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Review Article

Roles and subtypes of cancer-associated fibroblasts (CAFs) in thyroid cancer

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Abstract: Thyroid cancer (TC) is one of the most common tumors of the endocrine system around the world. Most thyroid cancer patients have a favorable prognosis, but a minority develop into treatment resistance, resulting in a very poor prognosis. In addition to the tumor cell component, TC is characterized by a reticula and dynamic tumor microenvironment (TME), in which tumor cells and stromal cells interact with each other in an intricate network of interactions. Cancer-associated fibroblasts (CAFs), one of the most abundant stromal cells in TME of thyroid cancer, actively participate in various aspects of tumorigenesis including immunomodulation, extracellular matrix (ECM) remolding, metastasis. With the advent of sing-cell sequencing, an increasing number of CAF subtypes in TME of thyroid cancer have been identified, and their tumor-promoting roles are becoming progressively clearer. To explicate the potential of CAFs as therapeutic targets for TC, this review will discuss the origin of CAFs, their heterogeneity, plasticity, crosstalk and role in tumorigenesis of TC.

Keywords: Thyroid cancer, cancer-associated fibroblasts (CAFs), immunomodulation, crosstalk, stiffness, extracellular matrix (ECM) remodeling, therapeutic targets

Introduction

The incidence of thyroid cancer (TC) has increased steadily in the United States over the past few decades, driven largely by the rise in papillary thyroid cancer (PTC) [1-3]. The remaining subtypes of thyroid cancer include follicular, anaplastic, and medullary thyroid cancer. Except for medullary thyroid carcinoma (MTC) originating from parafollicular c-cells, most thyroid cancers originate from follicular cells. Based on histological and clinical characteristics, thyroid cancers originating from follicular cells can be divided into well-differentiated carcinoma, poorly differentiated carcinoma (PDC) and anaplastic (undifferentiated) carcinoma (ATC). Well-differentiated carcinomas, namely papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), account for 90% of thyroid cancers [4, 5]. Localized tumors are often curable through surgical resection, however, some of them have developed to locoregional or even distant metastatic disease without timely treatment. In the recurrent or metastatic settings, surgery combined with radioactive iodine (RAI) ablation and thyroid stimulating hormone (TSH) suppression therapy can still achieve a favorable prognosis for most patients [6], while a subset of patients will eventually progress to a RAI-refractory status or even succumb to it [7], who may be suitable for alternative therapies including molecular targeted inhibitors and immunotherapies [8, 9].

Since its discovery in the 19th century, tumor microenvironment (TME) has proven to be associated to tumor growth, invasion, resistance to current treatments and poor prognosis [10]. TME is a complex ecosystem surrounding a tumor, composed of cancer cells, stromal (including blood vessels, immune cells, fibroblasts and signaling molecules) and the extracellular matrix [11]. Cancer associated-fibroblasts (CAFs), a group of mesenchymal cells

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that reside in or near tumor cells, are considered a prominent and heterogeneous cell population in the desmoplastic tumor TME, at the center of a multidirectional network of interactions with tumor, immune and endothelial cells [12]. By secreting a wide range of factors and performing diverse functions, CAFs actively promote tumorigenesis in a bulk of cancers, including thyroid cancer.

In this work, it primarily focuses on CAFs in thyroid cancer and their roles in tumor progression. It also explores the potential of targeting CAFs as a novel therapeutic strategy.

Characteristics of cancer-associated fibroblasts (CAF) in TC

The tumor microenvironment (TME) of thyroid cancer comprises a complex microenvironment composed of a dynamic stroma containing both tumor and stromal cells as well as acellular components. All these components lead to the stiff extracellular matrix (ECM) characteristic of thyroid cancer [13]. With the application of single-cell RNA sequencing (scRNA-seq) technology in pan-cancer research, growing number of molecular components of TME are identified in TC [14]. The cellular components of the TC TME include, but are not limited to, cancer cells, CAFs, tumor-associated endothelial cells (TECs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), tumor infiltrating lymphocytes (TILs), natural killer (NK) cells and myeloid-derived suppressor cells (MDSCs) [15, 16]. These cells communicate with each other in a complex network, leading to tumorigenesis [17]. The acellular components of the TME in thyroid cancer mainly secreted by CAFs include periostin (POSTN), collagens, fibronectins and tenascin-C (TNC), creating a highly stiff and desmoplastic environment [18].

Cancer-associated fibroblasts (CAFs), which belong to the stromal compartment, are predominant components of the tumor microenvironment (TME). More recently, researchers have proposed that this subpopulation of hyperactivated fibroblasts - characterized by anti-apoptotic signaling, enhanced proliferative capacity, elongated morphology, localization within or adjacent to tumor masses, and the absence of mutations found in cancer cells - can be defined as CAFs [19, 20]. This has sparked growing interest in exploring the origins of CAFs. To date, the precise origin of CAFs remains unclear. However, multiple studies have demonstrated that they can arise from diverse cellular sources, including resident stromal fibroblasts, endothelial cells via endothelial-to-mesenchymal transition (EndMT), epithelial cells via epithelial-to-mesenchymal transition (EMT), and resident mesenchymal stem cells (MSCs). Additional sources include pericytes undergoing pericyte-to-fibroblast transition (PFT), stellate cells, smooth muscle cells, and adipocytes [21-24]. CAFs may also originate from recruited cell populations such as bone marrow-derived MSCs, fibrocytes, and hematopoietic stem cells. Recent studies suggest that quiescent fibroblasts adjacent to tumors are the principal sources of CAFs in thyroid cancer [25, 26]. Resident thyroid MSCs may also be one of the major sources, however, this requires further experimental validation. Other precursor cells may also contribute to the CAF pool in thyroid cancer through mediation by tumor cell-derived factors [25, 26]. The origin and subtypes of CAFs in thyroid cancer are shown in **Figure 1**. Although some studies have suggested that CAFs may originate from tumor cells themselves, this has not yet been reported in thyroid cancer. Under neoplastic conditions, quiescent fibroblasts become activated, begin secreting extracellular matrix (ECM) proteins, and express specific markers such as α-SMA, FAP, and PDGFR-α [27, 28].

