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THE EFFECT OF CANCER-ASSOCIATED FIBROBLASTS ON ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Cancer-associated fibroblasts (CAFs) are pivotal components of the tumor microenvironment (TME) that critically influence the progression and therapeutic resistance of oral squamous cell carcinoma (OSCC). This review provides an in-depth synthesis of current knowledge regarding the diverse roles of CAFs in OSCC, emphasizing their contributions to tumor growth, angiogenesis, metastasis, immune modulation, and drug resistance. CAFs, which originate from normal fibroblasts through activation processes such as TGF-β signaling and epithelial-mesenchymal transition, exhibit distinct markers including α-smooth muscle actin (α-SMA), fibroblast activating protein (FAP), and fibroblast specific protein-1 (FSP-1). Unlike their normal counterparts, CAFs secrete a complex array of cytokines and growth factors, such as IL-6, IL-8, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF), which activate oncogenic pathways including EGFR, Wnt/β-catenin, Hippo, and JAK2-STAT3. These signaling networks facilitate not only enhanced tumor cell proliferation and invasion, but also the induction of epithelial-mesenchymal transition, thereby promoting metastasis. In addition, CAF-derived factors stimulate angiogenesis by recruiting endothelial progenitor cells and remodeling the extracellular matrix to support neovascularization. CAFs further contribute to an immunosuppressive TME by inducing T cell apoptosis and promoting M2 macrophage polarization, which impairs antitumor immunity. Notably, CAFs are implicated in resistance to conventional chemotherapies, underscoring their role in treatment failure. Targeting CAFs or their downstream effectors represents a promising therapeutic strategy to overcome drug resistance and improve patient outcomes. Overall, this review highlights the multifaceted impact of CAFs in OSCC and advocates for the development of CAF-directed therapies as an integral component of comprehensive cancer management. Future studies should aim

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to elucidate the molecular heterogeneity of CAFs and to develop innovative strategies that effectively target their tumor-promoting functions without compromising normal tissue integrity.

KEYWORDS: Cancer-associated fibroblasts (CAFs); Oral squamous cell carcinoma (OSCC); Tumor microenvironment (TME); Epithelial-mesenchymal transition (EMT)

INTRODUCTION：

The incidence rate of cancer has been increasing rapidly [1].Although significant progress has been made in studying the mechanisms underlying the occurrence and development of different types of cancer, addressing cancer related issues through these mechanisms still poses certain challenges [2].The recurrence, metastasis, and tumor microenvironment (TME) of tumors remain three key and unresolved issues that hinder clinical treatment of cancer [3, 4].The components of TME, such as cancer associated fibroblasts (CAFs), are activated fibroblasts in the tumor matrix and are associated with the occurrence and progression of malignant tumors [5].Related studies have found that CAFs contribute to tumor growth and proliferation, angiogenesis, invasion and metastasis, and resistance to treatment [6].Because CAFs are one of the most abundant matrix components in TME, they can serve as important therapeutic targets in many solid tumors [4], Some of the solid tumors include head and neck cancer [6-8],breast cancer [9-11] ,lung cancer [12-15],Gastrointestinal ,biliary cancers [16-18]and Urogenital system cancer [19, 20],etc.Our focus here is on head and neck squamous cell carcinoma, which is the seventh most common cancer worldwide and causes patient death [21, 22]，Therefore, it is important to understand and study how the TME of HNSCC promotes tumor progression [23, 24].In this review， We have outlined the key role played by CAFs in head and neck squamous cell carcinoma, as well as some mechanisms of action, and may become potential targets for new treatment methods.

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Tumor microenvironment：

The tumor microenvironment (TME) is the cellular environment in which tumors exist. The process of tumor progression and metastasis is the result of the joint action of non tumor cells and tumor cells [25].In addition to tumor cells, TME mainly includes the following parts: (1)immune microenvironment (TIME): composed of various innate immune cells, such as tumor associated macrophages (TAMs), natural killer cells (NK) cells, neutrophils, mast cells, dendritic cells (DC), bone marrow-derived suppressor cells (MDSC), and adaptive immune cells, including CD4+T helper lymphocytes (Th), CD8+cytotoxic T cells NK-T cells γδ T cell, regulatory T cell (Treg), and B cell composition[26-28].(2) Vascular components: The generation of tumor vascular networks is mainly achieved through the formation of new blood vessels, co selection and modification of existing blood vessels in tissues, and differentiation of bone marrow endothelium, all of which lead to heterogeneity of blood vessels within tumors[25].(3) Extracellular matrix (ECM): mainly composed of various collagen molecules, glycoproteins, and proteoglycans [29, 30].(4) Non immune cells: such as cancer associated fibroblasts (CAFs) and mesenchymal stromal cells (MSCs). Among them, CAFs cells are the focus of this article's description.

