DOI: 10.53469/jcmp.2025.07(09).09

Research Progress on the Role of Cancer-related Fibroblasts in the Metastasis and Drug Resistance of Non-small Cell Lung Cancer

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Abstract: ***Objective: To summarize the latest research progress and related mechanisms of cancer associated fibroblasts (CAFs) in the invasion and metastasis of non-small cell lung cancer, and to provide new diagnostic and therapeutic ideas and basis for the treatment of non-small cell lung cancer metastasis patients. Method: Retrieve recent literature on the study of CAFs in non-small cell lung cancer and conduct a review. Result: CAFs are the main stromal cells in the tumor microenvironment (TME), and by altering the tumor microenvironment, the biological characteristics of CAFs can be altered, inducing the growth and invasion of non-small cell lung cancer cells. In TME, CAF regulates the biological behavior of tumor cells and other stromal cells through cell-cell contact; By releasing a large number of regulatory factors, synthesizing and reconstructing ECM, it affects the occurrence and development of tumors [1]. Conclusion: Through searching relevant literature, certain progress has been made in the study of CAFs in non-small cell lung cancer. Cancer associated fibroblasts can interact with various components in the tumor microenvironment, affecting tumor invasion and metastasis. Therefore, targeting CAFs for anti-tumor therapy has good application prospects. However, due to the fact that CAFs from different sources can express different biomarkers and exhibit certain heterogeneity. The heterogeneity of cancer associated fibroblast function requires the determination of the biological phenotype of cancer associated fibroblasts before treatment. Therefore, studying the biological characteristics and heterogeneity of CAFs can provide a reliable theoretical basis for targeted therapy of CAFs.***

Keywords: Non small cell lung cancer, Tumor, Fibroblast, Tumor microenvironment, Tumor metastasis.

1. Introduction

Lung cancer is one of the most common malignant tumors in the world today. In recent years, the incidence rate and mortality rate around the world have significantly increased. Lung cancer originates from respiratory epithelial cells (bronchi, bronchioles, and alveoli). The tumor microenvironment is a special internal environment during the occurrence and development of tumors, which is a comprehensive system composed of tumor cells, fibroblasts, endothelial cells, macrophages, microvessels, and various other types of cells. Cancer associated fibroblasts (CAFs) are fibroblasts activated in the tumor microenvironment (TME). Among all the stromal cells that make up TME, CAF is the most abundant tumor stromal cell [2]. Previous studies [2,3] have found that cancer associated fibroblasts (CAFs) are fibroblasts activated in the tumor microenvironment (TME), mainly producing ECM that supports tumor cells by secreting various growth factors, chemokines, and cytokines, thereby promoting tumor invasion and metastasis. Therefore, targeting CAFs for anti-tumor therapy has good application prospects. This article reviews the role of CAFs in the invasion, metastasis, and treatment of non-small cell lung cancer, in order to provide a better theoretical basis for the treatment and research of non-small cell lung cancer.

2. CAFs

2.1 Source of CAFs

Research has found that CAFs mainly come from the following sources: (1) CAFs can be induced by various cytokines secreted by cancer cells, such as platelet-derived factor and transforming growth factor - β (TGF - β), to differentiate normal fibroblasts. (2) Derived from epithelial mesenchymal or endothelial mesenchymal transformation. (3) Mesenchymal stem cells derived from bone marrow directly differentiate. (4) Derived from the differentiation of vascular smooth muscle cells and vascular adventitia cells. (5) Research has found that aging fibroblasts can also exhibit biological characteristics related to cancer associated fibroblasts. (6) CAFs can also differentiate from other cells in the tumor stroma, such as smooth muscle cells, adipocytes, etc. In summary, CAFs have multiple sources and also demonstrate the heterogeneity of CAF functions.

