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Hidden forces: the impact of cancer-associated fibroblasts on non-small cell lung cancer development and therapy

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Abstract

Non-small cell lung cancer (NSCLC) continues to be a leading cause of cancer-related deaths globally, primarily due to its late diagnosis and the complex nature of its tumor microenvironment (TME). Within this environment, cancer-associated fibroblasts (CAFs) play a crucial role in regulating NSCLC progression and therapeutic resistance. Recent advancements in single-cell and spatial technologies have uncovered significant heterogeneity among CAFs, revealing distinct subpopulations with varying cellular origins, phenotypes, and functions. Besides, the role of small extracellular vesicles (sEVs) in facilitating bidirectional communication highlights functional importance of CAF derived sEVs in mediating the crosstalk between cancer and TME, implicating the potential of CAF-sEVs to be un-invasive diagnostic biomarkers for NSCLC. Despite such new insights, challenges remain exist, particularly concerning the mechanisms that drive CAF plasticity, the interactions between specific CAF subsets with cancer cells or immune cells, and the translational significance of CAF-sEVs. In this review, we summarize the latest advances in our understanding of CAF heterogeneity, the functional roles and clinical relevance of CAFs and their secreted sEVs in driving NSCLC, and the translational landscape of CAF-targeted strategies. By critically evaluating the most recent evidence, this review provides clinically relevant insights and highlights future directions for overcoming CAF-mediated barriers to therapy. Our aim is to facilitate the development of more precise, biomarker-driven, and safe approaches for targeting CAFs, ultimately improving personalized treatment and outcomes for patients with NSCLC.

Background

Despite significant progress in elucidating the mechanisms of cancer development over recent decades, addressing these complex mechanisms remains challenging. Non-small cell lung cancer (NSCLC), encompassing lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell lung cancer (LCLC), is the predominant subtype of lung cancer and is frequently diagnosed at advanced stages. While traditional treatments including chemotherapy, radiotherapy, targeted therapies, and immunotherapy, have improved outcomes for some patients, the mortality rate for NSCLC remains high. Increasing evidence highlights the important role of the tumor microenvironment (TME), particularly the stromal compartment, in driving tumor heterogeneity and complexity beyond what is explained by cancer cell-intrinsic genetic mutations alone.

As one of the dominant components of TME stroma, cancer associated fibroblasts (CAFs) have emerged as

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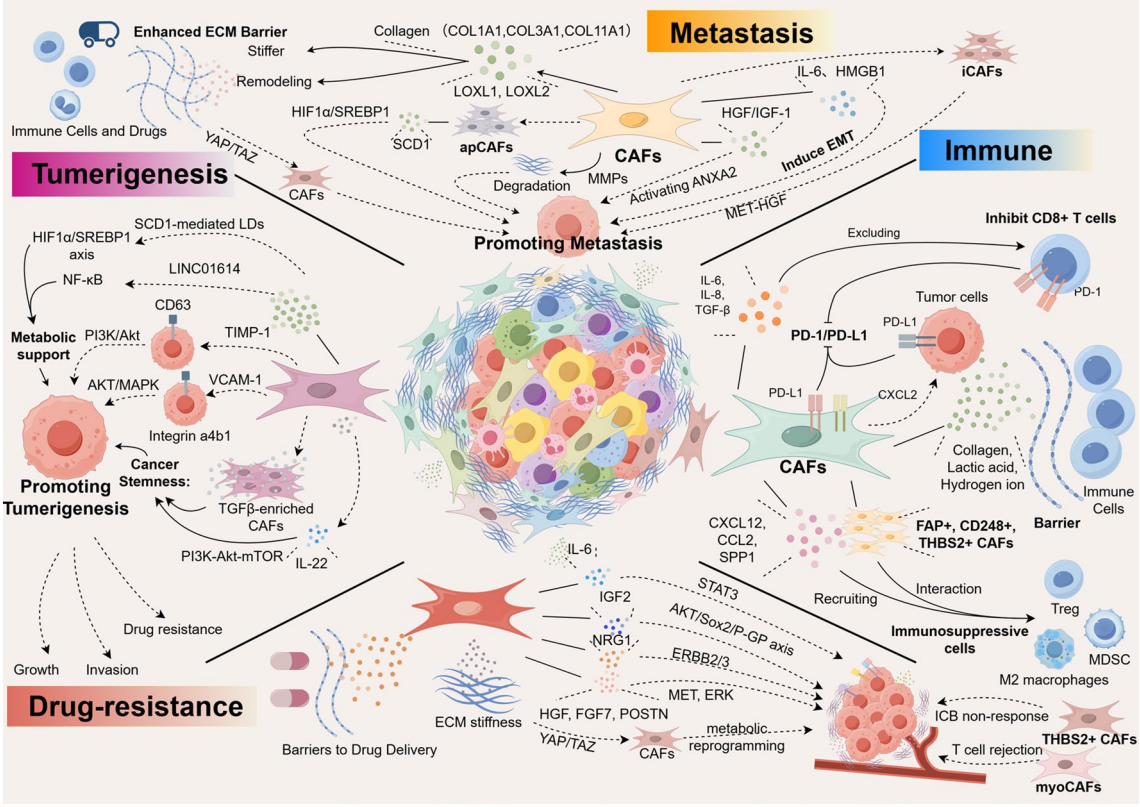
Graphical Abstract



Keywords Non-small cell lung cancer, Cancer associated fibroblast, Heterogeneity, Immune suppression, Extracellular vesicles, Drug resistance, Therapeutic targeting

principal regulators of NSCLC biology [1–3]. They form an intricate crosstalk network for dynamic regulation among tumor cells and stromal cells, which is crucial for cancer progression [4, 5]. Unlike quiescent fibroblasts, CAFs are activated fibroblasts characterized by metabolic adaptation [6]. Once viewed as a relatively uniform population of activated fibroblasts, recent advances in single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and multiplex imaging have reshaped our understanding of CAF heterogeneity [7]. These studies reveal that CAFs are a highly diverse population, comprising multiple subtypes distinguished by distinct molecular signatures, spatial distributions, and functional roles. Notably, specific CAF subsets have been implicated in promoting tumor growth, metastasis, immune evasion, and therapy resistance, while others may exert tumor-restraining effects [8]. This functional plasticity and diversity pose both challenges and opportunities for developing CAF-targeted therapies.

Recently, more and more research elucidates the critical role of CAF-derived small extracellular vesicles (sEVs) in mediating the dynamic crosstalk between CAFs, tumor cells and TME. These sEVs transport oncogenic microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and proteins to cancer cells and TME, leading to acquisition of metastatic, stemness, and drug-resistant phenotypes. Conversely, tumor-derived sEVs can reciprocally reprogram CAFs into pro-tumorigenic phenotypes, establishing a bidirectional communication axis to support tumor progression. Although the clinical validation of EV-based biomarkers remains a critical challenge, their diagnostic and therapeutic potential remains highly promising.

The heterogeneity of cancer-associated fibroblasts (CAFs), their diverse functional roles in tumor progression, and the therapeutic potential of targeting CAFs have been comprehensively addressed in previous reviews [5, 9]. In particular, Cheung et al. provided an in-depth analysis of the origins and functional contributions of CAFs in driving NSCLC progression [10]. Recent advances in single-cell sequencing have gained new insight into the understanding of the complexity and diversity of CAF subtypes, revealing novel clinical implications in NSCLC. Additionally, emerging research on small extracellular vesicles (sEVs) reveals their significant role in driving

cancer progression, highlighting the importance of elucidating the specific contribution of CAF-sEVs in driving NSCLC development. In this review, we summarize the most recent updates about CAFs in NSCLC, with a particular focus on the CAF heterogeneity, sEV-mediated communication, and their translational significance. By critically examining the ways in which CAFs contribute to tumor growth, therapy resistance, and disease evolution, we aim to delineate both the current challenges and emerging opportunities in targeting these cells. Furthermore, we propose integrative approaches to harness CAF plasticity for improving NSCLC outcomes. Our aim is to provide a comprehensive foundation that will not only inspire further research, but also support the development of more effective, personalized treatment approaches for patients with NSCLC.

Method

In this review, data collection methods included a comprehensive search of English peer-reviewed literature from 2017 to 2025 to ensure that an extensive range of studies addressing the CAFs and NSCLC were included, mainly focusing the latest studies from 2023 to 2025. The PRISMA flow diagram illustrates the study selection process (Fig. 1) [11]. Search was conducted in PubMed employing relevant keywords related to the "CAFs" and "NSCLC", which initially retrieved 191 relevant articles. After removing duplicates, the titles and abstracts were screened to assess their potential eligibility. Studies did not investigate the interaction between CAFs and NSCLC were excluded, resulting in a total of 163 eligible studies. The remaining articles were further evaluated based on the predefined inclusion and exclusion criteria, resulting in the final inclusion of 95 eligible studies in the review. These 95 studies were selected through the aforementioned PRISMA screening process and are related to NSCLC and CAFs. This ensures academic rigor. We systematically sourced studies (95/121) and incorporated supporting citations (26/121), ensuring both structural integrity and substantive content of the article, while demonstrating the meticulousness of our citations.

The goal was to systematically collect and analyze both descriptive and numerical data from studies that investigated the role of CAFs in NSCLC, focusing on their heterogeneity, functional mechanisms, therapeutic resistance, and clinical relevance as biomarkers or therapeutic targets. Additionally, when available, insights from clinical trials and observational studies were included to enrich the findings and support the overarching narrative. This review synthesizes the latest advancements in understanding CAFs and their roles in NSCLC progression and therapy resistance.

Origin and heterogeneity of CAF

Origin of CAF

CAFs are integral to the solid TME. Normal fibroblasts (NFs), also known as quiescent fibroblasts, are major sources of CAFs. In breast cancer, it has demonstrated that $CD26^{+}$ NFs can transform into inflammatory CAFs (iCAFs), which exhibit enhanced aggressiveness through the secretion of pro-inflammatory cytokines and the suppression of anti-tumor signaling. In contrast, $CD26^{-}$ NFs give rise to myofibroblastic CAFs (myCAFs), which increase stromal stiffness via collagen remodeling, thereby highlighting the impact of NF heterogeneity on CAF phenotypes [12]. Additionally, NFs can be recruited and activated into CAFs through various stimuli, including transforming growth factor-beta (TGF-β) [13], homeodomain-interacting protein kinase (HIPK2) [14], epiregulin (EREG) [15], and hepatocyte growth factor (HGF). CAFs can also originate from mesenchymal stem cells (MSCs) [16]. In chronic lymphocytic leukemia (CLL), it has been shown that tumor cell-secreted exosomes can induce the transition of MSCs into CAFs via miR-146a-mediated suppression of SUP16 [17]. In lung cancer, CAFs have recently been found to arise from M2 macrophages through a process termed macrophage-myofibroblast transition (MMT), which is driven by Smad3. Inhibition of MMT, either by macrophage-specific genetic deletion or pharmacological suppression of Smad3, can effectively suppress MMT-driven CAF formation and tumor progression, indicating the therapeutic potential of targeting the MMT process [18]. A more recent study from the same group further dissected the downstream effectors of Smad3-driven MMT, identifying the hematopoietic transcription factor RUNX1 as a key regulator via TGF-β1/Smad3 signaling. Stromal expression of RUNX1 is positively correlated with infiltration of MMT-derived CAFs and poor survival in lung cancer patients, further implicating its therapeutic relevance. Specific inhibition of RUNX1 effectively suppresses tumor growth by inhibiting MMT [19]. Collectively, these studies indicate that targeting CAF plasticity represents a promising therapeutic strategy for lung cancer.