Table 1: Components of the tumor microenvironment (TME)

Category	Components	Description
Immune Microenvironment (TIME)	- Tumor-associated macrophages (TAMs)	Various innate and adaptive immune cells interact with tumor cells.
	- Natural killer (NK) cells	

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	- Neutrophils, mast cells, dendritic cells (DC)	
	- Bone marrow-derived suppressor cells (MDSCs)	
	- CD4+ T helper lymphocytes (Th)	
	- CD8+ cytotoxic T cells	
	- NK-T cells, γδ T cells, regulatory T cells (Treg)	
	- B cells	
Vascular Components	- Tumor vascular networks	Formed through new blood vessel formation, co-selection and modification of existing vessels, and differentiation of bone marrow endothelium.
Extracellular Matrix (ECM)	- Collagen molecules	Provides structural and biochemical support.
	- Glycoproteins, proteoglycans	
Non-Immune Cells	- Cancer-associated fibroblasts (CAFs)	Play a significant role in tumor progression.
	- Mesenchymal stromal cells (MSCs)	

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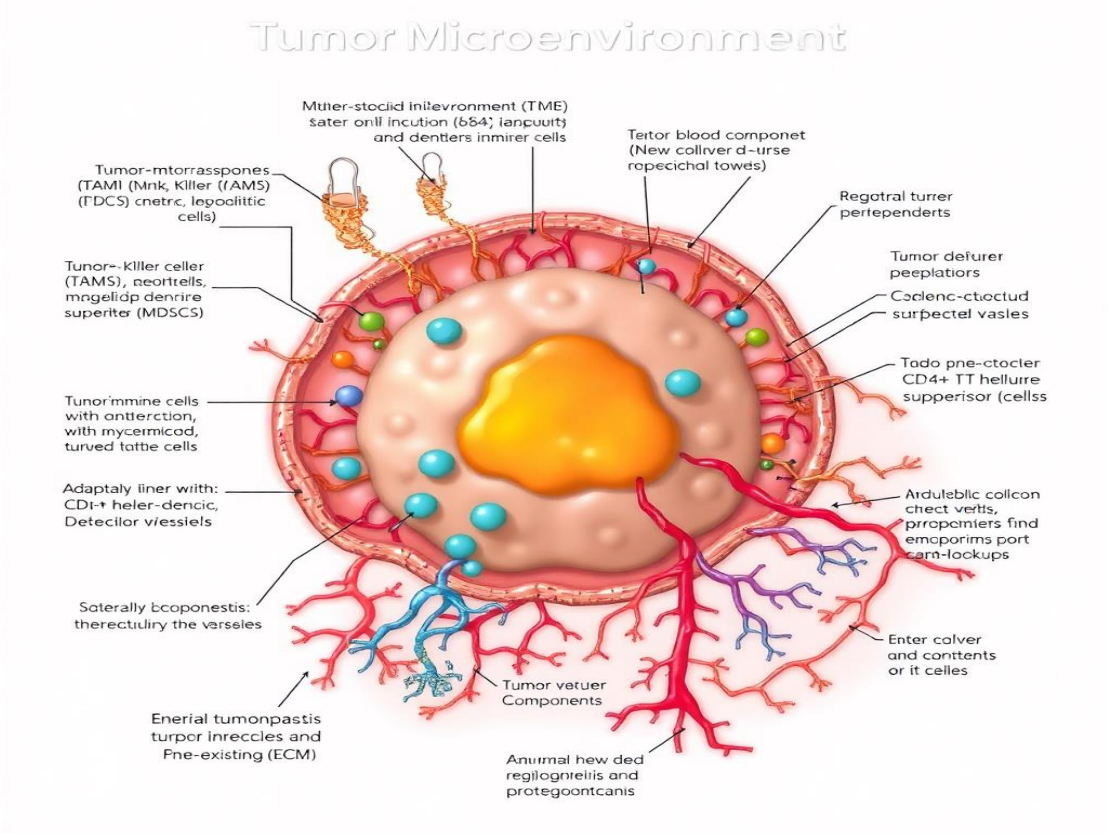

Image1: Comprehensive illustration of the tumor microenvironment (TME) and Its key components

Cancer associated fibroblasts (cancer-associated fibroblasts;CAFs):