Clinical evidences have confirmed that CAFs played a pivotal role in tumor promotion and invasion. Indeed, high CAF scores have been reported to be positively correlated with predicting tumor aggressiveness, lymph node metastasis and poor prognosis in thyroid cancer [26, 29]. Recent studies also indicate that CAFs may aid in patient stratification [30]. Notably, anaplastic thyroid cancer exhibits the highest CAF levels, whereas *RAS*-like well-differentiated cancers show the lowest predicted levels [31], Moreover, patients with a high abundance of α-SMA$^+$ CAFs tend to present with advanced tumor stages (III/IV) and poorer clinical outcomes [32]. CAFs have also been implicated in therapeutic resistance, likely due to the extracellular proteins they secrete, which act as physical barriers to drug penetration and thereby facilitate tumor growth and invasion. Furthermore, Tocilizumab, an inhibitor targeting

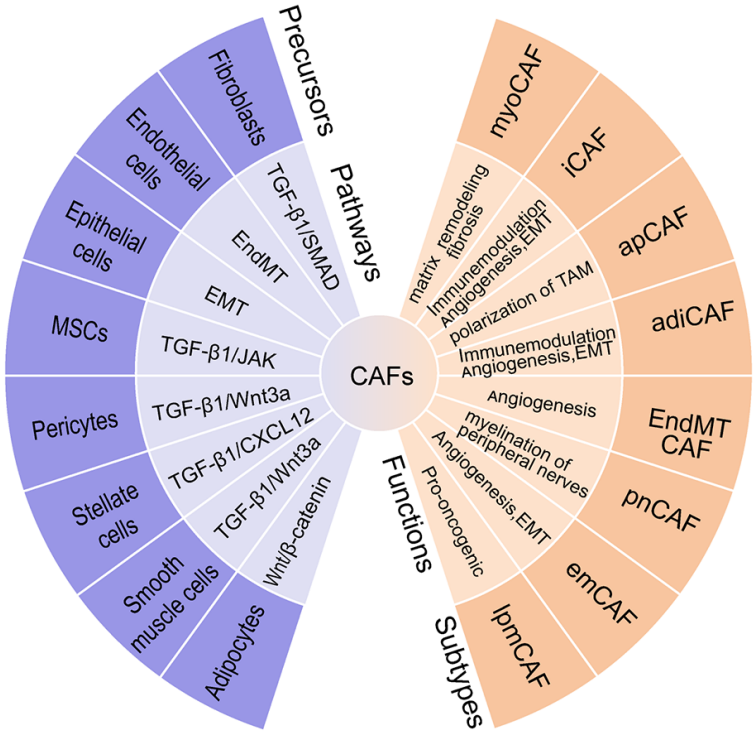

Figure 1. Origin, activation signals, subtypes, and function of cancer-associated fibroblasts (CAF) in thyroid cancer.

CAF-secreted factors, has been shown to suppress tumor cell proliferation and dedifferentiation in B-CPAP and TPC-1 cell lines [33]. With the advent of single-cell RNA sequencing (scRNA-seq), the classification of CAFs in thyroid cancer has become increasingly refined. Pu et al. identified two major fibroblast subpopulations: myofibroblastic CAFs (myoCAFs) and inflammatory CAFs (iCAFs) [34, 35]. Further studies demonstrated that iCAFs are predominantly present in anaplastic thyroid cancer (95%), whereas myoCAFs represent the major CAF population in papillary thyroid carcinoma (75%) based on relative cellular frequency analyses [35]. Recent findings indicate that tumor-adjacent myoCAFs are closely associated with invasive tumor cells exhibiting partial epithelial-to-mesenchymal phenotypes, while tumor-distant iCAFs are enriched in inflammatory autoimmune thyroid lesions [36].

Papillary thyroid carcinoma (PTC) can be classified into two molecular subtypes: *BRAF*-like (BL) and *RAS*-like (RL), based on gene expression profiles resembling either $BRAF^{V600E}$ or *RAS* mutations [37]. *BRAF* mutations, the most prevalent genetic alterations in thyroid cancer, are typically associated with increased tumor aggressiveness. Differential gene expression analyses by Lim et al. revealed that CAFs are more abundant in aggressive BL-PTCs but less enriched in RL-PTCs, and are significantly associated with older age, extrathyroidal extension, and advanced TNM stage [37, 38]. These findings are consistent with *in vitro* studies by Yang et al [39]. Similarly, Minna et al. reported that CAFs are enriched at the invasive front and in senescent tumor cells in *BRAF*-mutant thyroid cancers (including PTC, PDTC, and ATC), where reciprocal interactions promote tumor invasion [40]. Moreover, *BRAF* activation enhances the secretion of factors that promote CAF recruitment, proliferation, and migration [41]. As observed in other tumor types, CAFs may function as a double-edged sword, exerting both pro- and anti-tumorigenic effects; however, their tumor-suppressive roles in thyroid cancer remain largely unexplored.

