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The Mechanism and Targeted Intervention of Cancer-Promoting CAFs and PD-1 Resistance in the Tumor Microenvironment

Jiayan Li

School of Public Health, Nantong University, Nantong, China
2317110204@stmail.ntu.edu.cn

Abstract. Recently, researchers have made great progress in the field of cancer immunotherapy. However, PD-1 inhibitors will encounter a difficult problem in the treatment of cancer, that is, drug resistance. There are many reasons for this PD-1 resistance, such as physical obstacles, metabolic rivalry, and immune checkpoint systems. It is found that physical barriers are the main cause of PD-1 resistance. This physical barrier is in the stroma, and there are CAFs in the stroma. The main reason for PD-1 resistance is the physical obstruction formed by CAFs in the stroma. CAFs are the primary drivers of stromal immune remodeling. Targeting CAFs and achieving stromal immune remodeling is crucial for overcoming drug resistance. Therefore, CAFs can be used to reshape the physical barrier, metabolic microenvironment, and immune checkpoint microenvironment. CAFs have numerous subtypes, with the tumor-promoting type predominating. This study aimed to investigate the multidimensional mechanisms of PD-1 resistance and to verify the close relationship between the construction of the physical barrier and CAFs. Given the diverse subtypes of CAFs, it is also important to investigate the mechanisms that dominate the tumor-promoting type. A key aim of this study is to research the mechanisms by which CAFs achieve stromal immune remodeling.

Keywords: Physical barriers, immune checkpoint networks, metabolic competition, tumor-promoting CAFs, stromal immune remodeling

1. Introduction

PD-1 inhibitors have now created a new pathway for the treatment of cancer. In particular, for most advanced solid tumors, PD-1 combined with PDL-1 inhibitor therapy has become the core [1]. However, clinical studies have shown that not all patients are sensitive to this approach [1]. According to available data, the five-year survival prospects for patients who have undergone esophagectomy alongside concurrent chemotherapy, radiotherapy by itself, or the combined approach of chemoradiotherapy stand at 6.3%, 24.9%, and 32.4%, respectively. These results are not ideal, partly due to the tumor acquiring treatment resistance [2]. Over one-quarter of patients become resistant to chemotherapy within six months of initial therapy, and 70% of patients will relapse within 2-3 years and eventually die due to acquired resistance [3]. As the most important

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matrix component, CAFs are closely related to immune cells and serve as a mechanism for cancer cell treatment escape and the development of chemotherapy resistance [4]. However, the specific relationship between CAFs and cancer cell behavior remains unclear [5]. CAFs account for a major proportion of the non-tumor matrix components of many human tumors. Many studies have shown that they can regulate tumor cells by establishing communication networks with cancer cells or other components, and are therefore closely related to cancer resistance [6]. Tumor cells trigger CAFs and are served by CAFs. In case activated in an existing tumor, CAFs become the chief ally of tumor growth, advancement, and response to therapy [7]. CAFs act as central hubs, promoting multicellular crosstalk and weakening the portion immune surveillance and anti-tumor immunity through direct contact and paracrine signaling [8]. The physical barrier is the dense ECM formed by CAF secretory components, which forms an obstacle, especially for complex polymer drugs. Controlled drug release of drugs to the tumor region [9]. As a considerable proportion of the tumor matrix, CAFs have a prominent role in cancer stage and metastasis, including ECM deposition, reshaping and drug resistance [10]. CAFs secrete TGF-β, which greatly inhibits CD8+ T cell infiltration [11]. In-depth analysis of the multidimensional mechanisms by which tumor-promoting CAFs drive PD-1 resistance and exploring strategies for matrix immune remodeling are of great significance for the development of efficient immunotherapy combination therapies.