Heterogeneity of CAF

CAFs were previously believed to be a relatively uniform population of matrix-producing cells. However, advances in scRNA-seq have revealed that CAFs are heterogeneous, exhibiting diverse phenotypes. By integrating scRNA-seq and scATAC-seq analyses, three conserved subtypes of CAFs, steady state-like (SSL) CAFs, mechanoresponsive (MR) CAFs, and immunomodulatory (IM) CAFs, have been identified across various cancers, including breast, pancreatic, and skin cancers. Disruption of underlying mechanical forces by depleting FAK expression leads to a reduction in IM and MR-CAFs but

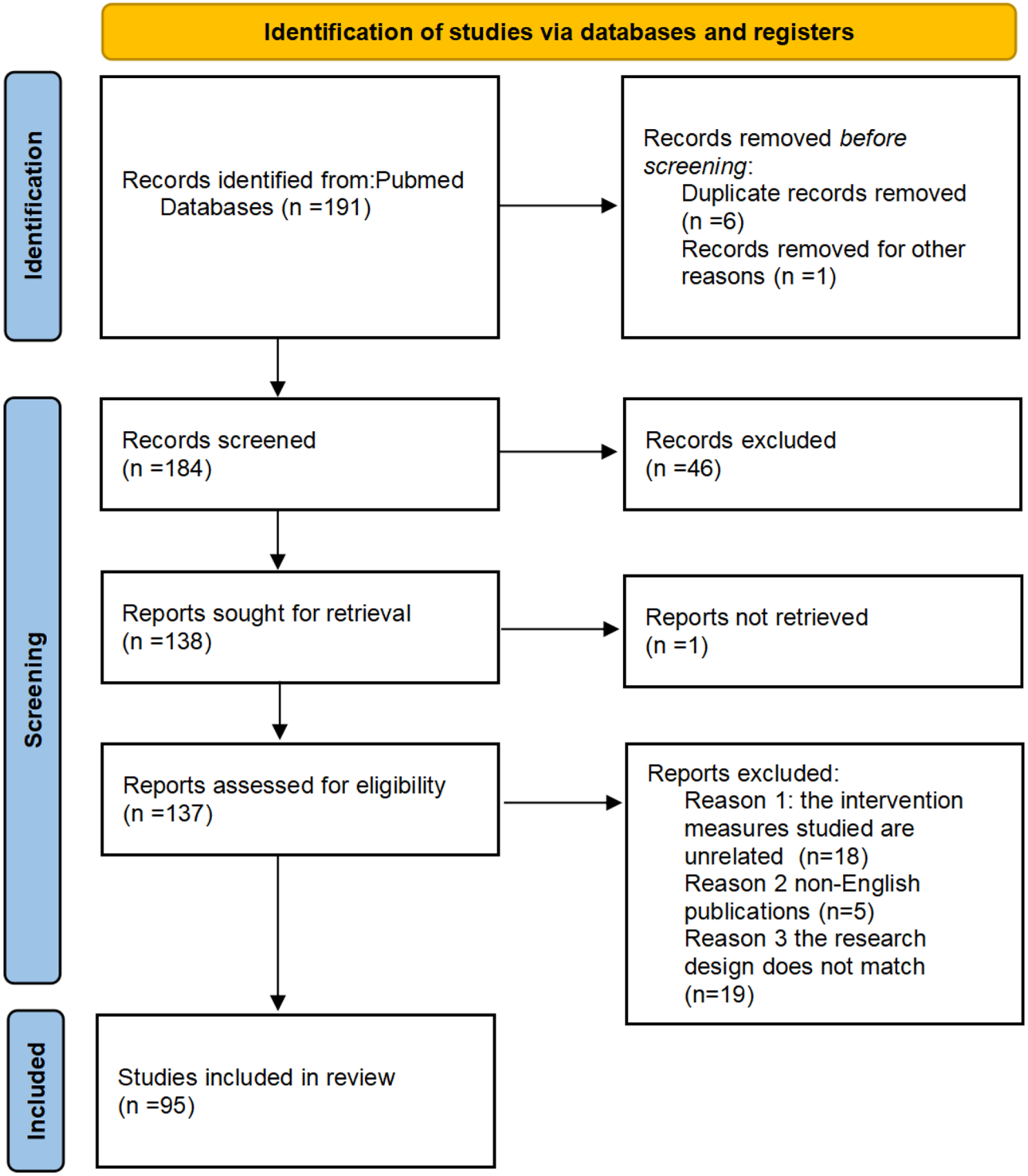


Fig. 1 Flow chart of review process. This flow chart illustrates the methodology employed in the systematic screening of CAFs research related to the NSCLC. A total of 191 records were identified from PubMed databases. After the removal of 7 records (6 duplicates and 1 for other reasons), 184 records were screened for eligibility. Of these, 46 were excluded and 138 reports were sought for retrieval. One report could not be retrieved, and 137 reports were assessed for eligibility. Ultimately, 42 reports were excluded (18 unrelated intervention measures, 5 non-English publications, and 19 with unmatched research designs), resulting in 95 studies being included in the final review

enrichment in SSL-CAFs with tumor-promoting effects. Conversely, immune checkpoint inhibition therapy significantly suppresses SSL-CAFs, indicating the translational significance of delineating the functional roles of different CAF subsets [20]. In lung cancer, multiplex fluorescence immunohistochemistry targeting CAF markers (PDGFRA, PDGFRB, FAP, and αSMA) has identified 15 distinct CAF subsets with differential associations with prognosis in NSCLC. Notably, CAF7 ($PDGFRA^-/PDGFRB^+/FAP^+/\alpha SMA^+$) correlates with poor prognosis and an immune-suppressive signature, while CAF13 ($PDGFRA^+/PDGFRB^+/FAP^-/\alpha SMA^+$) is associated with better prognosis and lower PD-1 expression in immune cells [21]. This finding emphasizes the importance of elucidating the functional roles and translational significance of CAF subclusters. In parallel, a novel CAF-S5 subset ($FAP^+/PDPN^+/\alpha SMA^-$) was discovered in NSCLC, characterized by an inflammatory phenotype and distal spatial distribution from tumor regions. CAF-S5, along with CAF-S1 ($FAP^+/\alpha SMA^+/PDPN^+$), independently predicts poor survival even after curative resection. Moreover, CAF-S5 predicts poor survival across several cancers based on TCGA validation, indicating its prognostic significance [22]. Consistently, these studies suggest that FAP^+ CAFs possess prognostic significance and represent promising therapeutic targets. Further scRNA-seq analyses have reported additional CAF subsets with prognostic and translational relevance. Kim et al. identified five CAF subsets from primary lung CAFs, including immunosuppressive CAFs, neoantigen-presenting CAFs, myofibroblastic CAFs, and proliferative CAFs. Neoantigen-presenting CAFs (UBE2T, TK1, and KPNA2) have been associated with poor prognosis. Functionally, KPNA2-overexpressing CAFs promote tumor progression by mediating metastasis, drug resistance, and immune suppression, implicating $KPNA2^+$ CAFs as potential therapeutic targets [23]. Through integrated analysis of multiple datasets across cancers and normal tissue, a subset of $COL11A1^+$ cancer-specific fibroblasts (CSFs) has been identified specifically in tumor tissues, characterized by high expression of LRRC15, ITGA11, SPHK1, and FAP. The proportion of $COL11A1^+$ CSFs is associated with poor prognosis in lung cancer and functionally promotes tumor progression through regulation of ECM remodeling and immune suppression [24]. By single-cell imaging mass cytometry (IMC) analysis, Cords et al. recently identified 11 CAF subtypes across 1,070 NSCLC patients and evaluated their prognostic significance. Among these clusters, tCAFs ($CD10^+/CD73^+$) and hypoxic tCAFs ($CAIX^+/CD10^+$) are correlated with poor prognosis, chemoresistance, and metastasis, while ifnCAFs, iCAFs, SMA CAFs, and dCAFs are associated with favorable prognosis in NSCLC. This study emphasizes the importance of dissecting the prognostic variation among CAF subtypes and targeting central regulators driving tCAFs and hypoxic tCAFs as potential strategies to improve patient outcomes [25]. Similarly, a recent study revealed the heterogeneous roles of CAF subsets in tumorigenesis and their plasticity in pancreatic ductal adenocarcinoma (PDAC). A novel interferon-response CAF subtype (ifCAF), characterized by elevated expression of interferon-stimulated genes and STING pathway activation, was identified by scRNA-seq. STING agonists induce ifCAF polarization while suppressing pro-tumorigenic myCAFs. IfCAFs displayed anti-tumor effects by polarizing tumor-associated neutrophils toward an anti-tumor phenotype and suppressing tumor invasiveness [26]. These findings highlight the importance of elucidating the dynamics and plasticity of CAFs. Therapeutic strategies targeting CAFs must prioritize subtype-specific approaches, such as suppressing pro-tumorigenic CAF-driven fibrotic remodeling or polarizing CAFs toward anti-tumorigenic phenotypes, in order to disrupt their tumor-promoting functions while harnessing context-dependent anti-cancer potential.