2.2 Markers and Heterogeneity of CAFs

CAFs represent a class of highly heterogeneous and multi-source cells, described as spindle like cells that do not express epithelial, endothelial, and leukocyte phenotypes. Irvine et al. conducted a meta-analysis of all published biomarkers of CAFs in NSCLC to determine their heterogeneity characteristics [4]. They found that five proteins, namely podoplanin, carbonic anhydrase IX, a-SMA, periostin, and FAP, were suitable for meta-analysis and showed that the CAF expression of podoplanin or a-SMA was consistently associated with poor prognosis in NSCLC patients. They also concluded that research linking CAF protein markers with cellular processes crucial for CAF function is crucial for understanding the biological characteristics of CAF.

The biomarkers of CAFs include alpha SMA, glial cell antigen 2 (NG2), platelet-derived growth factor receptor alpha/beta (PDGFR alpha/beta), FAP, and Thy-1 (CD90) [5,6] Among them, the most common biomarkers of CAFs are alpha SMA and fibroblast activation protein (FAP). Due to the high number of myofibroblasts in tumor stroma, which are only a subtype of CAF, not all CAFs express alpha SMA. FAP

is also a marker of myofibroblasts, but FAP can also be positive in malignant epithelial cells [2]. In addition, collagen 11-A1, bone junction protein, and CD90 have also been identified as relatively specific CAF markers [7]. Due to the lack of specific markers for fibroblasts or CAFs, it is difficult to determine their exact sources, so the combination of multiple markers may help identify CAFs. At present, single-cell RNA sequencing technology can preliminarily determine the sources of different biomarkers on the surface of CAFs, which can help us further clarify the heterogeneity of tumors. Kim et al. preliminarily identified a subset of CAFs isolated from human lung adenocarcinoma using single-cell RNA sequencing technology and revealed two branching points, allowing for the definition of the following lung CAF subsets: immunosuppression, neoantigen presentation, myofibroblasts, and proliferating CAFs [8]. They also found that the karyopherin subunit alpha2 protein on CAFs is involved in the nuclear cytoplasmic transport pathways of various tumor associated proteins and is one of the new antigen presentation CAF specific markers. Its expression affects the occurrence and metastasis of lung cancer cells in mouse models, indicating that CAF subtype markers may be involved in the tumor microenvironment Provide therapeutic targets.

3. The impact of CAFs on NSCLC

3.1 Value Added

In TME, CAFs affect the occurrence and development of tumors and promote the proliferation of tumor cells by releasing a large amount of growth factors, synthesizing and reconstructing ECM. For example: (1) CAFs can release stromal cell-derived factor SDF-1, which promotes cancer cell proliferation and chemotherapy resistance by activating the CXCR4 mediated signaling pathway. (2) Research [9] has demonstrated that SULF1 derived from CAF has a pro cancer effect and found that high expression of SULF1 upregulates the expression of core proteins in the Wnt3 and β - catenin signaling pathways. The Wnt/β - catenin pathway is the classic Wnt signaling pathway, and Wnt3 is the core factor of Wnt signaling. Inhibiting the expression of Wnt3 and β - catenin in NSCLC cells can inhibit their proliferation and migration [10]. The use of Wnt/β - catenin pathway inhibitor IWR-1 suppresses the expression of Wnt3 and β - catenin. Meanwhile, IWR-1 treatment weakened the oncogenic effect mediated by CAFs MC overexpressing SULF1 [9]. Therefore, reducing or knocking down the overexpression of SULF1 may become a therapeutic strategy for inhibiting the proliferation of NSCLC. (3) TGF-B1 derived from cancer cells can activate the expression of miR-21 in LNFs and induce differentiation into CAFs, which can promote cancer cell proliferation by secreting calumenin [11].

3.2 Drug Resistance

Cancer fibroblasts (CAFs) interact with lung cancer cells by utilizing EMT signals in the tumor microenvironment and inducing drug resistance through paracrine circuits. At present, most cancer treatments target cancer cells, but this type of treatment is prone to developing drug resistance. Therefore, the tumor microenvironment is the environment that tumor cells rely on for survival. Targeting the cells that make up the tumor microenvironment to treat cancer can become a new treatment strategy, and targeting the cells that make up the tumor microenvironment is not easy to develop drug resistance.