CAF heterogeneity and plasticity in TC

The CAFs heterogeneity exists at multiple levels: cellular level depending on the state/function of the fibroblast, microenvironment level depending on the communication with other cellular and acellular components, regional level depending on the residing tissue and its function [42]. Conceptually, CAFs are better defined as a dynamic cellular state rather than a fixed entity. Primarily derived from quiescent fibroblasts and resident thyroid MSCs, recent scRNA-seq studies have revealed significant transcriptomic diversity among CAF subtypes within the thyroid cancer TME. Although no consensus has been reached regarding the exact number or nomenclature of CAF subtypes, several widely recognized categories include myofibroblastic CAFs (myCAFs), enriched in ECM-related transcripts; inflammatory CAFs (iCAFs), enriched in inflammatory and growth factor-related transcripts; and antigen-presenting CAFs

Table 1. Cancer-associated fibroblast (CAF) subtypes in thyroid cancer and their functions, markers identified by scRNA-sequencing

CAF subpopulation	Markers	TC type (studies included)	Function	Experimental evidence
myoCAF	*ACTA2, TAGLN, MYLK, MYL9, RGS5*	PTC (main) PDTC, ATC	Matrix remodeling and fibrosis	H&E imaging, GSVA, SCENIC analysis
iCAF	*CFD*, *PLA2G2A*, *CCDC80, S100A10, IGFBP5*	ATC (main) PTC	Immune modulation, Angiogenesis, EMT	SCENIC analysis, EMT score, Trajectory analysis
apCAF	*HLA-DRA, LYZ, TYROBP, HLA-DRB1, HLA-DPB1*	ATC	Polarization and function of TAMs	SCENIC analysis
adiCAF	*CFD, PTGDS, FBLN1, GSN, IGFBP6*	PTC	Angiogenesis, EMT, immunomodulation	SCENIC analysis, EMT score, Trajectory analysis
EndMTCAF	*PLVAP, RAMP2, SLC9A3R2, RGCC, FLT1*	ATC	Angiogenesis	Gene ontology enrichment analysis
pnCAF	*S100B, GPM6B, PLP1, LGI4, NRXN1*	ATC	Myelination of peripheral nerves	SCENIC analysis
emCAF	*LAMP5, CYP1B1, AGT, F2R, ENC1*	PTC	Angiogenesis, EMT	SCENIC analysis
lpmCAF	*CD36, STEAP4, FABP5, C20CRL27, GJA4*	PTC	Pro-oncogenic	Scratch assay Transwell assay

Abbreviations: EMT, epithelial-to-mesenchymal transition; TAMs, tumor-associated macrophages; GSVA, gene set variation analysis; SCENIC, single-cell regulatory network inference and clustering.

(apCAFs), characterized by major histocompatibility complex class II (MHC II) expression [15, 34]. More recently, additional subtypes have been identified, including lipid metabolism-associated CAFs (lpmCAFs) and extracellular matrix-related CAFs (emCAFs), further underscoring CAF heterogeneity in thyroid cancer [43]. The continuous discovery of new CAF subtypes through single-cell transcriptomic analyses highlights the heterogeneity of these cells (**Table 1**).

Morphologically and transcriptionally distinct from their precursor cells, CAFs exhibit considerable phenotypic plasticity (**Figure 1**). Different CAF subtypes, such as myoCAFs and iCAFs, can arise from the same precursor cells and coexist within the same tumor, supporting the presence of a dynamic plasticity program in thyroid cancer [36]. Moreover, CAF subtypes can interconvert in response to specific microenvironmental cues, although the underlying mechanisms remain to be fully elucidated. Notably, Luo et al. identified a TAM-CAFap-CAFmyo evolutionary trajectory contributing to dynamic transitions between myoCAFs and apCAFs in anaplastic thyroid cancer [15]. Using pseudotime trajectory analysis, Wang et al. demonstrated a transition from iCAFs to myoCAFs, potentially associated with late-stage metastasis [30]. The inferred cellular transitions described in this study are based on computational trajectory inference derived from transcriptomic data. While these approaches (e.g., pseudotime analysis) suggest potential lineage relationships, they do not constitute direct evidence of cellular differentiation. Importantly, these findings lack validation through lineage-tracing or *in vivo* fate-mapping experiments. Therefore, the proposed transitions should be interpreted as hypothetical models rather than definitive differentiation pathways. Similarly, Zhang et al. found that adipocyte-related CAFs (adi-CAFs) exhibited the highest pseudotime scores, whereas vascular smooth muscle cells (VSMCs) and myoCAFs appeared in earlier stages, suggesting that adi-CAFs may differentiate from VSMCs or myoCAFs under tumor-derived stimuli [44]. In addition, circ_14580 secreted by PTC cells has been shown to promote CAF marker expression by stabilizing CTSW, indicating its role in modulating CAF phenotypes [45]. Overall, the presence of dynamic phenotypic transitions, rather than static CAF subtypes, suggests that CAFs can rapidly adapt to tumor demands and the evolving TME, thereby promoting tumor progression. The mechanisms underlying these transitions remain poorly understood and warrant further investigation.