The functional association between CAF heterogeneity and various hallmarks of cancer has also been investigated recently. A single-cell and spatial transcriptomics study identified $POSTN^+$ CAFs enriched in advanced NSCLC tumors, which are spatially co-localized with $SPP1^{++}$ macrophages that drive immune suppression via T cell exclusion/exhaustion and ECM remodeling. $POSTN^+$ CAFs independently predict poor prognosis in lung cancer, underscoring their clinical utility as prognostic biomarkers and therapeutic targets to disrupt CAF-macrophage crosstalk and enhance immunotherapy efficacy in NSCLC [27]. CAFs are also crucial for mediating drug resistance to targeted therapies, and their effects on treatment response are heterogeneous. Based on their capacity to regulate resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs), three functional subtypes of CAFs have been identified: $HGF7^+/FGF7^{+/-}$ subtype I with the strongest resistance to both EGFR- and ALK-TKIs, $HGF7^-/FGF7^+$ subtype II with moderate TKI resistance, and $HGF7^-/FGF7^-$ subtype III with the weakest TKI resistance. Both in vitro and in vivo studies demonstrated that combined treatment with a MET inhibitor (targeting HGF signaling) and FGFR inhibitor successfully overcame type I CAF-induced resistance, while FGFR inhibitor alone was effective against type II CAF-induced resistance. These data suggest that various combination regimens tailored to CAF heterogeneity are effective strategies for overcoming TKI resistance [28]. Jing Hao et al. linked specific CAF subtypes to tumor invasiveness, classifying NSCLC tumors into high desmoplastic CAFs (HD-CAF) and low desmoplastic CAFs (LD-CAF) based on the degree of connective tissue proliferation, with HD-CAF serving as an independent

prognostic factor for NSCLC. HD-CAFs, characterized by high ST8SIA2 expression, play a functional role in promoting NSCLC invasion, suggesting ST8SIA2 as a potential therapeutic target against NSCLC metastasis [29]. A study by Xu et al. further delineated three metastasis-specific CAF subpopulations (myCAF, iCAF, apCAF) in advanced NSCLC through single-cell transcriptomics. ApCAFs dominate in bone metastasis via SPP1-CD44/SPP1-PTGER4 signaling to promote osteolysis, while iCAFs prevail in brain metastasis through MET-HGF-mediated neural niche remodeling. These CAF subtypes exhibit distinct prognostic implications and organotropism, with apCAF-enriched cases showing shorter bone metastasis-free survival and iCAF-high tumors correlating with immunosuppressive TME features. Spatial IHC confirmed that MET^+ tumor cells are spatially aligned with HGF^+ iCAFs in brain metastases, suggesting that CAF subtype-specific inhibitors could serve as precision therapies to disrupt organ-specific metastatic niches [30].

In summary, the origin and heterogeneity of CAFs are complex (Fig. 2). Understanding this heterogeneity may facilitate the discovery of novel biomarkers for patient stratification and prognosis. Furthermore, elucidating the functional roles of different CAF subsets could enable the development of targeted therapies and inform strategies to overcome CAF-mediated resistance to both conventional and immune-based treatments.

Role of CAF in tumorigenesis

Collagen, a crucial extracellular matrix (ECM) structural component, along with its receptor integrin α11, regulates the matrix cross-linking enzyme LOXL1 expressed by CAFs. This process reshapes and aligns collagen fibers, facilitating tumor cell dissemination and correlating with

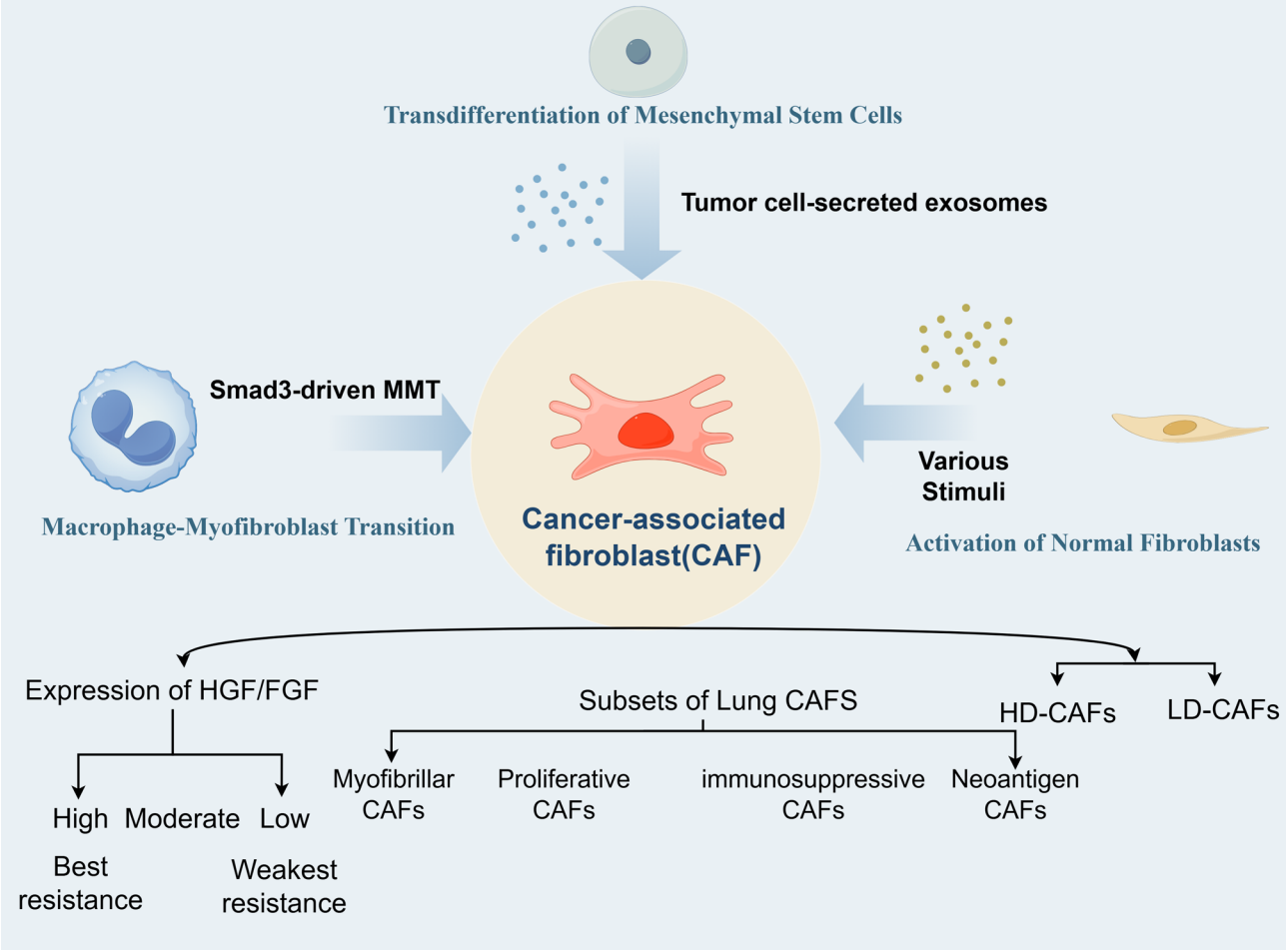


Fig. 2 Origins and heterogeneity of CAFs in NSCLC. This schematic illustrates the diverse origins and subtypes of CAFs in NSCLC. CAFs can originate from multiple sources including NFs, MSCs, and macrophages. The figure also highlights the heterogeneity of CAFs, indicating subgroups based on their expression levels of HGF and FGF. These subgroups exhibit varying levels of resistance to therapy, with high expression correlating to the best resistance and low expression correlating to the weakest resistance. Additionally, specific subtypes of CAFs identified in lung cancer include myofibrillar CAFs, proliferative CAFs, immunosuppressive CAFs, neoantigen-presenting CAFs, and subtypes based on the degree of desmoplasia such as high desmoplastic CAFs (HD-CAF) and low desmoplastic CAFs (LD-CAF)

poor prognosis in NSCLC [31]. CAF-secreted VCAM-1 activates the AKT and MAPK signaling pathways by binding to integrin α4β1 on cancer cells, thereby promoting lung cancer growth. Clinically, high expression of VCAM-1 in CAFs significantly correlates with unfavorable outcomes [32]. Additionally, the autophagy protein p62 is critical for CAF activation under hypoxic conditions in lung adenocarcinoma. p62-dependent autophagy activates CAFs by stimulating the Nrf2-ATF6 pathway, leading to tumor progression [33]. TIMP-1 exhibits a paradoxical dual role: initially regarded as a tumor suppressor via MMP inhibition and antiproliferative effects [34], it becomes pro-tumorigenic when overexpressed by CAFs in lung adenocarcinoma. Hyperactivated TGF-β1/SMAD3 signaling drives excessive TIMP-1 secretion, which binds CD63 on cancer cells to activate PI3K/Akt and pro-invasive pathways, bypassing its traditional MMP-dependent tumor-suppressive functions. TIMP-1 may exhibit stage- and subtype-specific roles in lung cancer, potentially driving tumor progression via CD63 in LUAD ($CD63^{high}/MMP9^{low}$), while acting as a tumor suppressor through MMP inhibition in LSCC ($CD63^{high}/MMP9^{low}$), suggesting context-dependent mechanisms in tumor microenvironment metabolism. High expression of both CD63 and TIMP-1 predicts poor prognosis in LUAD patients, underscoring the translational significance of targeting the CD63-dependent tumor-promoting effects of CAF-derived TIMP-1 [35]. CAFs can also promote lung cancer progression by affecting lipid metabolism. Compared to NFs, CAFs in lung cancer exhibit increased lipid droplet (LD) accumulation. Mechanistically, hypoxia-induced stabilization of HIF1α activates SCD1 transcription, leading to LD accumulation in CAFs and subsequent tumor progression. High SCD1 expression in CAFs is associated with poor prognosis in lung cancer [36]. While the pro-tumorigenic effects of CAFs are well documented, recent evidence suggests that the interplay between CAFs and apoptotic cancer cells can suppress lung cancer cell growth. This is achieved through NOTCH1-dependent WISP-1 secretion from CAFs, which activates STAT1 in cancer cells. In vivo treatment with recombinant WISP-1 or CAF-derived WISP-1 significantly suppresses tumor growth, highlighting the translational potential of reprogramming CAFs by apoptotic cancer cells [37]. Collectively, these observations suggest that the dual role of CAFs in cancer progression depends on subtype-specific secretomes and their interactions with the microenvironment, which vary across tumor stages and molecular subtypes. Specifically targeting the pro-tumorigenic subtypes of CAFs may represent a promising treatment strategy.

Role of CAF in metastasis

CAFs are integral to the tumor stroma, altering the mechanical properties of the ECM through synthesis and remodeling. This activity promotes cancer cell proliferation and invasion. A higher proportion of CAFs is linked to the progression of lung cancer from adenocarcinoma in situ (AIS) to invasive lung adenocarcinoma (IAC), highlighting the role of ECM remodeling by CAFs in facilitating metastasis [38].

Additionally, CAFs promote metastasis by secreting both paracrine and autocrine cytokines. It has been shown that CAFs in NSCLC exhibit higher levels of autophagy, which is essential for HMGB1 secretion. HMGB1, in turn, promotes cancer cell migration and invasion by upregulating factors such as D-F, Twist, MMP2, and MMP9 in CAFs. Further in vivo studies demonstrated that targeting CAF autophagy using the autophagy inhibitor chloroquine (CQ) effectively suppressed tumor growth, indicating its therapeutic potential [39]. Recent research has demonstrated that $\alpha\text{-SMA}^{+}$ CAFs induced by activation of Notch signaling (via increased expression of Jag1/2 from cancer cells) promote NSCLC metastasis. This finding indicates that cell–cell communication between CAFs and cancer cells can induce pro-metastatic phenotypes in CAFs, suggesting that targeting microenvironmental communication pathways may be an effective strategy to suppress metastasis [40].