Fibroblasts are abundant mesenchymal cells that maintain the structural framework of tissues. R. Kalluri's laboratory is the first to draw people's attention to the heterogeneity of CAF by describing the two kinds of mice in breast cancer and pancreatic cancer models and their oncophilic CAF subsets [31].Static fibroblasts have different responses to damage, and after the damage occurs, they can be activated to repair damaged tissue. The process of differentiation of some cells into CAFs is usually accompanied by epithelial mesenchymal transition (EMT), such as epithelial cell transformation into myofibroblasts, or activation of Ras signaling or TGF- β The signal causes the loss of

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E-cadherin, resulting in the formation of mesenchymal morphology [32, 33],Although normal fibroblasts (NFs) typically inhibit tumor formation[34],cancer associated fibroblasts (CAFs) can significantly promote tumor development[35].Compared with NFs, CAFs not only increase cell proliferation, but also promote the production of extracellular matrix and the secretion of some special cytokines (such as stromal cell derived factor 1-SDF1, vascular endothelial growth factor VEGF, platelet derived growth factor PDGF, and hepatocyte growth factor HGF)[36].Transforming growth factor-1 (TGF) secreted by stromal cells and tumor cells- β1) Is the main factor promoting the mobilization and activation of NFs into CAFs [37, 38].TGF- β 1. Activate fibroblasts to transform into CAFs and express smooth muscle actin through SMAD dependent or non dependent pathways（ α- SMA, Periosteal Protein (POSTN) α- Fibroblast activating protein（α- FAP) and fibroblast specific protein-1 (FSP-1), and produce type I collagen [39].However, CAFs can not only express α- SMA α FAP and FSP-1, which can also produce vascular endothelial growth factor (VEGF) and cytokines such as IL-6 and IL-8 [40].Research has shown that in TGF- β Under the influence of, cancer cells, especially cancer stem cells, can be a source of CAFs [41].The maintenance of stem cell characteristics is an important influencing factor for tumor formation; And the matrix can support and regulate the differentiation and proliferation of tumor stem cells [42].Fibroblasts are the main component of TME and regulate the occurrence and development of tumors by releasing various cytokines and interacting with various cells such as tumor cells [4, 43].

In human head and neck squamous cell carcinoma samples, CAFs typically express myofibroblast markers α- SMA, showing spindle like cells [44-46],Rarely co-expressed with other biomarkers [47, 48].After chemotherapy α- The expression of SMA may also increase [44].Studies have shown that the higher the density of CAFs, the worse their clinical manifestations (such as TNM staging, cervical lymph node metastasis, vascular