Multiple roles of CAFs in thyroid cancer

Crosstalk and signaling of CAF-mediated tumor promotion and invasion

Cancer-associated fibroblasts (CAFs) primarily interact with tumor cells and other stromal components within the tumor microenvironment (TME) during thyroid tumorigenesis by secreting cytokines, chemokines, growth factors, extracellular vesicles (EVs), and extracellular matrix (ECM) proteins [46]. Recent single-cell RNA sequencing (scRNA-seq) studies have demonstrated that CAFs engage in extensive and dynamic interactions with diverse cell populations in the TME, thereby activating multiple signaling pathways that contribute to tumorigenesis [47, 48]. Among the various components of the CAF secretome, cytokines play a central role in mediating tumor cell-CAF crosstalk. CAFs synthesize and secrete CXCL12, a potent inflammatory chemokine that enhances thyroid cancer cell proliferation, migration, and invasion [23]. CXCL12, also known as stromal cell-derived factor-1 (SDF-1), binds to CXCR4 and CXCR7 receptors on thyroid cancer cells, thereby activating several downstream signaling pathways, including mTOR, ERK1/2, SAPK/JNK, Akt, p38, and BTK [26, 49]. In addition, co-culture experiments have shown that CAFs produce high levels of IL-6 [50, 51]. The accumulation of IL-6 subsequently activates the JAK/STAT3 signaling pathway, promoting the proliferation of HTh74 and HTh74R cells [52]. Conversely, thyroid cancer (TC) cells also secrete IL-6, which induces quiescent fibroblasts (such as MRC-5 cells) to acquire CAF-like characteristics, including the expression of markers such as FAP and α-SMA [50], Furthermore, IL-6 promotes CAF proliferation through activation of the SRC/AKT pathway. Notably, IL-6 has also been reported to suppress sodium/iodide symporter (NIS) expression via the ERK and JNK pathways, leading to reduced iodine uptake and resistance to radioiodine therapy [33]. Another cytokine secreted by CAFs, IL-8, has been shown to enhance the stemness of thyroid cancer cells through activation of the IL-8/CXCR1/CXCR2 signaling axis [53-55]. Beyond cytokines, CAFs can exert pro-oncogenic effects through the secretion of exosomes containing molecules such as LncRNA-MEG3 and CREB1. LncRNA-MEG3 has been reported to inhibit Rac1 expression by interacting with its 3'-UTR in thyroid cancer cell lines. Given that Rac1 is a key Rho GTPase involved in cell motility and cytoskeletal remodeling [56, 57], this interaction suppresses tumor cell migration and invasion, suggesting a tumor-suppressive role of CAF-derived LncRNA-MEG3. CREB1, an important transcription factor regulating gene expression, can also be delivered by CAF-derived exosomes. Acting as a transcriptional activator of CCL20, CREB1 enhances thyroid cancer progression by upregulating CCL20 expression and facilitating immune evasion through the inhibition of $CD8^+$ T cell proliferation and the induction of apoptosis [58]. In addition, CAFs secrete several pro-tumorigenic proteins, including WNT2, Protein S (PROS1), and POSTN, which promote tumor cell proliferation and invasion. WNT2, produced by CAFs at the invasive front of tumors, interacts with TNC to activate and potentiate the Wnt/β-catenin signaling pathway, thereby enhancing tumor burden, invasion, and metastasis [59]. PROS1, which is highly expressed in adipogenic CAFs, is significantly upregulated in thyroid tumor tissues compared to normal tissues. Intercellular communication analyses have revealed that the PROS1-MERTK ligand-receptor interaction is markedly enhanced in stage II and III thyroid tumors. *In vivo* studies further demonstrate that PROS1 promotes papillary thyroid carcinoma (PTC) progression by activating both the Wnt/β-catenin and TGF-β/SMAD2 signaling pathways [44]. Moreover, POSTN secreted by CAFs activates the integrin-FAK-STAT3 signaling pathway, leading to increased tumor cell proliferation and IL-4 production. The accumulation of IL-4, in turn, stimulates CAFs to produce more POSTN via activation of the IL-4/STAT6 pathway, forming a positive feedback loop [29]. In addition to IL-4 and IL-6, thyroid cancer cells can also secrete IL-1α and TGF-β to activate CAFs. Flow cytometry analysis has shown that IL-1α stimulation combined with CREB3L1 knockdown in anaplastic thyroid cancer (ATC) cells reverses the reduction of $\alpha\text{-SMA}^+$ CAFs co-cultured with 8505C cells [60]. Furthermore, through paracrine signaling mediated by TGF-β, thyroid cancer cells induce CAF activation and upregulate FAP expression, which in turn promotes tumor cell proliferation, invasion, and migration [61].

In addition to their interactions with tumor cells, CAFs also communicate extensively with