Low expression of miR-101-3p in CAFs has been shown to correlate with worse prognosis. Downregulation of miR-101-3p in CAFs releases the expression of VEGF, stimulating the AKT/endothelial nitric oxide synthase (eNOS) signaling pathway in cancer cells and promoting metastasis. This study suggests miR-101-3p as a potential candidate for metastasis therapy [41]. High expression of Musashi-2 (MSI2) in CAFs is correlated with poor prognosis in NSCLC and has been identified as a critical mediator of metastasis. Depletion of MSI2 suppresses NSCLC metastasis by attenuating IL-6-driven EMT, underscoring the therapeutic potential of targeting the MSI2/IL-6 axis in CAFs to inhibit advanced NSCLC metastasis [42].

Although CAFs generally promote metastasis, under certain conditions they can display anti-metastatic effects. The anti-metastatic role of CAFs can be influenced by intercellular communication with cancer cells. Apoptotic cancer cells can reprogram CAFs into an anti-metastatic phenotype by inducing WISP-1 secretion, which suppresses cancer cell metastasis. Enhanced expression of Notch ligand delta-like protein 1 on apoptotic cancer cells triggers this signaling cascade, ultimately suppressing metastasis [43]. This finding suggests that reprogramming CAFs into anti-metastatic phenotypes could be a potential strategy for treating metastatic

NSCLC. Furthermore, high expression of nicotinamide N-methyltransferase (NNMT) in CAFs has been correlated with better disease-free survival, indicating a negative regulatory role on aggressiveness. $NNMT^{low}$ CAFs display a greater pro-metastatic effect on cancer cells compared to $NNMT^{high}$ CAFs. In vitro and in vivo experiments have validated that NNMT suppresses metastasis by downregulating genes involved in ECM remodeling through methylation regulation. Therefore, $NNMT^{high}$ CAFs may suppress lung cancer metastasis [44]. Overall, while CAFs play a significant role in promoting metastasis by modulating epithelial-to-mesenchymal transition (EMT) and influencing numerous signaling pathways, they may also have suppressive roles under certain circumstances. Understanding the interactions between CAFs and cancer cells during metastasis could provide valuable insights for developing targeted therapies to inhibit metastatic progression.

Role of CAF in mediating immune suppressive microenvironment

The hallmarks of cancer include chronic inflammation, immune cell infiltration, and the ability of cancer cells to evade immune responses [45]. The TME comprises various immune cells, including natural killer (NK) cells, T cells, tumor-associated macrophages (TAMs), neutrophils, B cells, and dendritic cells (DCs). Both the innate and adaptive immune systems are activated during cancer development, playing dual roles in tumor suppression and promotion. CAFs are instrumental in enabling cancer cells to evade immune surveillance by recruiting immune cells to the TME and inducing immunosuppressive phenotypes. The influence of fibroblasts on lung cancer immunity has been extensively studied.

Recent advances have revealed the extensive roles of CAFs in modulating various immune cell populations. CAFs actively interact with TAMs in lung cancer. Analysis of TCGA datasets from NSCLC cases has shown that CAF infiltration is positively correlated with M2 macrophage infiltration and predicts poor immunotherapy response. Mechanistically, FGF5 is a key factor regulating the interaction between CAFs and M2 macrophages, making it a potential therapeutic target for NSCLC. Glycerophospholipid metabolism, in contrast, is negatively correlated with CAF-associated genes and influences the TME composition in NSCLC patients [46]. Wu and colleagues reported that $CD248^{+}$ CAFs in NSCLC, whose infiltration correlated with poor survival, promote tumor progression through polarization of M2 macrophages via the CXCL12-CXCR4 interaction [47]. However, the mechanisms by which other CAF subtypes regulate TAM infiltration and recruitment in NSCLC remain to be elucidated. Additionally, CAFs can affect the recruitment and polarization of monocytes. Bioinformatic analysis of LCSC patient databases revealed a positive correlation between CAF infiltration and monocytic myeloid cells. Functional assays confirmed that CAFs recruit $CCR2^{+}$ monocytes via CCL2 secretion and induce their polarization into immunosuppressive myeloid-derived suppressor cells (MDSCs) [48].

Advancements in scRNA-sequencing have facilitated the identification of interactions between CAF subtypes and immune-suppressive signatures. Integrated analysis of bulk and scRNA-seq data from LUAD revealed that CAF cells exhibit heterogeneity between clusters characterized by "cold" (low immune infiltration) and "hot" (high immune infiltration) tumor features. An activated CAF cluster (caf_c1_scissor), characterized by upregulation of CXCL12, TGFB1, and COL3A1, is associated with "cold" tumors. Interaction analyses showed high CXCL12 expression involved in interactions with TAMs and T cells, while IGF2 and POSTN are significant in interactions with $C1QA^{+}$ and $GPNMB^{+}$ TAMs, respectively [49]. A similar activated CAF cluster, defined as $COL11A1^{+}$ CAFs, was reported by Zhang and colleagues through integrated scRNA-sequencing datasets from multiple cancers, including lung cancer. Upregulation of CXCL12 in the $COL11A1^{+}$ CAF cluster is thought to mediate interactions between CAFs and immune cells such as macrophages, MDSCs, and regulatory T cells (Tregs) [24]. CAF-related risk features based on gene expression can predict LUAD prognosis and immunotherapy responsiveness. Integrated bioinformatic analysis identified EXO1, CCNB1, CLEC3B, and CD302 as hub genes for stratifying CAFs into high-risk (high EXO1, CCNB1; low CLEC3B, CD302) and low-risk groups, with the high-risk group correlating with poor prognosis and poor immunotherapy response. Patients with low-risk features show higher immune infiltration and are more likely to establish an immune-responsive "hot" tumor state [50]. Interestingly, while the immune-suppressive effects of CAFs are well documented, Koeck et al. reported a stromal fibroblast signature associated with improved overall survival in NSCLC, as analyzed using local patient cohorts and TCGA datasets. Further functional validation showed that CAFs recruit B cells and $CD4^{+}$ T cells through CXCL16 and CCL13, suggesting an immune-promoting role for CAFs. Moreover, patients with $stroma^{high}$/$B\ cell^{high}$ signatures had significantly improved survival [51]. It should be noted, however, that this signature may also include non-cancer-associated lung fibroblasts, highlighting the importance of further dissecting CAF subsets to elucidate their heterogeneous translational significance in NSCLC.

In summary, CAFs play a crucial role in modulating the immune landscape of the TME, influencing cancer progression and patient outcomes. Understanding these interactions provides insights into potential therapeutic

strategies targeting CAFs to enhance the efficacy of cancer treatment.

Role of CAF in cancer stemness

Cancer stem cells (CSCs) possess the ability to self-renewal, exhibit enhanced metastatic potential, and resist anti-cancer therapies. These pluripotent cancer cells share similarities with normal stem cells in their capacity to differentiate into various cancer cell types, contributing to primary tumor progression and the formation of secondary tumors. Additionally, CSCs often express high levels of ATP-binding cassette (ABC) transporters, enabling the efflux of chemotherapeutic agents and contributing to multidrug resistance (MDR), while dysregulation of key signaling pathways further facilitates their survival [52]. CSCs can also enter a quiescent, dormant state, making them inherently resistant to chemotherapy and allowing them to survive and regenerate, thereby sustaining tumor growth.

CAFs regulate CSC characteristics by secreting ECM components and various growth factors. For example, $CD10^+$ CAFs expressing transmembrane hydrolase support tumor stemness and induce chemoresistance by degrading osteogenic growth peptide (OGP), an antitumoral peptide. $CD10^+/GPR77^+$ CAFs can secrete IL-6 and IL-8 to maintain CSC stemness, thereby promoting chemotherapy resistance in patients with lung cancer [53]. In addition, study in mice has shown that TGFβ-enriched CAFs promote sphere formation and invasion of CSCs, facilitating TGFβ-dependent squamous cell carcinoma metastasis and survival in the lung [54]. Given the critical crosstalk between CAFs and CSCs, targeting specific CAF subsets, CSCs, and their interactions could represent an effective strategy against CSC-driven chemoresistance. To explore this, a tumor microenvironment-based drug screening platform using patient-derived lung cancer cells and CAFs has been established to identify and repurpose compounds targeting both cancer cells and CSCs. Among 1,524 compounds screened, aloe-emodin and digoxin were identified as having anticancer and anti-CSC activity in vitro and in vivo, findings further confirmed in patient-derived xenografts (PDX). The combination of digoxin and chemotherapy demonstrated efficacy in lung cancer models [55]. Thus, understanding the role of CAFs in promoting cancer stemness and their interactions with CSCs provides critical insights into potential therapeutic targets and strategies for overcoming chemoresistance in lung cancer.

In summary, cancer-associated fibroblasts (CAFs) are central regulators of the NSCLC tumor microenvironment, contributing to tumorigenesis, metastasis, immune suppression, and cancer stemness. By remodeling the extracellular matrix, CAFs facilitate tumor invasion and spread. They secrete factors that enhance cancer cell growth and survival, and modulate the immune landscape to promote immune evasion. Moreover, CAFs support the maintenance of cancer stem cells, driving therapy resistance. Together, these diverse functions position CAFs as key orchestrators of NSCLC progression and attractive targets for therapeutic intervention (Fig. 3).

Role of CAF in drug resistance

Chemotherapy

Chemoresistance remains a significant challenge in NSCLC treatment, with CAFs playing a crucial role in promoting resistance. In LUAD, CAFs physically modulate the ECM by enhancing collagen cross-linking. ECM stiffening reprograms metabolism, promoting glycolysis and mitochondrial respiration in CAFs through a YAP/TAZ-dependent pathway, while increasing glycolysis in cancer cells. This metabolic interaction promotes nucleotide biosynthesis and cancer cell proliferation [56]. Therefore, CAFs contribute to NSCLC chemoresistance through ECM remodeling and metabolic reprogramming.