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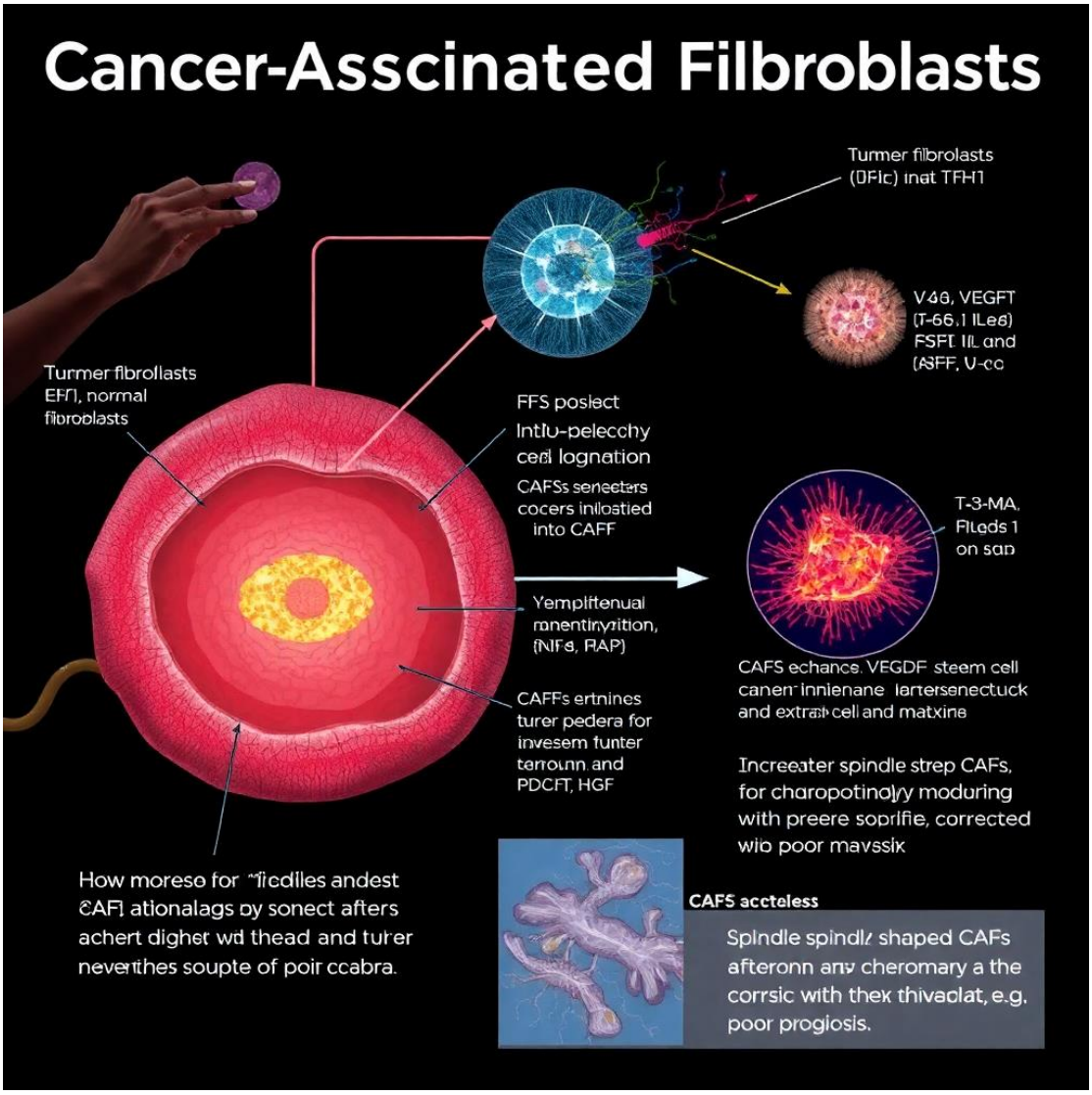
infiltration, postoperative recurrence, etc.)[46, 49-51], the worse the prognosis after treatment. [46, 49, 52, 53]

TGF- β It has been proven to increase the cell strength of NFs and CAFs; It also increases the ability of CAFs to elongate and diffuse, which has never occurred in fibroblasts without activation; It also enhances the invasiveness of the tumor matrix [54].



The effect of CAFs on HNSCC。

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Promoting tumor growth：

Unlike normal fibroblasts, CAFs can promote the growth and malignancy of non tumor epithelial cellsSexual transformation; This function was first discovered in a human prostate cancer mouse model [55].It is widely believed that cancer cells and stromal cells (such as CAFs) dynamically co evolve during tumor progression [42].In a three-dimensional co culture model, normal breast fibroblasts inhibit the growth of breast tumors and the transformation of breast epithelial cells, while induction by CAF promotes the transformation of normal breast epithelial cell lines (MCF10A and EIII8 cells, respectively)[56].

Table 2: CAFs can lead to an increase in the malignancy of HNSCC, promoting tumor progression and metastasis, as shown in the table

Related signaling pathways	Impact on tumors	drug
EGFR	EGFR gene is amplified, overexpressed, or mutated in HNSCCs [57, 58].The collective invasion of squamous cell carcinoma cells (SCCs) is driven by EGF signals [59]	Verapamil, Diltiazem [59]
WNT	Cyclins produced and secreted in large quantities by CAFs in HNSCC, through typical Wnt/ β-The catenin signaling pathway promotes CSC phenotype and promotes tumor progression and metastasis in HNSCC [60]	Erotinib [60]

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Hippo	Transcription factor YAP is activated in CAFs [61],YAP activation in the matrix is further enhanced in the surrounding tumor areas of advanced cancers such as breast cancer and squamous cell carcinoma [62]	Gemcitabine [63]
NOTCH3	The expression of NOTCH3 in CAFs is significantly correlated with microvascular density in cancer stroma, and the expression of NOTCH3 in CAFs is associated with poor prognosis in OSCC patients [64]	Taristazumab [64]
JAK2-STAT3	The up-regulated protein recombines cancer related fibroblasts and promotes the invasion of oral squamous cell carcinoma through the JAK2-STAT3 pathway [65]	XX
IL-1β	IL-1 β Inducing the production of CXCL1, which in turn activates EGFR through CXCR2, leading to autocrine proliferation of oral malignant precursor cells [66]	Elotinib, Gifitinib, and Afatinib [66]
Hedgehog	CAFs are not only potential sources of HH ligands in tumor stroma, but may also respond to HH signaling through nuclear GLI-1 activation [67]	XX