3.2.1 Radiotherapy resistance

Research has shown that CAFs can induce non-small cell lung cancer cells to resist radiation therapy, thereby increasing tumor cell activity and reducing apoptosis. Radiotherapy uses radiation to generate reactive oxygen species (ROS) such as hydroxyl radicals and superoxide anions in tumor tissue, which damage cells by oxidizing proteins, lipids, and DNA to achieve therapeutic goals [12]. Research has shown that GSH in tumor cells can counteract the effects of ROS, thereby maintaining the survival of tumor cells, increasing tolerance to cell damage, and inducing tumor cell invasion and metastasis [13]. Research by Han Ruozhen et al. [14] has shown that CAFs can protect lung cancer cells after radiation by releasing GSH. Meanwhile, interferon - γ downregulates the expression of cystine transporter xCT in CAFs and reduces GSH release, thereby reversing the radiation resistance of non-small cell lung cancer.

3.2.2 Chemotherapy resistance

(1) Related studies have shown that CAFs can reduce the sensitivity of tumor cells to chemotherapy by promoting EMT. ⑵CAFs can also secrete cytokines or activate an important signaling pathway to induce drug resistance in non-small cell lung cancer. In non-small cell lung cancer, CAFs promote TGF - β - induced epithelial mesenchymal transition and resistance to cisplatin by releasing IL-6. (2) Research has found that CAF induces drug resistance in cancer cells through the IGF2/IGF-1R paracrine pathway [15]. Therefore, blocking the activation of IGF2/IGF-1R paracrine pathway induced by CAF can effectively inhibit the occurrence of chemotherapy resistance and delay the development of non-small cell lung cancer. Research has found that OSI-906 can serve as a potential drug to block the IGF2/IGF-1R paracrine pathway induced by CAF, and can be used in combination with multiple chemotherapy drugs to effectively reverse drug resistance. (3) CAFs can release IL-11 and promote chemotherapy resistance in cancer cells by activating the STAT3 signaling pathway [16,17]. (4) CAFs enhance chemotherapy resistance by activating the attachment factor A3/JNK pathway to inhibit caspase-3 and caspase-8. (5) CAFs also activate IGF2/AKT/Sox2/ATP binding cas-sette B1 signaling and upregulate P-glycoprotein expression in NSCLC cells through the insulin-like growth factor (IGF) 2/IGF receptor (IGFR) -1 paracrine pathway, inducing acquired chemotherapy resistance [15].

3.2.3 Targeted drug resistance

CAFs can also promote tumor cells to develop resistance to targeted therapy drugs. (1) Research [18] found that co culture of CAFs highly expressing GPER1 with tumor cells can reduce the sensitivity of tumor cells to osimertinib and induce osimertinib resistance in NSCLC. However, when co cultured with CAFs knocking down GPER1, the effect of inducing osimertinib resistance disappears. Transforming growth factor - β is the main cytokine secreted by CAFs, among

which GPER1 and TGF - β 2 expressed in CAFs are positively correlated. Therefore, the induction of tumor cell resistance to osimertinib by CAFs is correlated with TGF - β (2) Pellinen et al. used multiple fluorescence immunohistochemistry to investigate the association between epidermal growth factor receptor mutations and CAF subtypes; Their research findings suggest that genetic changes may affect the characteristics of CAFs in the tumor microenvironment [19]. Thereby reducing the sensitivity of tumor cells to targeted therapy. CAF induces EMT through its mediated signaling pathway and plays a key role in the resistance of lung cancer to epidermal growth factor receptor (EGFR) TKIs [20,21]. Yoshida et al. also found that when co cultured with CAFs expressing podoplanin, lung adenocarcinoma cell lines showed increased resistance to epidermal growth factor receptor TKIs, indicating that podoplanin positive CAFs may help predict response to epidermal growth factor receptor TKIs [22]. Studies have found that IL-6 released by CAFs induces acquired tolerance of NSCLC to epidermal growth factor receptor TKIs through the JAK1/STAT3 signaling pathway [23]. (3) In addition, it was found that CAFs increased the expression and phosphorylation of annexin A2 by secreting HGF and IGF-1, while HGF and IGF-1 regulated EMT and EGFRTKI resistance in a paracrine manner [21].