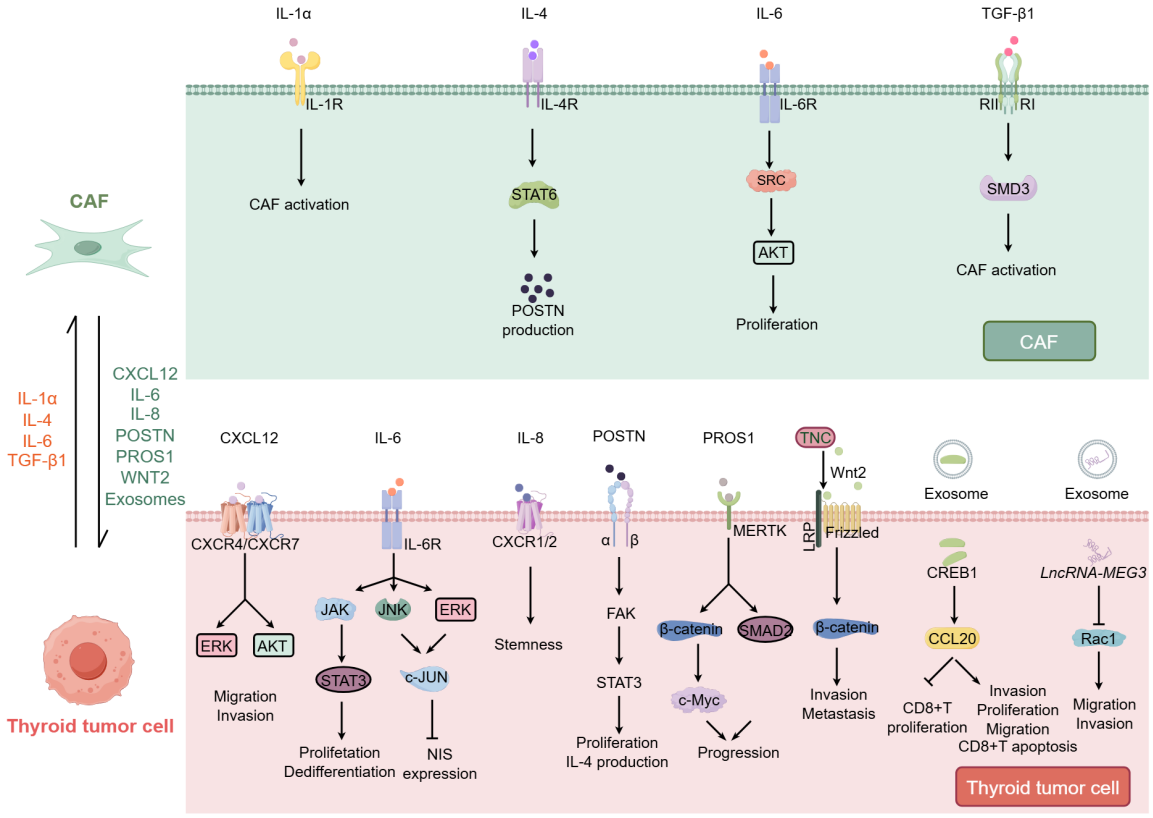

Figure 2. Tumor cell-CAF crosstalk in thyroid cancer: mechanisms and pathways. The crosstalk between tumor cells and CAFs triggers the activation of multiple signaling pathways in both cell types. This contributes to tumor cell invasion, proliferation, metastasis and migration, CAF activation that facilitates tumor growth. Abbreviations: CAF, cancer-associated fibroblast; CXCR, C-X-C chemokine receptor; CXCL, C-X-C chemokine ligand; ERK, extracellular regulated protein kinases; AKT, Protein kinase B; IL, interleukin; JNK, c-Jun, N-terminal kinase; JAK, Janus kinase; NIS, sodium/iodide symporter; POSTN, periostin; FAK, focal adhesion kinase; STAT, signal transducer and activator of transcription; PROS, Protein S; MERTK, mer tyrosine kinase; TNC, tenascin-c; LRP; CREB, cAMP response element-binding protein; CCL, C-C motif ligand; TGF-β1,transforming growth factor beta 1.

immune cells in the TME to regulate antitumor immunity. Cell-cell communication analyses have revealed that CAFs interact with multiple immune cell types, including $CD4^+$ T cells, $CD8^+$ T cells, B cells, regulatory T cells (Tregs), natural killer (NK) cells, and monocytes. These interactions are mediated through signaling pathways such as the macrophage migration inhibitory factor (MIF) pathway via CD74-CXCR4 and CD74-CD44 complexes, CXCL12-CXCR4 signaling, and MDK-NCL interactions. Conversely, CAFs receive signals from immune cells through the MIF-ACKR3 pathway [62]. The complex crosstalk between CAFs and tumor cells, along with the associated signaling pathways, is shown in **Figure 2**.

ECM remodeling and tumor stiffness

Like other tumors, cancer-associated fibroblasts (CAFs) in thyroid cancer remodel the extracellular matrix (ECM) of the tumor microenvironment (TME) through diverse mechanisms. One of the most distinctive features of CAFs is their ability to secrete ECM components [63]. They synthesize and release proteins directly into the extracellular space, including POSTN, TNC, FN1, and COL1A1, which facilitate crosstalk between tumor cells and stromal cells and contribute to tumor progression and invasion. POSTN, a glycoprotein, is produced by CAFs in thyroid cancer via activation of the STAT6 pathway. Its abundance promotes thyroid tumor growth both *in vivo* and *in vitro* through the integrin-FAK-STAT3-IL-4 signaling pathway and is associated with poorer overall survival in patients with thyroid cancer (TC) [29]. TNC, another ECM protein, is overexpressed at the tumor-stroma interface in thyroid cancer [59] and functions as a tumor-promoting mediator. Hartmann et al. demon-

strated that the interaction between TNC and WNT2 enhances the Wnt/β-catenin signaling pathway, thereby promoting tumor invasion and metastasis in mouse models. FN1 has been well established to play critical roles in wound healing, cellular differentiation, growth, migration, and adhesion [64]. Geng et al. reported that FN1 overexpression in thyroid cancer is associated with increased M2 macrophage infiltration and poor prognosis [65]. Furthermore, Wang et al., using bulk and single-cell RNA sequencing, identified aberrant interactions between T/NK cells and other cell types mediated by FN1 in papillary thyroid carcinoma (PTC), suggesting that FN1 may serve as a potential therapeutic target within the TME [66]. Type I collagen (COL1A1) is one of the most abundant and extensively studied ECM components in the TME. Using a mouse model driven by thyroid-specific expression of oncogenic *BRAF*^{V600E}, Jolly et al. found that COL1A1 is secreted by CAFs at the invasive front of tumors and subsequently cross-linked by lysyl oxidase (LOX) produced by thyroid cancer cells [67]. This coordinated process increases matrix stiffness and promotes the progression from PTC to poorly differentiated thyroid carcinoma (PDTC) [40]. Consistently, the content of type I collagen in PTC lesions is positively correlated with tissue stiffness. Moreover, Hu et al. identified enhanced ECM deposition, integrin-mediated signaling, and growth factor activity in COL1A1-rich PTC samples [68], supporting its potential as a therapeutic target in the TME. Notably, recent findings indicate that miR-29b-3p suppresses PTC cell invasion and metastasis by directly targeting the 3'-UTRs of COL1A1 and COL5A1 [69]. Interestingly, although COL1A1 is generally considered to promote tumor progression by increasing tissue stiffness, it has been reported to inhibit tumor growth in pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC) metastasis [70], providing new insights into its context-dependent roles. COL1A1 promotes the progression and metastasis of PTC [71], especially in *BRAF*-mutant PTC [40, 67]. In *BRAF*^{V600E} tumor cells model, fibroblasts are recruited to the thyroid TME, which activate fibroblasts to produce and deposit Col 1. In turn, tumor cells cross-link the fibroblast derived Col 1 fibers in the TME via upregulation of *Lox*, resulting in a stiffer Col 1 matrix that augments tumor cell motility and promotes tumor progression [67].