2. Physical barriers

2.1. Physical barriers and CAFs

More than half of tumor tissues are composed of stromal tissue secreted by tumor-promoting CAFs and other components [12]. TME is composed of tumor cells, immune cells, CAFs, and ECM and other components. [8]. As the most plentiful stromal cell in TME, CAFs secrete collagen after activation, forming a dense physical barrier, which inhibits the percolation of effector T cells and creates an immune "desert" that suppresses anti-tumor immunity [8]. CAFs are prominently involved in the formation of TME and are the primary component in the formation and regulation of tumor physical barriers [12]. The physical barrier formed can also reduce blood flow by compressing peripheral blood vessels, thereby hindering chemotherapy and immunotherapy drugs from reaching the cancer site, thereby reducing drug delivery efficiency [13]. CAFs can enhance the generation of these ECM constituents, which further lead to increased tumor matrix stiffness and the formation of a defensive block near tumor cells [14]. Therefore, these findings indicate that the formation of the physical barrier is closely linked to CAFs.Top: 3.5 cm

2.2. The main mechanism leading to PD-1 resistance

ECM stiffness is a key factor in cancer progression; increases in stiffness alone can stimulate tumor growth [15]. Furthermore, stiffness is a biophysical property of ECM that influences a variety of cellular functions, including proliferation, invasion, differentiation, and therapeutic response [16]. Therefore, the physical barrier formed by ECM stiffness is crucial. Studies have also shown that stiff TME affects the regulation of cell communication network factor 1 in ECs, which increases the engagement between melanoma cells and the endothelium, thus stimulating the relocation of cancer cells by the vascular system [15]. These findings also demonstrate that physical barriers are the primary factor leading to drug resistance.

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3. Immune checkpoint network

In cancer cells, dysregulation and mutation of key signaling pathway molecules lead to abnormal activation of multiple pathways, which form a complex cross-regulatory network that together promotes the development of tumor resistance [17]. CAFs form an immune checkpoint inhibitory network by secreting a variety of cytokines in collaboration with PD-1 signals. They can stimulate tumor-promoting pathways in an autocrine or paracrine manner, including proliferation, metastasis, and progression [18]. In addition, cytokines and chemokines in the TME are closely associated with chemotherapy resistance and poor prognosis in cancer patients [18].

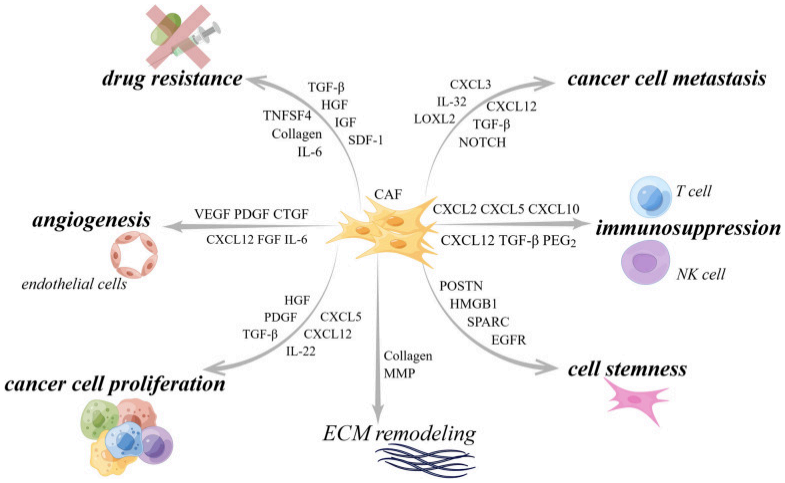

Figure 1. Immune checkpoint network mechanisms [10]

Figure 1 shows the immune checkpoint interaction network. CAFs regulate angiogenesis, cancer cell proliferation, cell stemness, ECM remodeling, immunosuppression and drug resistance by secreting a variety of cytokines. CAFs cause immunosuppression by interacting with T cells and NK cells, leading to drug resistance. The main signaling molecules and pathways are chemokines such as CXCL12, CXCL2, and TGF-β. CAFs cause drug resistance through HGF, TGF-β, IL-6, etc. Given its pivotal role in regulating cancer cell proliferation, differentiation, and survival, the expression of TGF-β is frequently known as an important therapeutic target [19].

4. Metabolic competition

4.1. Metabolic reprogramming

Cancer cells exhibit metabolic changes that differ from those of normal cells [20]. This change is called metabolic reprogramming, and CAFs are the main regulators of tumor metabolic reprogramming [21]. Due to metabolic reprogramming, nutrients in the tumor microenvironment become scarce, and they compete with activated T cells for nutrients such as glucose and amino acids, leading to T cell functional exhaustion.