3.2.4 Immunosuppression

CAFs can participate in tumor immune regulation by secreting cytokines such as tumor necrosis factor (TNF), IL-6, and interleukin-10 (IL-10). Among them, cytokines such as IL-6 and IL-10 can achieve immunosuppressive effects by inhibiting the functional activation of T lymphocytes and B lymphocytes. 1. CAFs can directly participate in immune regulation of tumor cells: In NSCLC, CAF regulatory medium induces programmed cell death ligand 1 (PD-L1) expression in NSCLC cells by secreting CXCL2, thereby promoting the formation of an immunosuppressive microenvironment [24]. Some CAF subgroups can directly inactivate the immune system by expressing FD-L1, thereby reducing T cell activation. PD-L1 expression on CAFs is an independent prognostic factor [25]. CAFs, through the involvement of PD-L2 and CD95 (known as FAS) ligands, will cross present antigens with major histocompatibility complex (MHC) class I to antigen-specific CD8+T cells, directly promoting inhibition of anti-tumor T cell responses in an antigen-specific and antigen dependent manner. This suggests that CAFs exert immunosuppressive effects in the tumor microenvironment through a mechanism dependent on immune checkpoint activation [25]. CAFs can mediate the immunosuppressive state of tumor cells by regulating the physical environment of various acquired immune cells (such as Treg cells, Th cells) and TME. Regulatory T cells (Treg cells) in tumor infiltrating lymphocytes play an important role in normal physiological processes by regulating immune destruction and preventing autoimmune diseases. Treg cells are typically present in solid tumors and promote tumor immunity through recruitment mechanisms, including secretion of immune suppressive cytokines, competition with effector T cells to activate chemokines, and direct contact with infiltrating effector T cells [26,27]. TGF - β is involved in immune suppression of tumors. TGF - β can disrupt T cell activation by limiting the migration and lifespan of dendritic cells, and promote the activation of Treg cells [28,29]. CAFs can also affect CD4+Th cells, transforming them from anti-tumor cells to pro tumor cells. CD4+Th cells can differentiate into multiple subtypes with different functions and cytokine secretion characteristics, thereby inducing, maintaining, or regulating anti-tumor immune responses. Immature CD4+Th cells can differentiate into Th17 cells, characterized by the production of IL-17 and IL-22, which may have pro tumor and immunosuppressive effects in TME, but there is still controversy [30].

3.3 Invasion and Metastasis

(1) CAFs can directly or indirectly stimulate epithelial mesenchymal transition (EMT) in lung cancer cells by releasing cytokines or chemokines, thereby enabling tumor cells to acquire the ability to invade and metastasize. (2) In addition, CAFs can secrete exosomes, thereby increasing the ability of tumor cells to metastasize and invade. Because extracellular vesicles derived from CAFs can provide a comfortable microenvironment for the growth of tumor cells, thereby enhancing their ability to metastasize and invade. For example: (1) In non-small cell lung cancer, Huang et al. ‘s study further confirmed that IL-17 can upregulate Vimentin expression and downregulate E-cadherin expression through the Stat3 signaling pathway in vitro, promoting EMT of lung cancer cells and indirectly promoting lung cancer cell proliferation. (2) Research has found that the level of SNAI1 in extracellular vesicles is positively correlated with EMT in lung cancer cells. (3) Yang et al. [31] reported that extracellular vesicles derived from CAFs contain highly expressed miR-210, which activates the PTEN/PI3K/AKT pathway by targeting UPF1 to promote EMT, thereby enhancing the migration, proliferation, and invasion ability of non-small cell lung cancer. The treatment of CAFs with extracellular vesicle release inhibitor GW4869 can significantly inhibit their EMT induction on receptor epithelial cells. In summary, CAFs can promote the invasion and metastasis of non-small cell lung cancer through direct or indirect induction by secreting various cytokines, exosomes, and other factors.