In addition to directly remodeling the ECM, CAFs can indirectly influence ECM dynamics through interactions with immune cells. CAFs interact with macrophages via the CXCL12/CXCR4 signaling axis, promoting their polarization toward the M2 phenotype [62]. These M2 macrophages, in turn, secrete increased levels of TGF-β, further activating CAFs and establishing a positive feedback loop that drives malignant progression [72, 73]. Recent studies have also shown that SPP1^{+} macrophages, activated through interactions with CD44^{+} CAFs, contribute to intratumoral angiogenesis [15].

CAFs in immunomodulation and immunosuppression

Tumor cell proliferation is facilitated within an immunosuppressive microenvironment, and one key strategy employed by tumor cells is the evasion of immune surveillance, a process in which CAFs play a pivotal role [74]. Accumulating evidence indicates that CAFs in the TME are critical regulators of both innate and adaptive antitumor immune responses by modulating tumor-infiltrating immune cells [75]. In addition, CAFs promote the expression of immune checkpoint molecules and remodel the ECM, thereby indirectly influencing immune cell recruitment and function [74, 76]. CAFs secrete a range of pro-inflammatory cytokines, including macrophage migration inhibitory factor (MIF), TGF-β, IL-4, IL-6, IL-8, IL-10, and IL-13 [13, 62, 77, 78], which are primarily involved in macrophage recruitment and tumor progression. Using single-cell and bulk RNA sequencing, Li et al. demonstrated that inflammatory CAFs (iCAFs) promote the M2 polarization of tumor-associated macrophages (TAMs) via the CXCL12/CXCR4 pathway in thyroid cancer. Notably, M2 macrophages downregulate METTL3, leading to stabilization and upregulation of CD70, which increases the proportion of regulatory T cells (Tregs) and terminally exhausted T cells [79]. Moreover, tumors with high CAF abundance exhibit reduced infiltration of immune cells such as CD4^{+} T cells, B cells, and plasma cells, alongside increased infiltration of Tregs, monocytes, and myeloid cells [80]. In co-culture experiments, Yang et al. showed that TPC1-*BRAF*^{V600E} cells promote CAF proliferation, which in turn upregulates multiple

immune checkpoint molecules, including PD-L1, CTLA-4, LAG-3, TIGIT, and ICOS [39]. However, direct evidence demonstrating checkpoint molecules expression specifically in CAFs at the protein level remains limited. CAF proliferation was also associated with increased monocyte and activated dendritic cell (DC) populations, along with a reduction in M0 macrophages [39]. Furthermore, Wen et al. used Gene Set Enrichment Analysis (GSEA) to demonstrate that CAF abundance is negatively correlated with $CD4^+$ T cell infiltration and positively correlated with neutrophil enrichment in differentiated thyroid carcinoma (DDTC). In patients with high CAF levels, immune checkpoint markers such as CD274, PDCD1LG2, CD86, CD80, and CTLA4 were significantly upregulated [81]. In addition to cytokine secretion, CAFs can release exosomes to modulate antitumor immunity. For instance, CAF-derived exosomes carrying CREB1 have been shown to upregulate CCL20 expression, thereby inducing apoptosis in $CD8^+$ T cells in xenograft models [58].

Although immune checkpoint molecules are predominantly expressed on immune and tumor cells, their expression on CAFs remains to be fully elucidated. Notably, programmed death ligand-1 (PD-L1) has been reported to be expressed on CAFs in non-small cell lung cancer and triple-negative breast cancer, where it is associated with favorable prognosis [82, 83]. Additionally, ECM components such as COL1A1, matrix metalloproteinases (MMPs), and hyaluronic acid have been implicated in immunomodulation within the TME in other tumor types [84]. However, their roles in immune suppression in thyroid cancer warrant deeper exploration.

Imaging CAF

Each epithelial tumor with a diameter greater than 1 mm comprises a complex and heterogeneous tumor microenvironment. More than 90% of these epithelial tumors - including breast, lung, ovarian, colorectal, and thyroid cancers-exhibit strong expression of the CAF marker fibroblast activation protein (FAP) [85, 86]. In contrast, FAP is generally absent in resting fibroblasts of normal healthy tissues [87]. The development of FAP-targeted probes has demonstrated significant diagnostic and therapeutic potential in oncology and inflammatory diseases. Consequently, FAP inhibitor (FAPI)-based positron emission tomography (PET) has emerged as a promising approach for cancer diagnosis and theranostics. Imaging of CAFs using FAP-specific enzyme inhibitors (FAPIs) has been achieved through the synthesis of derivatives labeled with radionuclides such as iodine-125 (^{125}I), gallium-68 (^{68}Ga), and lutetium-177 (^{177}Lu) [88, 89]. These derivatives include FAPI-02, FAPI-04, FAPI-46, and related compounds. In vivo studies comparing FAPI-02 and FAPI-04 demonstrated that FAPI-04 achieves higher tumor accumulation and a more favorable tumor-to-blood ratio [90]. Several studies have reported that ^{68}Ga-DOTA-FAPI-04 PET/CT may offer greater sensitivity and accuracy than ^{18}F-FDG PET/CT for detecting metastatic lesions in thyroid cancer, particularly in lymph nodes and pulmonary metastases, owing to its higher uptake and improved tumor-to-background contrast [91-93]. More recently, a novel FAP inhibitor, ^{68}Ga-labeled DOTA.SA.FAPi incorporating a squaric acid motif, has been developed and demonstrated promising performance across multiple cancer types compared with ^{18}F-FDG PET/CT [94]. In addition to diagnostic applications, ^{177}Lu-labeled DOTAGA.$(SA.FAPi)_2$ has been explored for targeted radionuclide therapy in advanced malignancies and shows potential in theranostic strategies for thyroid cancer (**Figure 3**). A small, single-arm pilot study (n = 15) by Ballal et al. evaluated the preliminary efficacy and safety of [^{177}Lu]Lu-DOTAGA.$(SA.FAPi)_2$ in RR-DTC patients who had exhausted all the standard line of treatment options including sorafenib/Lenvatinib. The agent was administered at eight-week intervals, and after a total of 45 treatment cycles, an overall response rate of 92% was reported [95, 96] based on biochemical and functional imaging response assessment by serum thyroglobulin assay and [^{68}Ga]Ga-DOTA.SA.FAPi PET/CT scans. Notably, this study lacked a control arm and included a limited number of patients, which restricts the generalizability of the findings. Additionally, the absence of randomization precludes definitive conclusions regarding treatment efficacy. In summary, FAP inhibitor-based imaging and therapy demonstrate considerable promise, however, further large-scale, prospective, and randomized studies are required to validated their clinical efficacy and utility.