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lncRNAH19/miR-675-5p/PFKFB3	Reprogramming of glycolysis in cancer related fibroblasts promotes the growth of oral cancer through the lncRNA H19/miR-675-5p/PFKFB3 signaling pathway [68]	Glycolytic enzyme inhibitors [68]

Later, two different subpopulations of CAF-N (normal) and CAF-D (different) were described in human oral squamous cell carcinoma (OSCC). CAF-N secretes hyaluronic acid (HA) and matrix metalloproteinases (MMPs), promotes tissue invasion of cancer cells and fibroblasts, and produces ECM rich in HA and immunosuppression, while CAF-D is TGF- β Source of induction of EMT in cancer cells and promotion of cell migration [69, 70].CAFs induce an increase in vimentin and a decrease in e-cadherin expression in oral cancer cell lines, indicating the occurrence of EMT [47, 71, 72].Epithelial regulatory proteins are a growth factor in the EGF family, and their overexpression can induce phosphorylation of JAK2/STAT3 and secretion of IL-6 in NFs, which plays an important role in promoting EMT in oral cancer cells [65].CAFs activate EMT signals through various cytokines, promote tumor cell invasion and metastasis, regulate the biological behavior of tumor cells, and thus affect the growth of OSCC [73, 74].

Promoting angiogenesis：

If new blood vessels are not formed to provide oxygen and nutrition, tumors cannot sustain their own growth in the body [75].The key steps in tumor angiogenesis include the aggregation of endothelial progenitor cells and the migration of vascular endothelial cells [76].CAFs enhance tumor angiogenesis by inducing the mobilization and aggregation of endothelial progenitor cells [35, 77].And CAF can secrete various vascular growth factors, such as VEGF, PDGF, CXCL-12, or HGF, promoting ECM remodeling, proliferation of ECs, and aggregation of ECs and surrounding cells into the tumor [78-

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[80].PDGF and VEGF also have an autocrine effect on CAFs, further stimulating the production of other angiogenic factors such as IL-6, IL-8, and placental growth factor (PGF)[81, 82].Studies have shown that in animal experiments, injecting CAFs and tumor cells subcutaneously into mice increases the rate of peripheral angiogenesis [83].Tumor angiogenesis is essential for tumor growth, invasion, and metastasis. Currently, the gold standard for describing tumor angiogenesis is histological MVD technology [84].Wang et al. found the characteristics of CAFs in head and neck squamous cell carcinoma (HNSCCs) [76];They found that in the matrix of nasopharyngeal carcinoma (NPC), fibroblasts α- The expression of SMA is significantly higher; In NPC cells, the immune response intensity of SDF-1 and CXCR4 secreted by CAFs is also high, indicating the presence of endothelial progenitor cells in both cancer and stromal cells of NPC. Stromal cells enhance neovascularization in a VEGF - and SDF-1 dependent manner.

Promoting tumor proliferation and metastasis：

CAFs secrete multiple factors, such as TGF- β 1. CXCL-12, FGF, POSTN, osteopontin (OPN), hepatocyte growth factor (HGF), IL-6, and IL-22 directly stimulate tumor proliferation and growth through their respective signaling pathways; For example: integer/FAK src (POSTN), Wnt/ β- Catenin (HGF and OPN), PI3K/mTOR (CXCL-12, HGF and IL-22), MAPK (IL-6, TGF- β And FGF) or Hippo (EVs)[85-92].Ramos Vega et al. demonstrated that, α- There is a significant association between SMA positive CAF cells and advanced clinical stages and poorly differentiated tumors of laryngeal cancer and HNSCC cancer [5].The possible mechanisms by which CAFs promote transfer are also diverse; CAFs can secrete cytokines and chemokines to specifically support tumor progression; For example, the chemokines of CCL5 acting on cancer cells can promote invasion and metastasis [93].For advanced CAFs, also as a subtype of CAFs, it can secrete excessive IL-8, which is the mediator of the interaction between cancer cells and CAF, and promotes the invasion and metastasis of pancreatic cancer

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cells [94].Late stage CAFs can also inhibit the immune response to tumors and reshape the extracellular matrix, promoting tumor invasion [95].

