

Heterogeneity and plasticity of cancer-associated fibroblasts

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Fibroblasts sense and respond to contextual cues to support tissue structure and function. In cancer, they engage a dysregulated wound-healing response that profoundly shapes tumor composition and progression. Efforts to therapeutically target these cancer-associated fibroblasts (CAFs) have been complicated by their heterogeneity and plasticity. However, recent advances, particularly in single-cell and spatial technologies, have greatly improved the understanding of the phenotypic consequences of distinct CAF states and functions. Here we review the current understanding of CAFs as heterogeneous, instructive regulators of tumor microenvironments across anatomic sites and highlight key challenges for the future.

Fibroblasts are ubiquitous stromal cells and serve as key regulators of tissue architecture, extracellular matrix (ECM) composition and homeostasis^{1,2}. In response to stress, inflammation and danger signals, fibroblasts become activated, undergoing transcriptional and functional rewiring that contributes to tissue remodeling and disease progression^{3–5}. In cancer, fibroblasts in these activated states are collectively referred to as cancer-associated fibroblasts (CAFs)^{6–8}.

Initially classified into two main subsets (inflammatory CAFs (iCAFs) that express inflammatory cytokines and interact with immune cells and myofibroblastic CAFs (myCAFs) that express α -smooth muscle actin (α -SMA) and modulate the ECM)^{6,9}, recent advances have revealed a much broader spectrum of CAF phenotypes. Interactions between CAFs and a wide variety of immune cell types, including T cells^{10–12}, macrophages^{13,14}, myeloid-derived suppressor cells^{15,16}, dendritic cells^{17,18} and natural killer cells^{19,20}, were reported, and these interactions were not limited to one subset of CAFs, nor were they only pro-tumorigenic²¹. Animal models and lineage tracing studies have also uncovered substantial heterogeneity in the cellular origins of CAFs^{22,23} in the tumor microenvironment (TME) of multiple types of cancer. These models have provided insights into how CAF identity and function are shaped by developmental history, spatial localization and environmental cues.

The phenotypic heterogeneity in the stroma is inflicted not by genetic mutations and chromosomal aberrations²⁴ but by transcriptional and epigenetic rewiring⁶, shaped by cues from the mutated cancer cells and from the TME, including cytokines, metabolic gradients,

mechanical stress and immune interactions. Consequently, the stromal landscape is dynamic and plastic, changing with disease progression and anatomic localization.

In this Review, we highlight recent insights into CAFs enabled by single-cell and spatial transcriptomic technologies, as well as functional data from lineage tracing and perturbation studies in mouse models. We explore CAF heterogeneity across three interconnected levels: their localization within distinct niches of the TME, their dynamic phenotypic states and functional roles across the tumor ecosystem and their adaptation to changes in the broader tumor macroenvironment over time. Through this layered lens, we examine how these advances are reshaping our understanding of CAF biology and informing emerging strategies to selectively target or reprogram CAFs for therapeutic benefit in solid tumors.

CAFs in different tumor niches

Across carcinomas, tumors are spatially heterogeneous. As they grow and progress, distinct niches emerge as environmental habitats within the broader tumor ecosystem. These habitats are shaped by unique combinations of cellular composition, nutrient availability, immune infiltration and mechanical stress^{25–27}.

Unlike cancer cells that display genetic heterogeneity²⁸, TME cells, in particular CAFs, are largely genetically stable²⁴. Instead, their plasticity is governed by transcriptional and epigenetic programs that respond to dynamic and spatially varied cues in the evolving tumor ecosystem.

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A major challenge in studying CAF interactions within the TME is the absence of specific, uniform markers for the many CAF phenotypes revealed by single-cell RNA-sequencing (scRNA-seq) studies. Typically, CAF subsets are defined by combining negative selection markers (for example, EPCAM and CD45) with broadly expressed positive markers (for example, α -SMA and fibroblast activating protein (FAP)) and subset-specific genes (for example, ECM proteins for myCAFs and cytokines for iCAFs). Although scRNA-seq helped uncover CAF diversity, it lacks spatial resolution for direct interrogation of cell–cell interactions. To bridge this gap, ligand–receptor inference tools such as CellChat²⁹ and CELLphoneDB³⁰ are used; however, spatial validation remains essential. Until recently, most spatial methods were low-plex, limiting the ability to profile specific CAF subsets and their interactions. Recent advances, including ultra-high-plex platforms such as Phenocycler³¹, MACSima³², MERSCOPE³³ and Visium HD³⁴, now enable detailed, single-cell-level spatial maps. These technologies illuminate how distinct CAF subsets form, which cells they engage with and the signaling circuits operating within specific tumor niches (Table 1).