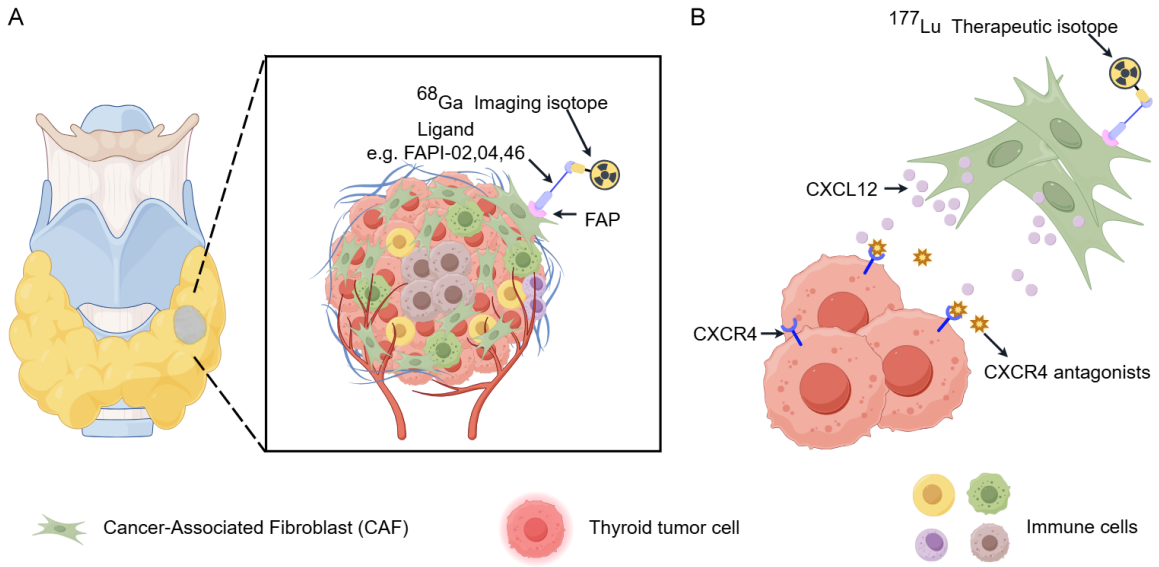

Figure 3. A. Schematic diagram of FAPI imaging; B. Schematic diagram of combined treatment of CXCR4 inhibitor and [^{177}Lu]Lu-DOTAGA.(SA.FAPi)$_2$. Abbreviations: FAP, fibroblast activation protein; FAPI, fibroblast activation protein inhibitor; CXCR, C-X-C chemokine receptor; CXCL, C-X-C chemokine ligand.

Target for CAF treatment in thyroid cancer

The pro-tumorigenic functions exerted by cancer-associated fibroblasts (CAFs) during thyroid tumorigenesis and thyroid cancer (TC) progression make them promising therapeutic targets [23, 97]. Several principal strategies have been proposed for CAF-directed anticancer therapies [98]: (1) direct depletion of CAFs through transgenic approaches or immunotherapy; (2) normalization of CAFs to an inactive phenotype using agents such as vitamin A or vitamin D; (3) inhibition of key signaling pathways and effectors of CAFs, including chemokines and growth factors, to suppress their activation and function; and (4) targeting CAF-derived extracellular matrix (ECM) proteins and associated signaling pathways to induce stromal depletion and enhance T cell infiltration. To date, however, no therapies specifically targeting CAFs in thyroid cancer have been approved. Kim et al. reported the innovative use of Siltuximab, an IL-6 inhibitor, in thyroid cancer patients with Castleman disease (CD), achieving encouraging outcomes [99]. Nevertheless, the limited number of cases precludes definitive conclusions regarding its efficacy. Currently, CAF-targeting inhibitors can be broadly categorized into five groups (**Table 2**): inhibitors of TGF-β, CXCR4/CXCL12 signaling, IL-6, matrix metalloproteinases (MMPs), and integrins. LY2157299, a TGF-β inhibitor, was shown to reverse CLIP170KD-mediated metastasis and epithelial-mesenchymal transition (EMT) in papillary thyroid carcinoma (PTC) cells (B-CPAP and TCP-1) [100]. Similarly, taraxasterol (TAR) significantly suppressed TGF-β1-induced migration and invasion by reversing EMT through modulation of the Wnt/β-catenin pathway [101]. CXCR4 antagonists such as AMD3100 and WZ811 [102] inhibited tumor cell proliferation, invasion, and xenograft tumor formation in PTC cell lines (e.g., BHP10-3M) [103]. In addition, CXCL12-CXCR4 axis inhibitors, including ursolic acid and BAY11-7082, reduced invasion, migration [49] and EMT processes [104] in B-CPAP and TCP-1 cells *in vitro*. In an anaplastic thyroid cancer (ATC) xenograft model, the MMP inhibitor minocycline, when combined with manumycin and paclitaxel, resulted in smaller tumor volumes compared with monotherapy [105]. Likewise, 3,3'-diindolylmethane (DIM), another MMP inhibitor, suppressed estrogen-mediated increases in thyroid cancer cell migration, adhesion, and invasion [106]. Furthermore, NSC-405020 (an MMP-14 inhibitor) and gallic acid (targeting MMP-2 and MMP-9) were shown to reduce the invasion and migration of K1 cells [107]. Integrin-targeting agents have also demonstrated therapeutic potential. Cilengitide, an antagonist of αvβ3 and αvβ5 integrins, inhibited cell viability while promoting apoptosis and

