSC, which ensures the chemoresistance of the tumor as a whole, is considered the main reason for the ineffectiveness of chemotherapy [38]. The mechanisms that cause chemoresistance include ABC transporters, pumps for efflux of chemotherapy drugs and ALDH1 [38].

CSC radioresistance develops due to the inhibition of apoptosis through the synthesis of antiapoptotic proteins, increased DNA repair and the ability to remove free radicals, slowing down the kinetics of the cell cycle, and transformation of non-stem tumor cells into CSC [39].

It is believed that the resistance of CSC to traditional radiation therapy and chemotherapy is associated with the activation of various signaling pathways in them, such as: Wnt, Notch and Hedgehog, which are involved in increasing oncogenicity and tumor invasiveness [40]. Currently, there is increasing evidence that these pathways are being deregulated and mutated in the CSC [41]. Aberrant Wnt signaling is found in many cancers, including NSCLC, especially adenocarcinomas [42], in which Wnt-reactive cells demonstrated proliferative potential and progression, which suggests that they possess the characteristics of CSC [42]. A growing number of publications confirm the association of abnormal regulation of Notch signaling with vari-

ous types of malignant neoplasms, including NSCLC. The Notch signaling pathway plays a role in stem cell maintenance in NSCLC; aberration in this pathway may lead to an increase in the number of CSC resistant to platinum drug therapy [42]. It was reported that the increased activity of Notch was associated with the formation of tumor spheroids *in vivo* [40]. The same authors associate Notch activity with a worse prognosis in patients with adenocarcinoma, which suggests a potential role of inhibition of Notch activity as a new therapeutic approach [41]. In NSCLC, the Hedgehog pathway is closely related to CSC [41, 42] and is involved in the formation of tumor drug resistance to targeted, chemo- and radiation therapy [42].

Some approaches to overcoming resistance mediated by OSC are also described in the literature. Some combinations of chemo- and targeted drugs have the property of inhibiting OSC in NSCLC, for example, the combination of trifluorperazine with gefitinib or cisplatin reduces the regulation of CD133 and CD44, reducing drug resistance and increasing the response to therapy [43].

It was found that the miR-29c tumor suppressor is significantly suppressed in radioresistant NSCLC CSC, but this resistance was overcome by restoring its expression, activating apoptosis, and suppressing the regulation of Bcl-2 and Mcl-1 target genes by this suppressor [44].

Yin and colleagues [45] conducted a study in which they found that certain cells in the lungs, called bronchoalveolar stem cells, transform into tumor stem cells due to two factors: the lack of a protein that usually protects the cell from becoming a tumor (Gprc5a), and exposure to nicotine-derived substances. These cells have a set of special markers (SPA+, CC10+, EGFR+, Abcg2+), thanks to which they can be updated. The researchers also found that cancer can develop not only from these stem cells, which underscores the need to study different cell types to understand the mechanisms of lung cancer development [45].

Approaches to the treatment of NSCLC targeted at CSC

The development of drugs for targeted therapy of oncological diseases is a consequence of the discovery of specific molecular genetic targets and receptors responsible for progression and chemoresistance. The CSC associated with these processes are considered in the literature as a promising target [46].

Three main approaches to CSC targeting have been proposed: identification of new CSC biomarkers, modification of their microenvironment, and sensitization to traditional medicines [8]. Combined treatment methods have been found to be the most effective [8, 9, 13–15]. Makena et al. Other therapeutic approaches have been investigated, including therapies that target dormant CSC and immunotherapy, but noted that additional research is needed in these new areas [8]. Dongre and Weinberg proposed inducing reverse EMF as a potential therapeutic strategy, representing promising approaches to reduce the number of CSC inside tumors and increase their sensitivity to various types of treatment, including chemotherapy, radiotherapy and immunotherapy [10].

It is known that chelation of intracellular iron is one of the targets of exposure to CSC, due to its ability to successfully restrain cell proliferation, as has been demonstrated in studies on models of breast and pancreatic cancer. However, despite these encouraging data, the efficacy and mechanisms of action of iron chelation in the context of squamous cell lung cancer remain poorly understood, emphasizing the need for further research in this area [47].

In the literature, increasing attention is being paid to the role of miRNAs and long non-coding RNAs (lncRNAs) in the regulation of transcription factors and pathways present in CSC [48]. It is known that the miR-17–92 cluster, acting as a stimulator of tumor growth, also has a noticeable effect on the development of lung cancer, which leads to the study of the relationship between microRNAs and tumor development, definitely emphasizing their important role in cancer biology. lncRNAs control gene expression and are involved in the maintenance and reproduction of CSC by activation of the Wnt/β-catenin and IL6/STAT3 signaling pathways. Consequently, lncRNAs can be used as predictors of an unfavorable prognosis for cancer patients and, thus, can play a major role in the eradication of CSC [48].