Several recent studies undertook cross-organ harmonization of CAF markers^{33,35–39} and integrated spatial methods to define where CAF subsets reside within the TME. Although each paper uses its own taxonomy, common marker sets and niche placements recur. Integrating multiple tumors, organs and disease states in human tissues also identifies organ- or state-specific fibroblast/CAF subsets that may be missed in single-tumor analyses. Across cancers, four recurrent niches emerge: (1) cancer cell-adjacent (Fig. 1a), (2) tumor periphery/perivascular (Fig. 1b), (3) tertiary lymphoid structures (TLSs) (Fig. 1c), and (4) perineural (Fig. 1d). Each niche is occupied (and primarily defined) by characteristic CAF programs and prominent ligand–receptor interactions.

- (1) **Cancer cell-adjacent:** myCAFs (ECM-secreting CAFs) were found to be the most common CAF subtype immediately adjacent to cancer cells across different cancer types^{33,36,38,39} and express collagens (I/III/IV), TGF β pathway components (TGF β and THBS1) and matrix metalloproteinases (MMP1 and MMP11). This niche is associated with immune exclusion/suppression, reflected by M2-like SPPI⁺ macrophages^{34,36} and exhausted/suppressive T cells^{38,39}. Reported signaling varies, but recurrent themes include galectin-3/galectin-9 as T cell suppressors^{36,38}, CXCL12 in immune exclusion³³ and TGF β /SPPI in macrophage M2-like activation. Enrichment of this niche is consistently linked to worse prognosis and poor immune checkpoint blockade response.
- (2) **Tumor periphery/perivascular:** iCAFs appear predominantly at the tumor periphery^{33,35,39}, often adjacent to myeloid cells or endothelial cells or near vascular structures. iCAF definitions are broad but generally refer to CAF populations enriched for complement, cytokine and chemokine expression, such as interleukin-6 (IL-6), IL-11 and C3. Their spatial proximity to vessels aligns with roles in angiogenesis, immune modulation and chemoattraction^{33,36}. Their enrichment is both associated with prolonged survival and poor survival depending on the specific signaling^{33,35,36}. These pan-cancer spatial analysis findings align with previous mechanistic *in vivo* studies showing that iCAFs can directly induce expansion of regulatory T (T_{reg}) cells^{40,41} and impede cytotoxic T cell activity⁴² via IL-6 secretion and indirectly lead to immunosuppression by enhancing macrophage infiltration⁴³, inducing a myeloid suppressive cell phenotype⁴⁴ and more.
- (3) **TLSs:** antigen-presenting CAFs (apCAFs) were historically difficult to resolve with conventional multiplex immunofluorescence due to signal overlap of major histocompatibility complex class II with professional antigen-presenting cells. Lineage tracing⁴⁵ and single-cell-resolution spatial multiomics^{46,47} analyses have enabled more robust identification of this relatively small CAF subpopulation, its interactions and its niche. Several studies show

that enrichment of apCAFs colocalized with TLSs correlates with better survival and response to immune checkpoint inhibitors^{46,47}. This response was shown to be mediated by induction of pro-inflammatory cytokines in CD4⁺ T cells or macrophages that in turn enhance cytotoxic T cell activation.