Recent research has identified a master transcription factor, PRRX1, which enhances tumor invasiveness and chemotherapy resistance by reshaping the super-enhancer landscape and coordinating the fibroblast-to-myofibroblast phenotypic shift through the TGF-β pathway. Depletion of fibroblast-specific PRRX1 in genetically engineered mouse models induces sustained remission of cisplatin resistance, indicating that the PRRX1-induced myofibroblast subset is a promising target for reversing cisplatin resistance. Clinically, high PRRX1 expression significantly correlates with poor prognosis [57]. Plasminogen activator inhibitor-1 (PAI-1) promotes pulmonary fibrosis by enhancing myofibroblast characteristics and inducing α-SMA expression in fibroblasts, contributing to cisplatin resistance. Inhibiting α-SMA expression using a PAI-1 inhibitor enhances cisplatin efficacy in lung cancer cells co-cultured with CAFs. High PAI-1 expression correlates with advanced pathological stages, indicating its association with aggressive NSCLC phenotypes and suggesting PAI-1 as a potential therapeutic target [58]. CAFs also drive immune-suppressive microenvironments that confer chemoresistance. Chemotherapy-induced upregulation of PDL-1 in CAFs further promotes resistance by increasing HGF secretion and inducing cancer stemness, positioning CAF-derived PDL-1 as both a prognostic biomarker and therapeutic target to reverse resistance [59].

In summary, CAFs contribute to NSCLC chemoresistance through ECM remodeling, metabolic reprogramming, and secretion of growth factors that activate key signaling pathways in cancer cells. Understanding these mechanisms provides essential insights for developing

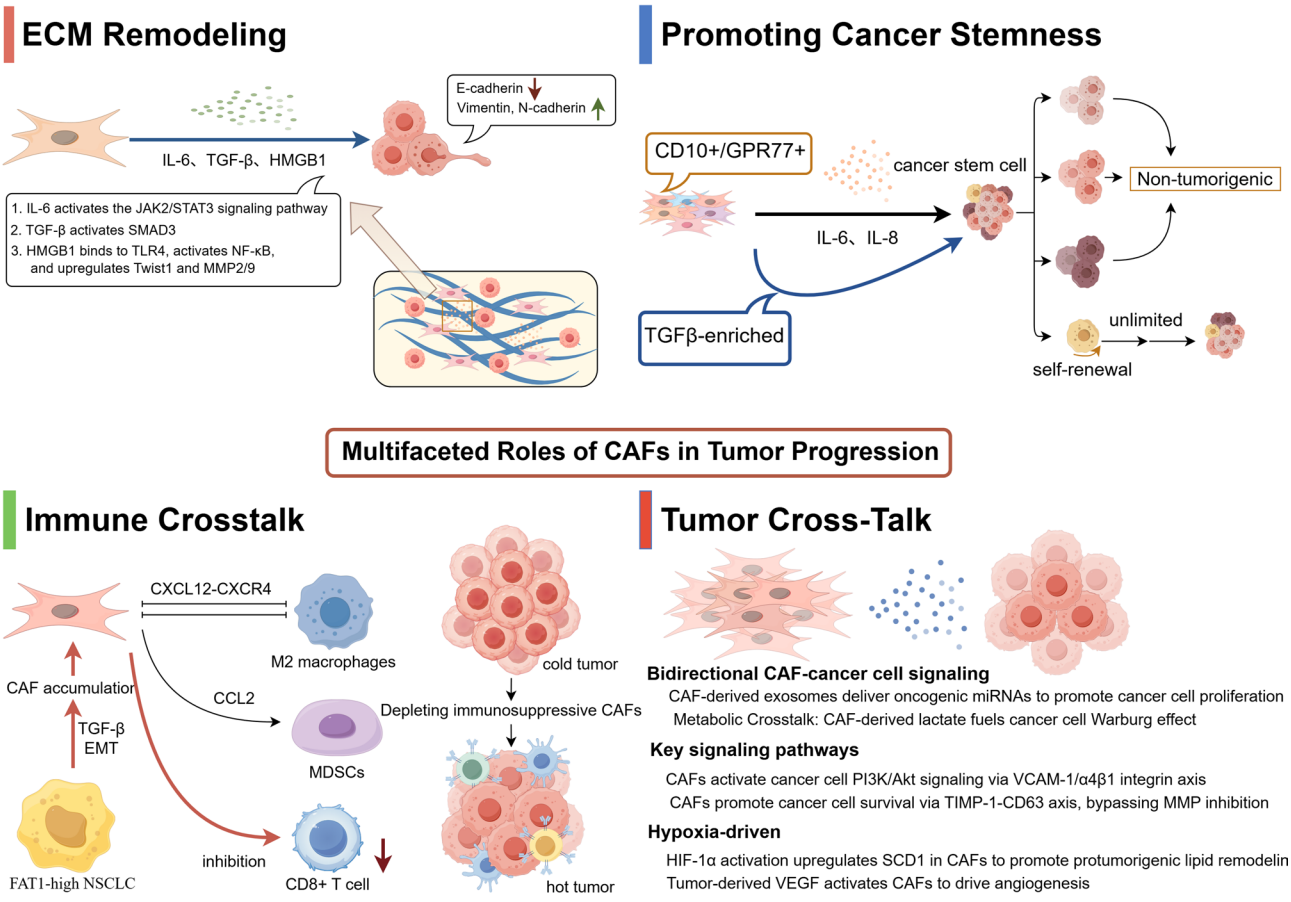


Fig. 3 Role of CAFs in tumor microenvironment. This figure illustrates CAFs, as coordinator, orchestrate tumor progression in NSCLC through multifaceted mechanisms. CAFs remodel the ECM to enhance stiffness and alignment, promoting cancer cell invasion and metastasis; CAFs regulate CSC characteristic through various growth factors; CAFs mediate immune suppression by recruiting regulatory immune cells and creating an immune-excluded microenvironment; CAFs engage in bidirectional communication with cancer cells to activate pro-tumorigenic signaling pathways. Collectively, these roles position CAFs as pivotal regulators of the tumor-stroma ecosystem, highlighting their potential as therapeutic targets

strategies to overcome chemoresistance and improve patient outcomes.

Targeted therapy

Mutations in the epidermal growth factor receptor (EGFR) are critical therapeutic targets in NSCLC. Three generations of EGFR-TKIs are in clinical use. First-generation EGFR-TKIs such as gefitinib and erlotinib are reversible inhibitors, while second- and third-generation TKIs were developed to address resistance, including T790M mutation-induced resistance [60]. ALK gene mutations and KRAS mutations also represent important targets, but drug resistance remains a significant challenge [61, 62]. One mechanism of acquired resistance to EGFR-TKIs mediated by CAFs is secretion of growth factors such as IGF-1 and HGF. Co-culture experiments have shown that these factors bind IGF-1R and c-Met in lung cancer cells, increasing annexin A2 (ANXA2) expression, triggering EMT, and conferring resistance to gefitinib [63]. In osimertinib treatment, CAFs induce oncogenic pathways including MET, Akt, EMT/stemness marker Snail, and β-catenin, leading to resistance. POSTN secreted from CAFs also contributes to osimertinib resistance in EGFR-mutant NSCLC by activating the ERK pathway, promoting proliferation, EMT, and drug resistance. Knockdown of POSTN restores osimertinib sensitivity [64]. CAFs can also promote resistance by secreting kynurenine, which activates the AhR pathway in tumor cells and triggers AKT/ERK signaling [65]. Tranilast, an antiallergic drug that interferes with the secretion of cytokines from inflammatory cells, has been reported to suppress TKI resistance conferred by CAFs in NSCLC. Mechanistically, tranilast inhibits the secretion of IL-6 from CAFs, leading to suppression of STAT3 signaling in lung cancer cells and inhibition of EMT. Combined treatment with tranilast reverses CAF-conferred resistance to osimertinib in EGFR-mutated NSCLCs and selumetinib in KRAS-mutated NSCLCs [66].

Signaling crosstalk between CAFs and NSCLC cells is crucial to TKI resistance. Primary CAFs from

osimertinib-resistant patients induce resistance in NSCLC cell lines by stimulating MET, Akt, EGFR, and Wnt/β-catenin signaling and CSC phenotypes. Osimertinib-resistant cancer cells can also activate CAFs from NFs. Targeting MET with capmatinib overcomes CAF-induced osimertinib resistance, indicating the therapeutic potential of disrupting CAF–cancer cell communication [67]. In almonertinib resistance, NSCLC cells activate CAFs via increased TGF-β1 secretion, and activated CAFs confer resistance by suppressing YAP/TAZ signaling. Targeting YAP/TAZ restores almonertinib efficacy, suggesting that dual inhibition of TGF-β1-CAF crosstalk and Hippo signaling may synergize with EGFR-TKIs [68]. Most recently, it has been reported that DKK1 secreted from gefitinib resistant cells can induced the transition of CAFs from myofibroblast to inflammatory fibroblast phenotype via activation of c-Jun pathway, which support gefitinib resistance. Blockade of DKK1 effectively reverse gefitinib resistance through disruption the crosstalk between inflammatory fibroblast and cancer cells [69].

Most recently, by scRNA-seq of NSCLC patients undergo EGFR-TKI treatment, specific CAFs subset responsible for EGFR-TKI resistance has been identified. CTHRC1$^+$ CAFs have been found to enriched in resistant tumor. Mechanistically, CTHRC1$^+$ CAFs enhance the glycolytic activity of cancer cells by activating the TGF-β/Smad3 signaling pathway. A natural compound called Gambogenic Acid, by disrupting the function of CTHRC1$^+$ CAFs, was found to be effectively reverse EGFR-TKI resistance of NSCLC cells. This study suggests the importance of investigating the specific TKI resistant CAF subsets for identifying CAF treatment target for reversing TKI resistance [70].

Immune therapy

In the past decade, immunotherapy has revolutionized oncology treatment with its rapid development. However, the majority of NSCLC patients exhibit resistance to immunotherapy, complicating cancer treatment. Therefore, research on immunotherapy resistance is crucial. The relationship between CAFs and immunotherapy resistance is of particular interest. TGF-β signaling plays a significant role in activating fibroblast phenotypes in cancers. This signaling pathway is associated with T cell exclusion and a lack of response to immune checkpoint inhibitors (ICIs). TGFβ-related genes expressed in the TME and increased infiltration of myofibroblastic CAFs (myoCAFs) in solid tumors correlate with reduced T cell infiltration and resistance to immunotherapy [71, 72]. In NSCLC, FBLIM1$^+$ CAF subtypes correlate with increased expression of TGFβ signaling molecules, indicating a poor prognosis for immunotherapy [73]. The DNA damage-sensing kinase ataxia-telangiectasia mutated (ATM) maintains the myoCAF phenotype in lung cancer. Inhibition of ATM in a murine lung cancer model suppresses tumor growth and increases CD8$^+$ T cell infiltration, suggesting that targeting ATM can potentially "normalize" myoCAFs, overcome myoCAF-mediated immune evasion, and enhance immunotherapy response [74].