It has been repeatedly noted in the literature that the acquisition of "stemness" by NSCLC tumors is a negative prognostic factor of survival. Loss of PTEN expression, for example, has important consequences for the NSCLC, and is also an inde-

pendent prognostic factor for the overall survival of patients with NSCLC [49]. Similarly, patients with stage IIIB/IV NSCLC with tumors enriched with CD133+ lung cancer stem cells tend to have a shorter progression-free survival after platinum chemotherapy [16].

Nevertheless, a serious problem is the identification of "silent" CSC, i. e., those that do not express well-known markers by which they can be identified. Conversely, many surface markers of CSC, such as r2R4 and CD34, are also expressed by normal embryonic or adult stem cells, while others, such as CD44 variants, are widely expressed even in normal cells of various tissues [16]. Thus, the identification of more specific markers of OSC remains a key goal for the development of more effective treatment strategies [16].

CSC and the tumor microenvironment

The tumor microenvironment consists of a variety of non-malignant cells, including tumor-associated macrophages (M1/M2), tumor-infiltrating lymphocytes, including regulatory T cells (Tregs), dendritic cells (DC), natural killer cells (NK) and myeloid suppressor cells (MDSC). These cells interact with each other and with tumor cells, organizing an immune response, and can influence the behavior of other cells in the tumor microenvironment either by direct regulation or with the help of produced mediators (cytokines, chemokines) interacting with receptors. These interactions can be mediated by both paracrine and autocrine pathways, as well as activation of co-inhibition or coactivation receptors. Cells are able to modulate the secretion of chemokines and cytokines with an imbalance between those that perform suppressive and activating immune functions. The source of intercellular communication is a complex network of cytokines, chemokines, growth factors, inflammatory mediators and enzymes. In general, the suppressive function of the immune system prevails in the tumor microenvironment, and the process of its formation is called "tumor immunoredition" [50, 51].

Some studies have also shown that CSC can activate mechanisms that allow tumors to avoid attacks from immune cells, for example, loss of cancer antigen expression and activation of oncogenic pathways leading to the development of tolerance [52]. CSC can also contribute to the creation of an immunosuppressive environment. Some studies have demonstrated that CSC derived from various solid tumors, including glioblastoma multiforme and melanoma, secrete various immunosuppressive cytokines such as IL-13, IL-10, TGF-β, GDF-15, PGE2 and galectin-3. These cytokines can protect the tumor microenvironment from effector immune cells. CSC can induce differentiation of mature DC or Treg by transforming growth factor beta (TGF-β) [51]. The tumor microenvironment (MO, TME) is an area that can simultaneously regulate tumor development and cell self-renewal. CSC can contribute to the development of the local vascular network and angiogenesis due to their production of vascular endothelial growth factor (VEGF) [52]. MO actively interacts with CSC, providing a basis for the induction or differentiation of immune cells that suppress tumor growth, including suppressive macrophages (M2-type) or regulatory T cells (Tregs) [51, 52]. In addition, the population of tumor-associated macrophages (TAMs) increases the activity of transcription factors such as Sox, Oct-4 and Nanog, which support the CSC in a state of proliferation and self-renewal. MDSCs are a heterogeneous group of immature myeloid cells that play a role in immune response and tissue remodeling. It has been shown that MDSCs have proangiogenic activity and induce the production of metalloproteinases, which can contribute to the formation of "metastatic" niches that facilitate the colonization of tissues by tumor cells. The tumor microenvironment induces differentiation of CD4+ T cells into various subpopulations of T cells, such as Tregs and T-17 cells (Th17). The exact role of Th17 cells in tumor immunity remains unclear, apparently depending on the tumor stage and histological subtype. Interestingly, recent reports suggest that Tregs, under certain conditions, express IL-17, which, together with hypoxia, plays a crucial role in the regulation of cancer stem cells. However, the interactions between CSC and Treg, which significantly contribute to the suppression of immunity in the tumor microenvironment, are still poorly understood.