Table 2. Potential inhibitors of cancer-associated fibroblast (CAF) in thyroid cancer

Target	Drug	Cancer type	Study subject	Effect	Reference
TGF-β	LY2157299	PTC	B-CPAP, TPC-1	metastasis↓, EMT↓	38705933
	Taraxasterol	PTC	B-CPAP, TPC-1	migration↓, invasion↓, EMT↓	34219514
CXCR4	AMD3100	PTC	BHP10-3M, mouse xenograft	Cell proliferation, invasion and xenograft tumor formation↓	27061747
	WZ811	MTC	TT	Cell invasion↓	29112684
CXCL12-CXCR4	Ursolic acid	PTC	B-CPAP, TPC-1, thyroid fibroblast, thyroid CAFs	Tumor cell migration↓, invasion↓, CAF proliferation and invasion↓	35786050
	BAY11-7082	PTC	B-CPAP	Migration, invasion and EMT↓	29316404
αvβ3, αvβ5	Cilengitide	PTC	B-CPAP, TPC-1, K1	Migration and invasion↓	27042110
FN/αvβ3	DisBa-01	PTC	B-CPAP, K1	Migration and proliferation↓	40423510
IL-6	siltuximab	PTC	PTC patients with CD	RFS, PFS↑	33495189
	Tocilizumab	PTC	B-CPAP, TPC-1	Proliferation and dedifferentiation↓	37260320
MMP	3,3'-diindolylmethane (DIM)	PTC, MTC	B-CPAP, 8505C, CGTHW-1, ML-1	Migration, adhesion and invasion↓	21267453
	minocycline	ATC	Mouse xenograft	xenograft tumor size↓	16154259
	NSC405020	PTC	B-CPAP, K1	Migration and invasion↓	40869275
	gallic acid	PTC	B-CPAP, K1	Migration and invasion↓	40869275

reducing migration and invasion in K1, TPC-1, and B-CPAP cells *in vitro* [108]. Similarly, DisBa-01, a novel inhibitor of the FN1/αvβ3 interaction, suppressed PTC cell proliferation and migration [109]. Tocilizumab, an IL-6 receptor antagonist, has been reported to reverse IL-6-mediated suppression of sodium/iodide symporter (NIS) expression, thereby potentially improving iodine uptake in radioiodine-refractory thyroid cancer. Regarding CAF depletion and normalization strategies, key targets include fibroblast activation protein (FAP), platelet-derived growth factor receptor (PDGFR) kinase, and vitamin D receptor (VDR) ligands; however, no studies have yet evaluated these approaches in thyroid cancer.

Conclusion and future perspectives

CAFs, as key tumor-promoting components, play a critical role in the tumorigenesis and progression of thyroid cancer, making them attractive therapeutic targets in this desmoplastic malignancy. In TC, various precursor cells - including quiescent fibroblasts and mesenchymal stem cells (MSCs) - are reprogrammed into CAFs by tumor-derived mediators, resulting in their enrichment within the tumor microenvironment (TME). Activated CAFs contribute to tumor progression through multiple mechanisms, including ECM remodeling, secretion of cytokines, Wnt proteins, and exosomes that activate oncogenic signaling pathways, and interactions with immune cells that suppress antitumor immunity. Moreover, CAF abundance is associated with oncogenic mutations such as *BRAF* and *RAS*, which correlate with poor clinical outcomes. Much of the evidence linking CAF enrichment to clinical outcomes is derived from bulk RNA-seq-based deconvolute on analyses, which are inherently correlative. The commonly used computational algorithms for estimating stromal cell populations include xCell, CIBERSORT and EPIC [39], however, these methods also have their own limitations such as (i) reliance on predefined gene signatures that may not fully capture CAF heterogeneity; (ii) variability across algorithms that may lead to inconsistent estimations of CAF abundance. Current knowledge likely represents only a fraction of the complex roles of CAFs in TC. Further research is needed to determine whether CAFs contribute to tumorigenesis through additional mechanisms. In other tumor types, CAFs have been implicated in processes such as metabolic reprogramming, cellular senescence, and post-translational modifications, yet these aspects remain largely unexplored in thyroid cancer.

Although considerable efforts have been made to develop CAF-targeting therapies, clinical success has been limited, partly due to the high plasticity and heterogeneity of CAF populations. Therefore, improved methods for isolating and maintaining specific CAF subtypes *in vitro* are urgently needed, as these cells rapidly undergo phenotypic changes. Notably, the combination of $[^{177}Lu]$Lu-DOTAGA.$(SA.FAPi)_2$ with AMD3100 has demonstrated promising therapeutic efficacy in breast cancer models [110], suggesting a potential strategy for targeting CAFs in thyroid cancer. In conclusion, CAFs play a predominantly pro-oncogenic role in thyroid cancer. A deeper understanding of their biological functions and underlying mechanisms will be essential for the development of effective CAF-targeted therapies in this malignancy.

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Disclosure of conflict of interest

None.

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