The ECM, composed of collagen, fibronectin, glycosaminoglycans, and proteoglycans, plays a critical role in the immunosuppressive microenvironment in NSCLC [75]. CAFs produce ECM proteins that contribute to the suppression of immunotherapy responses [76]. The dense collagen fiber network produced by CAFs can restrict T cell entry into the tumor tissue and increase matrix density, leading to reduced infiltration of CD8$^+$ T cells, which are crucial for anti-tumor immune responses. Thrombospondin 2 (THBS2), a tumor biomarker secreted by a THBS2$^+$ CAF subset, contributes to immune escape and resistance to immunotherapies in LUAD. High levels of THBS2 are associated with an increased ECM/stromal signature, reduced immune cell infiltration, and markers of immune exhaustion, resulting in poor response to immunotherapy and shorter post-treatment survival [77]. The abundance of cancer-associated ECM (C-ECM)-up genes, linked to ECM protein production by CAFs, may serve as potential indicators for predicting responsiveness to ICB therapy. Non-responders to ICB therapy often show significant upregulation of C-ECM-up genes compared to responders [78]. Additionally, high expression levels of AMPD1, associated with several immune cells, correlate with higher TIDE (Tumor Immune Dysfunction and Exclusion) scores and poorer response to immunotherapy in LUAD patients [79]. Together, these studies suggest the crucial effects of CAF in inducing immunotherapy resistance through driving ECM remodeling. The effects of CAFs on the immune response are heterogeneous, and certain subtype of CAFs might show supportive effect for immunotherapy. Miyai et al. identified a Meflin$^+$ CAF subset in LUAD, characterized by low expression of α-SMA and positive PDGFRα expression. Meflin$^+$ CAFs are preferentially found in invasive LUAD and correlate with a favorable response to immune checkpoint blockade (ICB) therapy, accompanied by increased CD4$^+$ T cell infiltration and angiogenesis in NSCLC tumors [80]. Additionally, the expression of PD-L1 on CAFs has been reported as an independent prognostic factor predicting favorable relapse-free survival in non-metastatic lung cancer. PD-L1 expression on CAFs is stimulated by IFN-γ from activated lymphocytes, suggesting an induction of an immune response [81]. On the other hand, CAFs can induce PD-L1 expression on lung cancer cells through CXCL2 secretion, potentially leading to resistance to ICB therapy [82], demonstrating the complex and cell-type dependent role of PD-L1 in driving response to ICB therapy.

Radiotherapy

In recent decades, the combination of chemotherapy and radiotherapy has emerged as a standard treatment strategy for stages 1 to 3 NSCLC, with significant advancements in radiotherapy techniques. Neoadjuvant therapy combining chemotherapy and radiotherapy followed by surgery for stage IIIA patients has reported a promising 5-year overall survival rate exceeding 50% [83]. However, overcoming radiotherapy resistance has become a significant challenge in NSCLC treatment. The role of CAFs in radiotherapy resistance is increasingly recognized.

CAFs exhibit inherent resistance to radiation and play a critical role in communication with tumor cells, as evidenced by their development of radiation resistance when co-cultured with cancer cells [84]. Recent research reveals that senescent fibroblasts can acquire CAF-like functions and regulate the CAF phenotype, leading to increased expression of α-SMA and Vimentin, which promote tumor invasion and metastasis [85]. Both α-SMA and Vimentin are regulated by the STAT3 pathway, which can be activated by the accumulation of intracellular reactive oxygen species (ROS) in senescent fibroblasts during CAF activation [86]. Recent studies highlight that irradiated CAFs, while resistant to apoptosis, upregulate immunosuppressive receptors (CD73 and CD276) and maintain cytokine secretion, potentially reinforcing TME immunosuppression post-radiotherapy, suggesting that targeting adenosine/CD73 pathways could enhance therapeutic efficacy in stroma-rich NSCLC [87].

Senescence-like CAFs induced by radiotherapy are reported to promote the proliferation of lung cancer cells and induce radio-resistance through the JAK/STAT pathway. Using FOXO4-p53 interfering peptide (FOXO4-DRI) to induce apoptosis in senescence-like CAFs significantly sensitizes NSCLC cells to radiotherapy both in vitro and in vivo [88]. While fractionated doses of radiation inhibit the proliferation, migration, and invasion abilities of lung CAFs, ionizing radiation can also activate CAFs, resulting in stronger pro-malignant behavior. This phenomenon, known as "radiation activation," promotes cancer cell survival, migration, and resistance to radiation therapy and chemotherapy [89]. Taken together, targeting CAFs or preventing their activation would be beneficial in improving the efficacy of radiation therapy.

In summary, CAFs contribute to resistance against chemotherapy, targeted therapy, immunotherapy, and radiotherapy in NSCLC through a variety of molecular pathways and cellular mechanisms, as detailed in Table 1.

Role of CAF secreted sEVs

sEVs are crucial mediators of communication within the tumor microenvironment, carrying miRNAs, mRNAs,

Table 1 Mechanisms of drug resistance in NSCLC mediated by CAFs

Therapy type	Drugs	Mechanisms	Refs.
Chemo-therapy	Cisplatin	ECM remodeling, YAP/TAZ-mediated metabolic reprogramming	[57]
	Cisplatin	PRRX1/ TGF-β driven fibroblast-myofibroblast shift	[58]
	Cisplatin	PAI-1 induction of α-SMA expressing CAFs	[59]
	Cisplatin	Induction of cancer stemness through PDL-1/HGF axis	[60]
Targeted therapy	Gefitinib /Erlotinib	Induction of ANXA2-mediated EMT by IGF-1/HGF from CAFs	[64]
	Gefitinib	Activation of c-Jun by DKKI from inflammatory CAFs	[70]
	Gefitinib /Erlotinib	AhR/AKT/ERK signaling activated by Kyn from	[66]
	Osimertinib	Activation of ERK pathway by CAF-derived POSTN	[65]
	Osimertinib /Selumetinib	Activation of STAT3/EMT signaling by IL-6 from CAFs	[67]
	Osimertinib	Activation of MET/AKT/EGFR/Wnt pathways by TGFβ1	[68]
	Almonertinib	Suppressing YAP/TAZ via Hippo pathway	[69]
	Osimertinib	Activation of TGFβ/Smad3 signaling by CTHRC1$^+$ CAFs	[71]
Immune therapy	ICIs	T cell exclusion induced by TGFβ from myoCAFs	[72, 73]
	ICIs	FBLIM1$^+$ CAFs with elevated TGFβ	[74]
	ICIs	MyoCAF phenotype maintained by ATM	[75]
	ICIs	THBS2$^+$ CAFs promote ECM-mediated immune exclusion	[78]
	ICIs	ECM produced from CAFs promotes ICI resistance	[77, 79]
	ICIs	CAF-derived CXCL2 upregulates PD-L1 on cancer cells to promotes ICI resistance	[83]
	ICIs	Meflin$^+$ CAFs (PDGFRα$^+$) improves ICB response and CD4$^+$ T cell infiltration	[81]
	ICIs	CAF-expressed PD-L1 (IFN-γ-induced) improves ICI response.	[82]
Radiotherapy	Radiotherapy	ROS/STAT3 pathway activates α-SMA/Vimentin in CAFs	[87]
	Radiotherapy	Irradiated CAFs upregulate CD73/CD276 and enhance adenosine-mediated immunosuppression	[88]
	Radiotherapy	FOXO4-DRI reverses radio-resistance by inducing apoptosis in senescence-like CAFs	[89]

proteins, and lncRNAs to recipient cells and inducing diverse cellular responses. sEVs mediate crosstalk between cancer cells and CAFs: cancer cell-derived sEVs can activate CAFs, while CAF-derived sEV cargos regulate cancer cell proliferation, metastasis, and drug resistance [90]. CAF-derived sEVs are emerging as promising non-invasive biomarkers for clinical diagnosis and prognosis. They carry bioactive molecules that can affect tumor behavior and patient outcomes. On one hand, sEVs can be easily isolated from bodily fluids like blood, allowing for repeated, real-time monitoring of tumor dynamics and treatment responses. On the other hand, they offer a comprehensive view of the tumor microenvironment, highlighting interactions between cancer cells and stromal components such as CAFs, which is crucial for personalized medicine.

miRNA

One type of cargo carried by sEVs is miRNAs, a major class of small non-coding RNAs that mediate post-transcriptional gene silencing by binding to the 3′-untranslated region (UTR) or open reading frames (ORFs) of target mRNAs. MiRNAs derived from CAF-sEVs have been reported to mediate various pathological processes in NSCLC.

Jiang et al. demonstrated that CAF-derived sEVs promote lung cancer tumorigenesis by suppressing the cytotoxic effects of T cells on cancer cells. Specifically, CAF-derived sEVs were enriched in OIP5-AS1, and these EVs carrying OIP5-AS1 suppressed the levels of miR-142-5p in lung cancer cells. This suppression led to the upregulation of PD-1, a downstream target of miR-142-5p, which prevents apoptosis induced by peripheral blood mononuclear cells (PBMCs) [91]. Additionally, CAF-derived EVs carrying miR-369 promote the proliferation and metastasis of LUSC cells by directly binding to NF1 and activating the MAPK signaling pathway. Clinically, miR-369 was found to be upregulated in LUSC tissue compared to normal, suggesting it as a potential LUCS diagnostic marker [92]. Furthermore, miR-210 carried by CAF-derived EVs targets UPF1 and activates the PTEN/PI3K/AKT pathway, thereby promoting the migration and invasion of NSCLC cells [93]. Additionally, CAF-sEVs deliver miR-3124-5p to suppress TOLLIP expression, thereby activating the TLR4/MyD88/NF-κB signaling axis, which drives NSCLC proliferation, migration, and invasion. The downregulation of TOLLIP correlates with poor patient prognosis, positioning miR-3124-5p as a promising serum biomarker and therapeutic target to disrupt CAF-mediated TME remodeling [94]. miRNA from CAFs-sEVs also play important role in drug resistance. High levels of miR-103a-3p in CAFs and their sEVs promote cisplatin resistance in NSCLC by suppressing apoptosis through targeting Bak1 [95]. CAF-derived sEVs also promote the proliferation and cisplatin resistance of lung cancer cells by transferring miR-20a, which leads to the downregulation of PTEN and activation of the PI3K/AKT pathway [96].