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4.2. Pathways and mechanisms of metabolic reprogramming

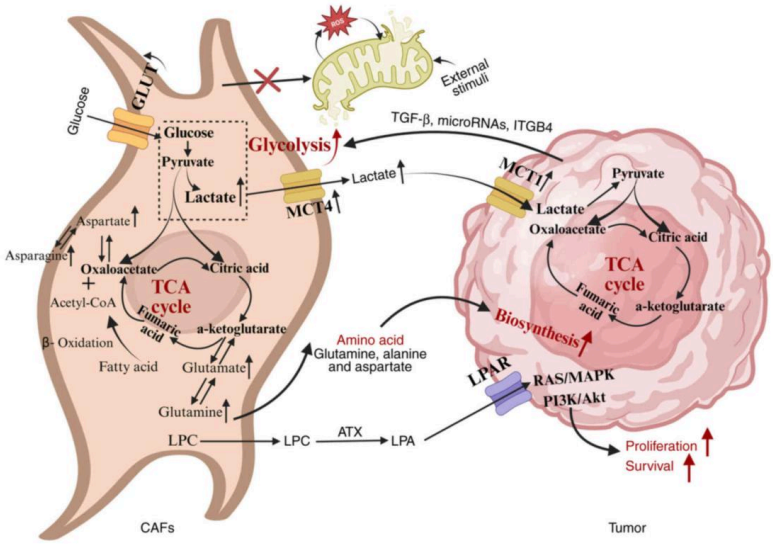

Figure 2. The relationship between CAFs and metabolic reprogramming [20]

Figure 2 shows the relationship between CAFs and metabolic reprogramming.

4.2.1. Glucose metabolism

TGF-β1 enhances glucose uptake by GLUT1 through the activation of Smad2/3, p38 MAPK, and PI3K/protein kinase B [21]. Through glycolysis, ketone bodies are generated, and further large amounts of lactate are produced. Even under normoxic conditions, CAFs tend to transfer glucose into lactate through aerobic glycolysis. This morphological type is motivated by aspects like TGF-β and is aggravated by hypoxia [21]. Lactate is excreted through MCT4 in CAFs and enters tumor cells through MCT1 in tumor cells.

4.2.2. Amino acid metabolism

Glutamine plays a critical role in amino acid metabolic reprogramming in CAFs [21]. CAFs increase Gln synthesis by upregulating glutamine synthetase [21]. CAFs provide energy for tumor cell proliferation by producing glutamine. In the process of producing glutamine, tumor cells extract intermediates through biosynthesis to provide energy for tumor cell proliferation. Apart from glutamine, alanine also plays a significant role in the TCA cycle of tumor cells. Tumor cells promote CAFs' metabolism of proteins through autophagy to generate alanine and convert it to pyruvate [22].

4.2.3. Lipid metabolism

Lipids play a vital role in cell composition and also participate in metabolic reprogramming. After activation, CAFs undergo lipidome remodeling, releasing large amounts of lysophosphatidylcholine, which promotes tumor cell migration and proliferation through the lysophosphatidylcholine-autotaxin-lysophosphatidic acid axis [21]. Ketone bodies produced by CAFs are also an important energy source for tumor cells. Ketone bodies enter tumor cells through the MCT1 receptor, enter the tricarboxylic acid cycle and promote tumor cell proliferation.

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5. Heterogeneity of CAFs

5.1. Classification of CAFs

CAFs have some attributes of phenotypic heterogeneity and plasticity. Single-cell RNA sequencing can be used to differentiate CAF subtypes by discovering cell heterogeneity [21]. Several research teams have used single-cell RNA sequencing to analyze the composition of solid tumors and have discovered multiple fibroblast subpopulations with different phenotypes and functions in pancreatic cancer, breast cancer, and colorectal cancer [23]. Based on single-cell RNA sequencing, they can be divided into myCAFs, iCAFs, and apCAFs. Based on functional classification, they can be divided into cancer-promoting CAFs and anti-cancer CAFs. Cancer-promoting CAFs include myCAFs, apCAFs, and iCAFs. Figure 3 shows the different subtypes of CAFs.