4. Application of Targeted CAFs in NSCLC Treatment

4.1 Specific Markers Targeting CAFs

Compared with normal fibroblasts, multiple membrane proteins in CAFs are upregulated, making them potential targets for inhibiting tumor growth. For example, FAP is a transmembrane serine protease highly expressed on CAFs in various tumors, and highly expressed FAP is considered an independent biomarker for poor prognosis in NSCLC patients. Therefore, FAP can be used as a target to treat malignant tumors. At present, targeted FAP therapy for tumors includes antibodies, FAP inhibitors, vaccines, and Chimeric antigen receptors (Chimeric antigen re).

Receptor (CAR) T cells [32]. In Lewis lung cancer and pancreatic ductal adenocarcinoma models, the deletion of FAP gene can significantly reduce the infiltration of FAP+CAFs, leading to rapid hypoxia necrosis of tumors, which is related to CD8+T cell infiltration [33,34]. Duperret et al. proposed a DNA vaccine targeting FAP that can

simultaneously drive CD4 and CD8 T cells [35]. Mice were inoculated with a recombinant adenovirus vector containing FAP cDNA, which produced FAP specific cytotoxic T lymphocytes capable of eliminating CAFs expressing FAP. This suggests that FAP is a potential target for eliminating CAFs and may lead to the development of immunogenic tumor vaccines [36].

4.2 Targeting the Signaling Pathway of CAFs

The TGF - β factor produced by tumor cells plays an important role in the activation of CAFs and the interaction between CAFs and immune cells. There are studies showing that TGF - β signaling transduction in CAFs promotes T cell rejection and weakens the effect of anti-PD-L1 drugs. The combination of TGF - β blockers and anti-PD-L1 antibodies can inhibit TGF - β signaling transduction in CAFs, which is beneficial for T cell infiltration into cancer nests, thereby stimulating effective anti-tumor immunity [37,38]. CAFs enhance TGF - β signaling in NSCLC and mediate the secretion of IL-6 to induce EMT in tumor cells, while IL-6 blocking antibodies can weaken this signaling pathway [39]. ALD518 is a humanized monoclonal antibody targeting IL-6. In preclinical and phase I/II trials, it has shown good tolerability and can improve anemia and cachexia associated with NSCLC by controlling inflammatory pathways related to oncogenes [40]. Tozumab is a specific monoclonal antibody targeting the IL-6 receptor, which is expected to control tumor related symptoms and reduce NSCLC related anemia and cachexia [40]. Therefore, targeting IL-6 may become a new strategy for treating NSCLC.

SULF1 derived from CAFs has a pro cancer effect, and it has been found that high expression of SULF1 upregulates the expression of core proteins in the Wnt3 and β - catenin signaling pathways. The use of Wnt/β - catenin pathway inhibitor IWR-1 suppresses the expression of Wnt3 and β - catenin. Meanwhile, IWR-1 treatment weakened the oncogenic effect mediated by CAFs MC overexpressing SULF1 [10]. Therefore, reducing or knocking down the overexpression of SULF1 may become a therapeutic strategy for inhibiting the proliferation of NSCLC.

5. Summary and Prospect

Numerous studies have shown that CAFs can provide a comfortable growth environment for tumor cells, thereby promoting the occurrence and development of tumors. In addition, targeted CAFs have been shown to alter the tumor promoting effect of CAFs and are less likely to develop drug resistance. This article provides a review of the role and drug resistance mechanisms of CAFs in the occurrence and development of NSCLC. It is hoped that targeting CAFs can achieve effective anti-tumor effects and provide effective theoretical basis for the treatment of tumors.

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