Conversely, tumor cell-derived sEVs can also promote the activation of CAFs. For example, upregulated SUR1 in NSCLC induces the phosphorylation of KHSRP by p70S6K, resulting in decreased levels of let-7a-5p in cancer cell-derived EVs, which is supported by clinical data showing elevated SUR1 expression correlates with CAF accumulation and poor prognosis in NSCLC patients. These EVs, with reduced let-7a-5p expression, promote the transformation of NFs to CAFs via TGFBR1-dependent activation of the TGF-β signaling pathway [97].

lncRNAs

Another type of cargo in CAF-derived sEVs is long non-coding RNA (lncRNA). CAFs support cancer growth by producing ATP and metabolic intermediates that nourish adjacent cancer cells, aiding in their metabolic reprogramming to overcome restricted nutrition and oxygen caused by competitive utilization and inadequate supply within the TME. It is now evident that CAFs also support their own metabolic reprogramming into patterns favorable to NSCLC growth through the secretion of sEVs. One example of how CAFs affect metabolism is through the upregulation of glutamine transporters SLC38A2 and SLC7A5. LINC01614 has been found to enrich in CAF-sEVs of LUAD, which correlated with poor prognosis and glutamine influx of clinical LUAD. sEVs-LINC01614 promote LUAD progression through enhancing glutamine uptake of LUAD cells by activating the ANXAS/p65/NF-κB /SLC38A2 and SLC7A5 axis. Blocking of sEVs-LINC01614 inhibits glutamine addiction and LUAD progression in vivo, indicating the therapeutic potential of targeting sEVs-LINC01614 [98]. LINC01833 has been found to up-regulated in NSCLC patients. CAF-derived sEVs carrying LINC01833 promote NSCLC progression by suppressing miR-335-5p to upregulate VAPA, driving tumor cell proliferation, invasion, and M2 macrophage polarization, highlighting its potential as a therapeutic target to disrupt TME-driven malignancy [94, 99].

Protein

In addition to the aforementioned lncRNAs and miRNAs, CAF-derived small sEVs can also facilitate lung cancer tumorigenesis through the transfer of their protein cargos. Notably, Snail1, a crucial mTF involved in EMT, was found to be overexpressed in CAF-derived sEVs, as evidenced by higher Snail1 levels in sEVs isolated from patient-derived CAFs compared to healthy controls of lung cancer. This overexpression significantly enhances the EMT process in A549 cells, which can be mitigated by treatment with GW4869, implicating the therapeutic

Table 2 List of EVs related to CAFs in NSCLC

Type	cargo	Effect	ref
miRNAs	miR-369	Promotes LUSC proliferation/metastasis by targeting NF1and activating MAPK signaling.	[92]
	miR-210	Enhances NSCLC migration/invasion by targeting UPF and activating PTEN/PI3K/AKT pathway	[93]
	miR-103a-3p	Induces cisplatin resistance in NSCLC by targeting Bak1 and suppressing apoptosis	[95].
	miR-20a	promotes proliferation/cisplatin resistance by downregulating PTEN and activating PI3K/AKT pathway,	[96]
	miR-3124-5p	Promotes NSCLC progression by targeting TOLLIP and activating TLR4/MyD88/NF-κB signaling	[94].
lncRNAs	LINC01614	Enhances glutamine uptake via ANXAS/p65/NF-κB /SLC38A2 and SLC7A5 axis	[98].
	LINC01833	Promotes NSCLC proliferation, invasion, and M2 macrophage polarization through suppressing miR-335-5p and upregulating VAPA	[94, 99]
Protein	Snail1	Enhances EMT in cancer cells	[100]
	METTL3	Promoting proliferation, invasion, stemness, and glutaminolysis through stabilizing SLC7A5 via m6A modification,	[101]
	THBS2	Promote tumor growth through suppressing immune cell infiltration	[77]

potential of targeting CAF-sEVs [100]. Additionally, METTL3, a methyltransferase enriched in CAF-derived sEVs, drives NSCLC progression by stabilizing SLC7A5 mRNA via m6A modification, promoting tumor proliferation, invasion, stemness, and glutaminolysis, with its inhibition showing potent antitumor effects in preclinical models, highlighting its therapeutic potential [101]. By comprehensively analyzing multiply omics datasets from clinical NSCLC samples, Yang et al. has revealed a distinct subset of CAFs characterized by high expression of THBS2, which is an independent prognostic factor predicting poor prognosis at early stage and poor response to immunotherapy. THBS2 is preferentially secreted from THBS2-positive CAFs via sEVs, promoting tumor growth by suppressing immune cell infiltration. Importantly, elevated plasma levels of EV-THBS2 serve as a prognostic marker for poor disease-free survival. This study highlights the potential of CAF derived sEVs-THBS2 to be a biomarker for prognosis and treatment response prediction, and its therapeutic potential is also warranted to be investigated in future [77]. These findings collectively suggest that CAF-derived sEVs play multifaceted roles in facilitating tumor growth and may serve as prognostic markers for poor clinical outcomes in NSCLC.

In summary, CAF-derived sEVs carry a variety of functional cargos—including specific miRNAs, lncRNAs, and proteins—that contribute to NSCLC progression, metastasis, drug resistance, and immune modulation. The major cargos and their corresponding effects are summarized in Table 2.

Translational significance of CAF-sEVs in NSCLC diagnosis and challenges

While current research of CAF-sEVs mainly focus on the functional role of their cargos and the underlying mechanisms, recent researches in the field start to pay more attention to the potential of CAF-sEV cargos to be biomarkers or therapeutic targets, with several prognostic biomarkers being identified in CAF-sEV cargos. Future studies should emphasize more about the translational significance of CAF-sEVs and their potential clinical application. Although specific CAF-sEVs based diagnostic biomarkers are not yet available in clinical practice for LUAD, clinically trials have been conducted to evaluate the potential of EVs to be a diagnostic and prognostic biomarkers NSCLC, shedding light on the future clinical application of CAF-sEV biomarkers. For example, the potential of lung cancer exosome derived proteins for early lung cancer diagnosis and staging through deep-learning analysis was investigated in clinical trial (NCT04529915). ExoDx™ Lung (ALK), the first exosome-based liquid biopsy tool has been developed for detecting EML4-ALK mutations in NSCLC patients [102].

While CAF-derived sEVs hold promise as biomarkers for clinical diagnosis and prognosis, the utilization of CAF-derived sEVs as biomarkers is subject to several limitations. The heterogeneity of CAFs might complicate the interpretation of data derived from sEVs. Moreover, isolation and characterization of sEVs requires the advanced techniques and standardized protocols to ensure consistent and reliable results in different clinical settings. Meanwhile, further research is required to address the challenges posed by the heterogeneity of CAFs and to establish standardized analytical methods. Further investigation of the molecular composition of CAF-derived sEVs and their functional roles within the tumor microenvironment will be crucial for their effective incorporation into clinical practice.

Therapeutic potential of targeting CAF

The recognition of CAFs as pivotal contributors within the TME has opened up promising avenues for therapeutic interventions in cancer treatment. Through the targeting of CAF-associated signaling pathways and interactions, investigators have pursued novel strategies aimed at halting tumor advancement and bolstering treatment efficacy. By unraveling the complex interplay among CAFs, immune cells, and the TME, innovative

treatment modalities are being developed to disrupt tumorigenic processes across various fronts, heralding the advent of more potent cancer therapies.

Targeting CAFs

As mentioned above, FAP^+ CAF has been shown to correlate with poor prognosis in NSCLC, which links to multiple aggressive cancer phenotypes. Recently, therapeutic strategy specifically targeting this subset have been developed. Fang et al. engineered human FAP-specific CAR-NK-92 cells (hFAP-CAR-NK-92) to selectively eliminate FAP-expressing cells, including CAFs and FAP^+ tumor cells. Results showed that hFAP-CAR-NK-92 cells successfully targeted hFAP-positive NSCLC and suppressed tumor growth by activating the Caspase-3/GSDME pyroptosis pathway [103]. FAP^+ CAF targeted therapy has been further explored by investigating the regulatory mechanisms of FAP expression and their effector molecule. It is reported that circNOX4 upregulated FAP by sponging miR-329-5p, which regulates FAP expression in CAF of NSCLC. Blocking of IL6 by IL6-neutralizing antibody effectively suppressed the growth of circNOX4 overexpressing xenograft, suggesting the therapeutic potential of targeting FAP regulatory pathway in CAF [104]. Further, FAP^+ CAF has been linked to the resistance of ICI therapy, making it a potential target for improving ICI efficacy. As demonstrated by Kraxner et al., FAP^+ CAF infiltration positively correlated with Treg infiltration and immune suppressive microenvironment, pointing this subset to be a target to reverse immunotherapy resistance [105]. Peyraud et al. additionally characterized $FAP^+\alpha SMA^+$ CAF subsets together with $MYH11^+\alpha SMA^+$ CAFs as key drivers of primary resistance in mature tertiary lymphoid structures (mTLSs) -positive NSCLC, both of which correlated with poor treatment response in ICI-treated mTLS-positive NSCLC. Spatial transcriptomic analysis revealed that $FAP^+\alpha SMA^+$ CAFs correlate with $CD8^+$ T cell exhaustion, while $MYH11^+\alpha SMA^+$ CAFs promote immunosuppression via $CD4^+$ Treg infiltration. These findings underscore the clinical relevance of dual CAF-targeted strategies to reverse immune exclusion and enhance ICI efficacy in NSCLC patients [106]. Together, these studies highlight the therapeutic potential of targeting FAP^+ CAF in NSCLC. Fascin, an EMT target associated with poor prognosis in tumors, exhibits potential as a therapeutic target due to its involvement in tumor invasion and migration. Recent research implicates Fascin expression in CAFs with poor prognosis in LUAD, suggesting its involvement in tumor-CAF crosstalk and highlighting anti-Fascin therapy as a novel treatment avenue for the cancer stroma [107].

Targeting the signaling pathways of CAFs

The critical role of TGF-β in activating CAFs and shaping their interactions with immune cells underscores the potential of TGF-β inhibition therapy as a targeted approach against CAFs [108]. Peyraud et al. demonstrated that TGF-β/IFN-γ signaling crosstalk in CAF-rich stroma drives T cell dysfunction, suggesting combined TGF-β blockade with ICIs could restore antitumor immunity [106]. Concurrently, CAFs undergo metabolic alterations, known as the reverse Warburg effect, in which tumor cells induce mitochondrial dysfunction, leading to increased glycolysis and release of high-energy metabolites into the TME. Strategies targeting reactive oxygen species (ROS) and TGF-β levels offer promising therapeutic avenues by modulating this metabolic interaction [109–111]. By exploring the intricate connection between TGF-β, CAF metabolism, and the TME, we can pave the way for innovative treatment strategies that aim to disrupt the tumorigenic processes at multiple levels. Developing strategies to disrupt the interaction between CAFs and cancer cells is thought to be a promising approach for developing effective anti-cancer drugs. The novel aptamer-based conjugate Gint4.T-STAT3, targeting PDGFRβ and STAT3, suppresses CAF-tumor crosstalk with cancer cells. Gint4.T-STAT3 suppressed CAF-driven proliferation and metastasis through inhibiting STAT3 activation, suggesting therapeutic potential for disrupting tumor microenvironment remodeling and resistance mechanisms [112]. Anlotinib, a multitarget antiangiogenic tyrosine kinase receptor inhibitor, has shown to enhance the efficacy of anti-PD1 therapy by inducing apoptosis of CAFs and suppressing its migration ability. Further, anlotinib inhibits the immune suppressive role of CAF, leading to the increased infiltration of $CD8^+$ T cells and PD-1 inhibitor-induced cytotoxicity. This study elucidates the underlying mechanisms of the synergistic effect of combined treatment of anlotinib and immunotherapy, with emphasis on the efficacy of targeting CAFs [113]. Further clinical trial regarding this regimen is worthy to be evaluated.