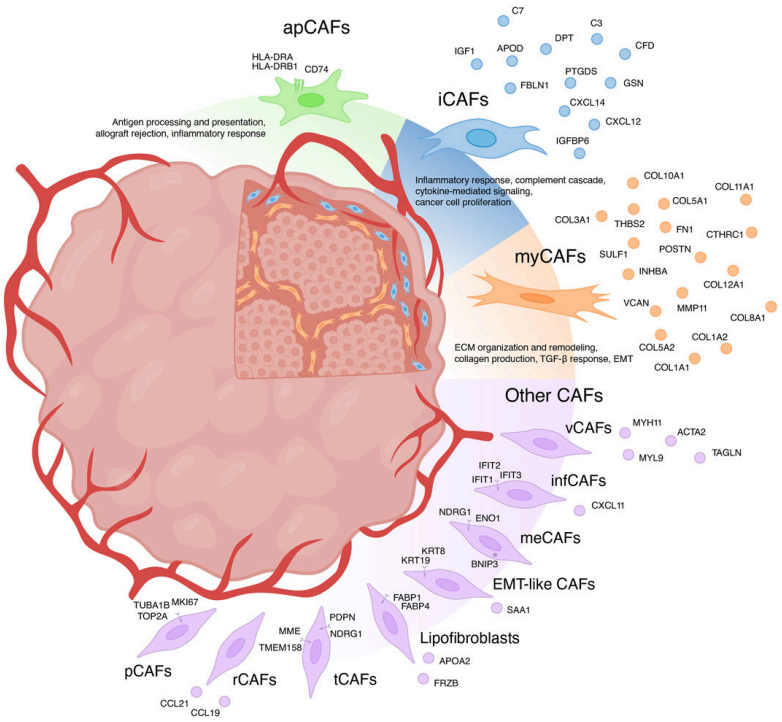

Figure 3. Heterogeneity of CAFs [24]

5.2. Cancer-promoting CAFs

5.2.1. iCAFs

iCAFs arranged on the outside of the physical barrier of the ECM produced by myCAFs, which enables them to efficiently secrete cytokines, potentially promoting the recruitment of Tregs and other immunosuppressive cell types [25]. CXCL12 is an important chemokine that promotes cancer cell proliferation, angiogenesis, and metastasis, and CXCL12 has been found to be primarily secreted by iCAFs in oral squamous cell carcinoma [26]. iCAFs are characterized by increased release of interleukins and activation of inflammatory pathways, promoting cancer stemness and immunosuppression [14].

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5.2.2. MyCAFs

MyCAFs have a large amount of collagen, which can form a dense matrix, blocking T cell infiltration and leading to PD-1 resistance. The TGF-β/SMAD2/3 pathway can induce the activation of myCAFs in PDAC. MyCAFs are associated with the metastasis and immunosuppression of PDAC [26]. PDGFRα, collagen genes, and α-SMA are all highly expressed in myCAFs, and myCAFs are engaged in ECM reconstruction and transformation [13].

5.2.3. apCAFs

apCAFs can stimulate CD4+ and CD8+ T cells in tumor tissues in an epitope-targeted mode, thereby endowing them with phenotypic characteristics with diverse immunomodulatory functions [27]. Further evidence from in vivo experiments shows that apCAFs express low levels of co-stimulatory genes necessary for T cell proliferation. This means that apCAFs may be involved in suppressing our immune response in the tumor microenvironment [26].

6. Stromal immune remodeling

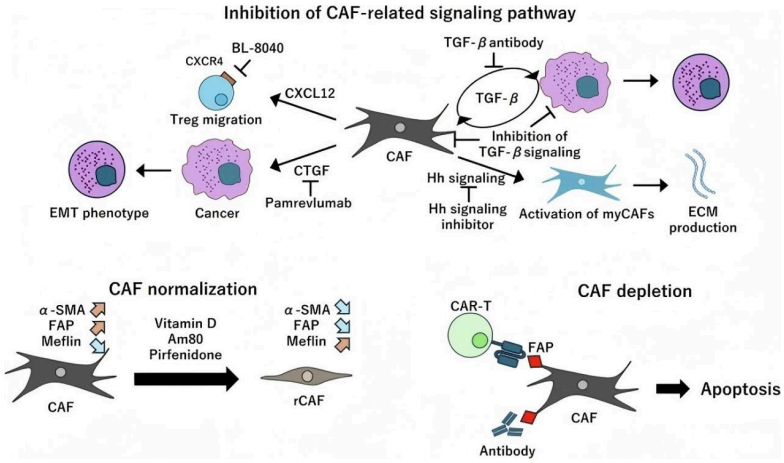

Figure 4. Methods for stromal immune remodeling [25]