CAFs may also lead to bone invasion of head and neck tumors [71].Bone resorption usually involves the activation of osteoblasts through the interaction between the receptor activator of nuclear factor kappaB (RANK) and its osteoblast secretory ligand (RANKL); Bone protein growth hormone (OPG), as a receptor for RANKL, prevents excessive bone resorption by preventing RANK-RANKL interactions [96, 97].Oral cancer cells and stromal cells both secrete RANKL, but CAFs have been shown to promote osteoclast resorption to a greater extent in vitro and induce multinucleation of mouse macrophages, which may be osteoblasts [96].

Research has shown that when cancer cells carry their own ectopic stromal cell fragments, their survival ability after entering the circulation is greater; In addition, when these circulating tumor cells with matrix components and cancer related fibroblasts are depleted, the number of lung metastases is significantly reduced and the survival rate is prolonged; This indicates the importance of CAFs in the development of transfer [94, 95].

Table 3: Role of cancer-associated fibroblasts (CAFs) in tumor angiogenesis, proliferation, metastasis, and bone invasion

Category	Mechanisms	Key Molecules/Factors	Effects	References
Promoting Angiogenesis	Aggregation of endothelial progenitor cells	CAFs mobilize endothelial progenitor cells	Enhances tumor angiogenesis	[35, 77]
	Migration of vascular	VEGF, PDGF, CXCL-12, HGF	Promotes ECM remodeling, endothelial cell	[78-80]

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	endothelial cells		proliferation, and tumor vascularization	
	Autocrine signaling in CAFs	IL-6, IL-8, PGF	Further increases angiogenic factor production	[81, 82]
	Experimental validation	Injection of CAFs and tumor cells in mice	Increases peripheral angiogenesis	[83]
	Tumor angiogenesis assessment	Histological MVD technology	Gold standard for describing angiogenesis	[84]
	CAFs in head and neck cancers (HNSCC, NPC)	α-SMA, SDF-1, CXCR4, VEGF	Enhances neovascularization via VEGF and SDF-1	[76]
Promoting Tumor Proliferation and Metastasis	Secretion of growth factors	TGF-β1, CXCL-12, FGF, POSTN, OPN, HGF, IL-6, IL-22	Stimulates tumor proliferation via multiple signaling pathways	[85-92]
	Key signaling pathways	Integrin/FAK/Src, Wnt/β-catenin, PI3K/mTOR, MAPK, Hippo	Drives tumor proliferation and metastasis	[85-92]
	CAFs in laryngeal and	α-SMA positive CAF cells	Associated with advanced clinical	[5]

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	HNSCC cancers		stages and poor differentiation	
	Secretion of cytokines and chemokines	CCL5, IL-8	Promotes invasion and metastasis, particularly in pancreatic cancer	[93, 94]
	Late-stage CAFs	IL-8, ECM remodeling	Inhibits immune response and promotes tumor invasion	[95]
Bone Invasion by Tumors	Bone resorption mechanism	RANK-RANKL interaction	Activates osteoclasts and promotes bone invasion	[96, 97]
	Regulation of bone degradation	OPG	Inhibits excessive bone resorption by blocking RANK-RANKL interaction	[96, 97]
	CAFs' role in bone invasion	RANKL secretion, osteoclast resorption induction	Promotes osteoclast activation and multinucleation of macrophages	[96]
Survival and Metastatic Potential	Circulating tumor cells (CTCs)	Tumor cells with CAF-associated stroma	Increased survival in circulation	[94, 95]
	Depletion of CAFs in CTCs	Reduced lung metastases, prolonged survival	Highlights importance of CAFs in metastasis	[94, 95]

The effect of CAFs on immune cells in tumor microenvironment：

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In HNSCC, CAFs can directly affect [98]And indirect impacts [49]Immune cells.On the one hand, CAFs induce apoptosis of CD4 and CD8T cells, while increasing the proportion and migration of regulatory T cells (Tregs) that inhibit T cell anti-tumor response [98, 99].Impaired T cell proliferation may be due to the secretion of immunosuppressive cytokines by CAFs, as well as the expression of B7 family, B7H1 (PDL1), and B7DC (PDL2) [98].On the other hand, CAFs, whether acting alone or in collaboration with cancer cells, can cause monocytes to differentiate into the M2 macrophage phenotype of the original tumor [49, 71, 100].Then, these macrophages may secrete TGF- β、 IL-10 and arginase I have inhibitory effects on T cells [49].Once macrophages differentiate into the M2 phenotype, they also enhance growth, invasion, migration, and CSC characteristics to affect oral cancer cells [97].Similar effects of CAF have also been observed in esophageal squamous cell carcinoma, where the HGF released by CAF and its receptor MET interact with tumor cells to enhance their invasiveness [101].Dendritic cells (DCs), as known cells with strong antigen-presenting function, are responsible for presenting tumor antigens and activating specific immune responses. CAFs secrete TGF- β And VEGF has the ability to inhibit antigen presentation to T cells, leading to an anti-tumor immune response [102].