Antifibrotic therapy

Fibrosis serves as a pivotal characteristic of the TME across numerous types of solid tumors. Notably, idiopathic pulmonary fibrosis (IPF) stands out as the most prevalent form of idiopathic interstitial pulmonary disease and is recognized for elevating the risk of NSCLC. DEGs in NFs and CAFs isolated from NSCLC patients play crucial roles in the fibrotic process, with up-regulation of ITGA11, COL1A1, and COL11A1 suggestive of the involvement of CAFs in lung fibrosis [114]. Consequently, there exist numerous overlapping genetic, molecular, and cellular mechanisms that bridge the connection between lung fibrosis and NSCLC, with

fibroblast activation being a noteworthy aspect [115]. Metformin, through AMPK activation and inhibition of NOX4 expression, inhibits the transformation of lung fibroblasts into myofibroblasts induced by TGF-β, offering a potential anti-fibrotic approach to overcome radiotherapy resistance [116]. Clinically, pirfenidone is utilized as an antifibrotic agent for the treatment of IPF. Pirfenidone not only attenuated fibroblast activity but also efficiently regulated the interactive communication between NSCLC cells and CAFs, leveraging its synergistic ability to restrain both IL-6 and TGF-β signaling [117].

Challenges of CAF targeting therapy

Several challenges exist for targeting CAFs as personalized therapy in NSCLC. One major challenge is the heterogeneity of CAFs. The existence of multiple CAF subtypes with different functions and phenotypes makes it difficult to develop a single - target therapy that can effectively inhibit all pro - tumor CAF activities while maintain the anti-tumor effects of CAFs. The application of personalized medicine through CAF heterogeneity analysis in NSCLC shows significant potential. The elucidation of different functions and phenotypes of CAF subtypes make it possible to develop targeted therapies that focus on specific CAF subsets for more precise patient stratification.

Additionally, the potential side effects of CAF targeted therapies need to be carefully considered. The distinction between NFs and CAFs is pivotal for developing targeted therapies against CAFs while preserving physiological fibroblast functions to avoid adverse effects on normal tissues. NFs, typically quiescent and reported marked by heterogeneous CD26 expression in breast cancer, maintain tissue homeostasis through transient activation by factors like TGF-β during wound healing [9, 12, 13, 118]. scRNA-seq identifies three major NF subpopulations: adventitial ($CD34^+$), alveolar ($AOC3^+$), and rare myofibroblasts ($ACTA2^+$/$POSTN^+$), with adventitial and alveolar fibroblasts enriched in histologically normal regions and associated with improved survival in LUAD [119]. In contrast, CAFs exhibit sustained activation via oncogenic pathways and express pro-tumorigenic markers such as α-SMA, FAP, POSTN, and COL1A1, which are absent or minimal in NFs [17, 103, 113, 120]. Therapeutic strategies must leverage these differences by targeting CAF-specific markers or pathways while avoiding NF disruption [18, 30, 103]. By exploiting molecular, functional, and spatial distinctions, precision CAF-targeted therapies could disrupt pro-tumorigenic niches without compromising stromal integrity, offering new avenues to improve NSCLC outcomes.

Conclusions

In conclusion, the intricate interplay between CAFs, signaling pathways, and the TME presents a multifaceted landscape ripe for therapeutic intervention in the context of cancer treatment. Targeting CAFs directly through various modalities, including genetic, pharmacological, and immunotherapeutic approaches, holds promise in impeding tumor progression and enhancing treatment responses. Furthermore, deciphering the signaling pathways involved in CAF activation and metabolism unveils novel avenues for targeted therapies, with potential synergies to disrupt tumorigenic processes at multiple levels. Antifibrotic strategies, particularly in the context of fibrosis-associated diseases such as IPF and NSCLC, offer additional therapeutic opportunities by modulating the fibrotic components of the TME. Collectively, these advancements underscore the transformative potential of targeting CAFs and their associated signaling pathways in the quest for more effective cancer therapies.

Future perspective

The evolving understanding of CAF heterogeneity and their dynamic interactions within the NSCLC microenvironment presents both challenges and opportunities for therapeutic innovation. Future research should prioritize elucidating the molecular mechanisms underlying CAF heterogeneity and plasticity, particularly focusing on how these CAF subpopulations influence patient prognosis and treatment responses, which will guide the development of more precise CAF targeted therapy. Meanwhile, the heterogeneity and versatility of CAFs, including their potential to act as both promoters and suppressors of cancer progression, underscore the complexity of targeting CAF-sEVs in NSCLC. Future research should aim to clarify the origins and roles of CAF-sEVs to create targeted therapies that disrupt the tumor-supportive microenvironment in NSCLC. Current limitations in the clinical translation of CAF include insufficient evidence from clinical trial. Overcoming CAF-mediated physical and functional barriers, such as ECM stiffness and immunosuppressive TME will require innovative approaches. These include combination therapies that integrate CAF-targeting agents with immunotherapy, small molecule inhibitors targeting CAF-secreted factors including sEVs, and strategies to deplete CAF subtypes associated with poor prognosis. Further, therapeutic modulation of CAFs to remodel the tumor microenvironment may improve clinical outcomes. We believe that bridging gaps in mechanistic understanding, biomarker discovery, and clinical Validation could change CAFs from "hidden force" into actionable targets for NSCLC management.

Abbreviations

CAF(s)	Cancer-Associated Fibroblast(s)
NSCLC	Non-Small Cell Lung Cancer

TME	Tumor Microenvironment
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
LCLC	Large Cell Lung Cancer
sEV(s)	Small Extracellular Vesicle(s)
scRNA-seq	Single-cell RNA Sequencing
scATAC-seq	Single-cell Assay for Transposase-Accessible Chromatin using sequencing
ECM	Extracellular Matrix
NF(s)	Normal Fibroblast(s)
MSC(s)	Mesenchymal Stem Cell(s)
CLL	Chronic Lymphocytic Leukemia
MMT	Macrophage-Myofibroblast Transition
SSL CAFs	Steady State-Like Cancer-Associated Fibroblasts
MR CAFs	Mechanoresponsive Cancer-Associated Fibroblasts
IM CAFs	Immunomodulatory Cancer-Associated Fibroblasts
FAP	Fibroblast Activation Protein
αSMA/α-SMA	Alpha-Smooth Muscle Actin
PDGFRA/PDGFRB	Platelet-Derived Growth Factor Receptor Alpha/Beta
PDPN	Podoplanin
CSF(s)	Cancer-Specific Fibroblast(s)
IMC	Imaging Mass Cytometry
ifCAF(s)	Interferon-Response Cancer-Associated Fibroblast(s)
myCAF(s)	Myofibroblastic Cancer-Associated Fibroblast(s)
iCAF(s)	Inflammatory Cancer-Associated Fibroblast(s)
apCAF(s)	Antigen-Presenting Cancer-Associated Fibroblast(s)
HD-CAF(s)	High Desmoplastic Cancer-Associated Fibroblast(s)
LD-CAF(s)	Low Desmoplastic Cancer-Associated Fibroblast(s)
EMT	Epithelial-to-Mesenchymal Transition
LOXL1	Lysyl Oxidase Like 1
VCAM-1	Vascular Cell Adhesion Molecule 1
TIMP-1	Tissue Inhibitor of Metalloproteinases 1
HGF	Hepatocyte Growth Factor
TGF-β	Transforming Growth Factor Beta
HIPK2	Homeodomain-Interacting Protein Kinase 2
EREG	Epiregulin
RUNX1	Runt-related Transcription Factor 1
LRRC15	Leucine Rich Repeat Containing 15
ITGA11	Integrin Subunit Alpha 11
SPHK1	Sphingosine Kinase 1
EGFR	Epidermal Growth Factor Receptor
TKI(s)	Tyrosine Kinase Inhibitor(s)
MET	Mesenchymal-Epithelial Transition (may also refer to MET gene or protein)
FGF	Fibroblast Growth Factor
SCD1	Stearoyl-CoA Desaturase-1
WISP-1	WNT1 Inducible Signaling Pathway Protein 1
ATM	Ataxia-Telangiectasia Mutated (kinase)
MDSC(s)	Myeloid-Derived Suppressor Cell(s)
TAM(s)	Tumor-Associated Macrophage(s)
DC(s)	Dendritic Cell(s)
NK cell(s)	Natural Killer Cell(s)
Treg(s)	Regulatory T Cell(s)
PD-1/PD-L1	Programmed Cell Death Protein 1 / Ligand 1
PI3K/AKT	Phosphoinositide 3-Kinase / Protein Kinase B Pathway
MAPK	Mitogen-Activated Protein Kinase
STAT3	Signal Transducer and Activator of Transcription 3
JAK	Janus Kinase
ROS	Reactive Oxygen Species
ABC transporter	ATP-Binding Cassette Transporter
MDR	Multidrug Resistance
ANXA2	Annexin A2
EML4-ALK	Echinoderm Microtubule-associated Protein-Like 4–Anaplastic Lymphoma Kinase (fusion gene)
AMPK	AMP-activated Protein Kinase
NOX4	NADPH Oxidase 4
IPF	Idiopathic Pulmonary Fibrosis
mTLS(s)	Mature Tertiary Lymphoid Structure(s)
mTF	Mesenchymal Transcription Factor
PDGFRβ	Platelet-Derived Growth Factor Receptor Beta
ICIs/ICB	Immune Checkpoint Inhibitors / Blockade
TOLLIP	Toll-Interacting Protein
UPF1	Up-Frameshift Protein 1
SLC38A2, SLC7A5	Solute Carrier Family 38 Member 2, Solute Carrier Family 7 Member 5
lncRNA	Long Non-Coding RNA
miRNA(s)	MicroRNA(s)
m6A	N6-Methyladenosine (RNA Modification)
FOXO4-DRI	FOXO4-p53 Interfering Peptide
CQ	Chloroquine
PI3K	Phosphoinositide 3-Kinase
ERK	Extracellular Signal-Regulated Kinase
AhR	Aryl Hydrocarbon Receptor
TIDE	Tumor Immune Dysfunction and Exclusion
PDGFRα	Platelet-Derived Growth Factor Receptor Alpha

Author contributions
Ziheng Wu, Meilin Luo, Huiyi Hu, Zhijun Jiangand yinan Lu wrote the main manuscript text; Ziheng Wu and Meilin Luo prepared figures and tables. Zhi-jie Xiao supervised and reviewed the manuscript and acquire funding.

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Data availability
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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Conflict of interest
The authors disclose no potential conflicts of interest.

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