The location, type, density and functional status of immune cells (T cells, B cells, NK cells, DC cells, macrophages, neutrophils, monocytes and

mast cells) in the immune microenvironment of a tumor characterize its heterogeneity. Using single-cell RNA sequencing technology, significant differences between the immune microenvironment of adenocarcinoma and squamous cell lung cancer were confirmed [53]. This diversity affects the occurrence, growth of tumors, as well as the response to treatment. Therefore, many studies have focused on studying the immune microenvironment of the tumor. Patients receiving neoadjuvant chemotherapy had higher levels of PD-L1 expression and T-cell subpopulations than those who did not receive neoadjuvant chemotherapy for NSCLC [54]. In a study by Peng et al. [55] analysis of 26 types of immune cells in the immunological microenvironment of the tumor in 681 NSCLC samples showed that patients with low levels of immune cells and a predominance of macrophages in the tumor had a shorter recurrence-free survival. The total proportion and characteristics of T cells in a tumor are the main factors determining the development of tumor progression. Depletion of T cells occurs immediately after oncogene initiation and is the cause of patients' insensitivity to anti-PD-1/PD-L1 therapy. During the depletion of T cells, inhibitory receptors such as CTLA-4, TIM-3, LAG-3 and PD-1 are usually overexpressed on T cells, and effector cytokines such as IFN-γ decrease [55].

It is known that the immune microenvironment of a tumor can be altered by epigenetic immune editing. Epigenetic changes can be caused by inflammation [56]. The hypoxia-adapted cellular phenotype is maintained in the tumor microenvironment due to the synergistic effect of epigenetic factors and hypoxia-induced transcription factors (HIF). Under conditions of hypoxia, intensive DNA methylation and histone modification occur, which promotes tumor growth, increases invasiveness and supports the stemness of cancer cells [56].

Currently, tumor-associated macrophages (TAM) are the most widely studied immunosuppressive cells [55]. TAMs are collected at the site of injury after identification of chemokines, cytokines, inflammatory mediators, pathogens, or damage-related molecular structures (damps). There are TAM phenotypes: M1 and M2. The M1 phenotype is characterized by antitumor activity and, as a rule, is represented by activated macrophages. After epigenetic reprogramming, M2 phenotype macrophages are formed by differentiation and polarization, which can potentially contribute to the development of tumors [55]. Phenotypic M2 supports tumor stem cell populations by secreting chemokines and ligands that activate stem cell development pathways [57]. Enhanced methylation modifications and decreased chemokine expression in TAMs under hypoxic conditions alter the immune landscape in TME [57]. It was found that NEAT1 is highly expressed in lung cancer and interacts with DNA methyltransferase DNMT1, regulating the infiltration of lung cancer by cytotoxic T cells by inhibiting the cGAS/STING pathway [58]. The proliferation, differentiation and survival of T cells depend on the activity of EZH2 enhancers, which are important epigenetic regulators of gene expression. It is noteworthy that GSK126, an EZH2 inhibitor, can stimulate the synthesis of Th1 chemokines CXCL9 and CXCL10 in tumors and enhance their infiltration by CD8+ T cells [59]. The presence of tumor-infiltrating B lymphocytes can be observed at all stages of lung cancer development, and it has been found that histone modification can also increase B cell infiltration [56]. Epigenetic suppression of NKG2DL in SCLC leads to the absence of stimulating signals for activation of NK cells, thereby increasing the aggressiveness and metastasis of SCLC [60].

These studies show that the tumor microenvironment plays an important role in the progression of lung cancer. In particular, the condition of lung cancer stem cells, which is influenced by epigenetic and immune changes in the tumor microenvironment, is an important cause of treatment resistance and the development of cancer recurrence. Potential targets for antitumor effects may be not only molecules present in tumor cells, but also the tumor microenvironment, primarily immune and cytokine.

CONCLUSION

Understanding the biology of tumor stem cells is one of the most important tasks in clinical oncology. Recent studies have shown that these cells play a significant role in the development of solid tumors, such as lung cancer, which is becoming more common.

The importance of tumor stem cells in lung cancer is manifested not only through their ability to form tumors, but also through interaction with the tumor microenvironment, which plays a critical role in tumor development and its response to therapy. The tumor microenvironment, consisting of immune cells, fibroblasts, vascular network and extracellular matrix, creates conditions that support the growth and survival of tumor stem cells, and also contributes to the development of resistance to chemotherapy and radiation therapy.

The integration of knowledge about the behavior of tumor stem cells and interaction with their microenvironment in the context of lung cancer in clinical practice opens up new prospects for improving treatment and prognosis of patients. Understanding the molecular mechanisms that regulate the activity and functionality of these cells, as well as their interaction with the microenvironment, offers new opportunities for developing treatments aimed at both suppressing the activity of tumor stem cells and modifying the microenvironment to fight the tumor. Successful research in this area may be the key to more effective control of lung tumors and improving the quality of life of patients.

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