There are two main roles of stromal cells (especially CAFs) in immune regulation of tumor tissue; On the first hand, CAFs promote tumor development by inducing a chronic inflammatory state in cancer cells; The second aspect is to promote the survival of tumors, which can alleviate the body's immune response to tumors, which is also a crucial aspect [42, 103, 104].For HNSCC, in a study to investigate the relationship between CAFs and TAMs, Yu et al. demonstrated through immunohistochemical experiments that, α- The density of SMA positive and CAFs is closely related to CD-163 positive TAMs [105].

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The impact of CAF on drug resistance:

Resistance to cancer treatment often leads to further exacerbation of tumors, and many studies have investigated the role of stromal cell CAFs in conferring treatment resistance based on their response to anti-tumor therapy [2].Some research results in the literature have found a relationship between the resistance of stromal cells, especially CAFs, and various cancers, some of which include HNSCC's resistance to cetuximab [8];Estrogen receptor (ER) negative breast cancer is resistant to 5-fluorouracil and cyclophosphamide (FEC) treatment [10];Triple negative breast cancer is resistant to adriamycin [106].Among them, in the study of HNSCC's resistance to cetuximab, Johansson et al. established a co culture model of HNSCC and CAFs, and the results showed that HNSCC and CAFs co culture were resistant to cetuximab treatment, and this effect was concentration dependent [8].In breast, colorectal, and pancreatic tumors, CAFs can produce IL-6, IL-17A, PDGF, and insulin-like growth factor (IGF), which can activate NF of doxorubicin, 5-fluorouracil, and cisplatin- κ B and ERK pathways promote the stability of anti apoptotic proteins and the proliferation of cancer stem cells [29, 107-111].Studies have shown that TGF secreted by CAFs- β Has a certain impact on tumors [112],So targeting TGF secreted by CAFs- β It can reduce the resistance of tumors. For HNSCC, survival of CAF can still be observed in the body after cisplatin and radiotherapy [113, 114]. And after treatment, it may induce the activation of advanced CAF phenotype in oral fibroblasts [115-117].

Treatment methods for CAFs:

The role of CAFs in promoting tumor occurrence, proliferation, and metastasis during the development of cancer makes them therapeutic targets for cancer intervention. However, the treatment of CAFs faces many obstacles and challenges. Due to the lack of specific CAF cell surface markers, this limits the direct action of drugs and makes it

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difficult to accurately target CAFs without damaging normal tissues [2].At present, there are two types of targeted treatments for CAFs, one is to directly act on CAFs (remove CAFs or inhibit their activity)[118, 119]The second type indirectly affects CAFs (by inhibiting downstream effector molecules of CAFs and targeting extracellular matrix)[120-122].

FAP is not only a surface marker activated by over 90% of human cancer fibroblasts, but also regulates the differentiation and proliferation of myofibroblasts [123]. FAP5-DM1 is a novel anti FAP monoclonal antibody (MAb) that can inhibit tumor growth for a long time in lung cancer and pancreas, and there are no toxic reactions observed even in head and neck cancer metastasis models [124].FAP monoclonal antibody F19 has in vivo safety and has been used in phase I clinical trials in patients with rectal cancer and small cell lung cancer [125].

α- SMA, as a myofibroblast marker in CAFs, has been shown in an animal experiment to target α- SMA enhances the infiltration of immunosuppressive CD3+Foxp3+Treg cells into tumors, ultimately leading to increased tumor invasiveness and reduced animal survival rate [126].

Due to FAP and α- SMA is not entirely expressed by fibroblasts, which greatly hinders the accuracy of targeting CAFs using the above methods. Therefore, the potential source of cells targeting CAFs may be another method to reduce CAF in tumors; Endothelial cells are a potential source of CAFs, and phase III clinical trials are underway to target these CAF precursors with bevacizumab [127].