6.1. Signaling pathways

One way is to suppress CXCR4, CTGF, TGF-β and Hh. In the tumor microenvironment, cancer cells will manipulate CAFs by releasing cytokines to help them grow. Therefore, blocking this interaction can prevent CAFs from promoting tumor tissue expansion (Figure 4)[25]. Because TGF-β is a multifunctional cytokine related to drug resistance, targeting CTGF may prevent fibroblasts from stimulating the proliferation of cancer cells, which provides a promising new direction for the treatment of cancer. [25].

6.2. Physical parrier

The second approach is to use FAP-targeted CAR-T or antibodies to reduce the physical barrier fabricated by ECM deposition. FAP has been the target in tumors for imaging and treatment through a variety of methods, including immunoconjugates, tumor immunotherapy, FAP inhibitors and antibodies [7]. Several studies have reported that the reduction of FAP-positive CAFs improves anti-

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tumor immunotherapy, demonstrating the effectiveness of targeting CAFs [7]. FAP-CAR-T cell therapy and FAP-targeted oncolytic adenovirus step up the immune system's precision strike against FAP-positive cancer-associated fibroblasts, crank up proinflammatory cytokine production, and give antigen presentation a boost. These treatments also supercharge T cell performance and improve their ability to migrate to tumor sites, ultimately packing a more powerful punch against cancer [5]. Studies have also shown that FAP vaccination combined with chemotherapy increased the uptake of chemotherapy drugs by transplanted tumors by up to 70% [28].

6.3. Normalization of metabolic competition

The third approach is to use various drugs to train activated CAFs to quiescent CAFs, changing the metabolic competition relationship with T cells from predatory to peaceful coexistence. CAFs are domesticated into relatively harmless rCAFs using drugs such as vitamin D, Am80, and pirfenidone. Meflin has been regarded as an indicator of CAFs that impede PDAC tumor growth [25]. Studies have shown that inhibiting lysyl oxidase inhibits collagen cross-linking and postpones the development of drug-induced pulmonary fibrosis [25]. Am80 is an artificial retinoid that can induce Meflin expression, soften tumor tissue, increase tumor vascular area, and enhance intratumoral drug penetration [25].

7. Combination immunotherapy

It is very important to understand the complex immunosuppressive mechanism caused by CAFs, because to develop new therapies aimed at the matrix and immune microenvironment, thus opening up new opportunities for treating this intractable disease [29]. Tranilast was originally used to treat allergies, but it can inhibit fibroblasts from producing collagen and TGF-β, and also reduce macrophages from releasing IL-11 [30], thus alleviating the physical barrier formed by excessive extracellular matrix. Previous studies have found that tranilast can prevent the activation of the STAT3 pathway and the EMT process of malignant cells, which shows that combining tranilast with targeted molecular therapy may be an effective method to overcome the drug resistance caused by CAF [30]. Although the effect of using tranilast or osimertinib alone may be limited, using them at the same time can significantly improve the response of cancer cells to these targeted drugs [30].

8. Conclusion

This article explains PD-1 resistance and immune remodeling in the tumor microenvironment, and studies the reasons behind them, as well as their relationship with CAFs. One of the main reasons for drug resistance of PD-1 is the formation of physical barriers, which make ECM and block the entry of T cells and drugs. In addition, the interaction between CAFs and tumor cells will also cause metabolic reprogramming, which will affect the pathways related to glucose, amino acids and lipids. The immune checkpoint network, regulated by various cytokines will form an inhibitory signal environment. In view of these mechanisms, people can strategically reshape the immune system, which includes changing the physical barrier, metabolic environment and key signaling pathways. However, there are many types of CAFs-many subtypes have their own unique functions it is necessary to study their different functions and possible treatment methods in the future, hoping to apply these findings to clinical oncology and provide better treatment schemes and drugs for cancer patients.

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