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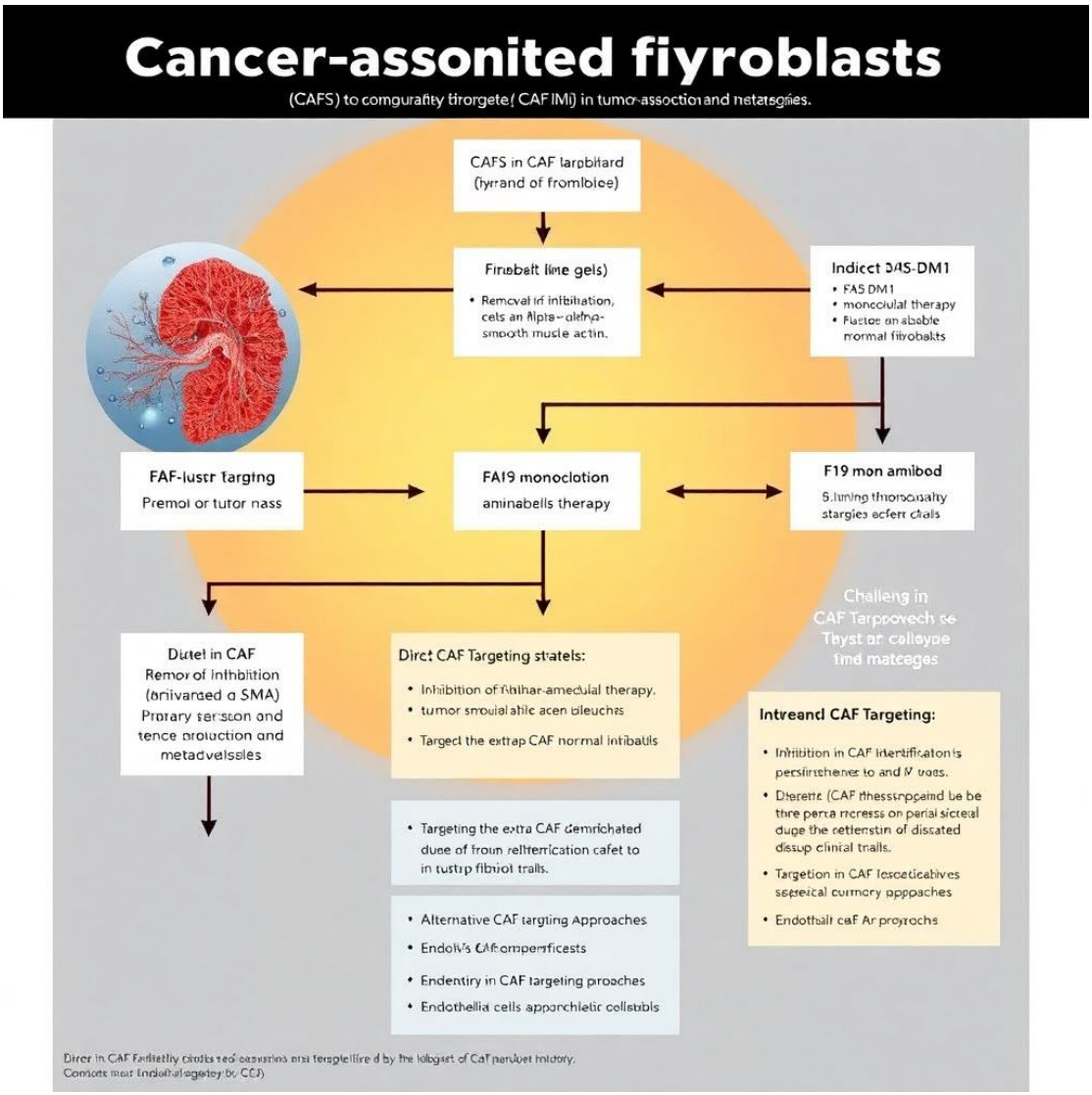

Conclusion：

In summary, CAFs are a unique and clinically relevant component of TME, which is indispensable for better understanding the complex interactions between TME, ECM, and cancer itself. CAFs are heterogeneous cells that promote the growth of HNSCC by secreting or transporting proteins and metabolites. If we can better understand the role of CAFs in head and neck TME, we can provide more specific personalized treatment plans for the function and phenotype of CAFs. The rapid development of CAF biology

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knowledge has laid a solid foundation for developing new treatment strategies for cancer treatment. In early studies, the difference between CAFs and normal fibroblasts could be distinguished by several typical markers, but the discovery of specific recognition markers for CAFs was not achieved. With continuous efforts and understanding of the molecular mechanisms underlying CAF pathology, many drugs targeting key regulatory factors are currently undergoing clinical and/or preclinical evaluations. With the development of single-cell sequencing and the advancement of cell specific new biomaterials and other technologies, we can selectively eliminate the ability to promote tumor CAF or reverse its tumor promoting activity, which may become an effective treatment method for cancer alone or in combination with other cancer treatment methods.

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