- (4) **Perineural niches:** TME–neural interactions in non-central nervous system tumors are an emergent research area. Given technical limitations, human neurons are often underrepresented in scRNA-seq or spatial transcriptomics data, and most in-depth studies are performed in mice. In experimental mouse models, including pancreatic ductal adenocarcinoma (PDAC), neurons are reprogrammed by cancer cells to interact with immune cells and CAFs, and often the removal of cancer-associated neurons is beneficial and improves treatment response^{48–52}. Cancer cells induce increased innervation by reprogramming of neurons within the tumor, leading to neurofilament medium upregulation, which is associated with chronic tissue damage and axonal guidance⁴⁸. Retrograde tracing of tissue- or tumor-innervating neurons to their respective ganglia, followed by scRNA-seq of these neurons, as well as of the innervated tissues, showed fibroblasts or CAFs as the top inferred partner of neurons for heterocellular signaling.

Understanding the signaling circuits defining each tumor niche, the specific cells that inhabit it and their consequences for therapeutic response lies at the core of CAF research and brings us closer to leveraging CAFs and their associated signaling pathways in a therapeutic setting.

CAF states and functions across the tumor ecosystem

Within and beyond these defined spatial niches, CAFs in primary TMEs display heterogeneity in their markers, origins and functions, but recurrent traits occur across tissue sites^{6,53–55} (Fig. 2). Importantly, CAFs are highly dynamic and capable of context-dependent interconversion between cell states. For instance, ECM-remodeling myCAFs can be converted into proinflammatory iCAFs and vice versa on the basis of changing microenvironmental or niche factors^{6,56}. Diverse CAF subsets have varying nonoverlapping functions, such as like immunosuppression and ECM remodeling, and these functions are broadly categorized as tumor promoting or tumor restraining^{6,57,58}; however, the underlying cause of CAF functional heterogeneity needs to be better characterized⁵⁹. In this section, we discuss three framings of CAF heterogeneity, as well as key determinants of heterogeneous CAF states at the level of the primary TME.

Transcriptional CAF heterogeneity

A pioneering study in PDAC identified iCAFs and myCAFs as two transcriptionally distinct CAF subtypes, as described earlier^{9,60}. These subtypes have since been robustly identified in other cancer types^{61–64}. For instance, three transcriptionally distinct subtypes of CAFs were identified in breast cancer⁶⁵ and termed steady-state-like, mechanoresponsive and immunomodulatory CAFs. Mechanoresponsive and immunomodulatory CAFs are similar to myCAFs and iCAFs, respectively, whereas steady-state-like CAFs express universal fibroblast markers PII6 and DPT⁶⁶, suggesting that they may represent a progenitor-like population of fibroblasts.

Several subsequently identified CAF transcriptional subtypes suggest additional functions (Fig. 2a). In PDAC, one such transcriptional subtype was found to express high levels of major histocompatibility complex (MHC) class II genes (*H2-Aa*, *H2AB1* and *CD74*) and was thus termed apCAFs⁶⁷. apCAFs have been also identified in other cancer types, including breast, lung and gastric cancer^{46,68,69}. The transcriptional profile of apCAFs was reflective of a mesothelial origin, at least in PDAC⁴⁵. Transcriptomic analysis of breast cancer tissue from an MMTV-PyMT mouse model revealed the presence of a unique

Table 1 | Summary of CAF subtypes parsed by niches and drivers of heterogeneity

Tumor niche	Ligand (sender cell)	Receptor (target cell)	Cell types involved	Functional consequence	Survival/outcome correlation	Source
(1) Cancer cell - adjacent (myCAF)	COL1A1, COL4A1, FN1	Integrins (ITGA1, ITGB1, ITGA2) on tumor cells	Tumor cell, myCAF	ECM remodeling, tumor stiffness, immune exclusion, increased tumor invasion	myCAFs (ECM rich) correlate with worse survival, immune exclusion	33,36,38
	THBS1	CD47 (tumor/immune)	Tumor cells, immune cells	Immune evasion by suppressing phagocytosis	Contributes to immunosuppression, worse prognosis	133
	TGFβ	TGFβR1 (tumor, CAF, immune)	Tumor cells, CAFs, immune	EMT induction, myofibroblast differentiation, immune evasion	Related to immune exclusion, worse survival	33,38
	FGF2	FGFR1 (endothelial tumor)	Endothelium, tumor	Angiogenesis, tumor proliferation	Proangiogenic, linked to worse prognosis	33
(2) Periphery/ perivascular (iCAF)	CXCL12	CXCR4, ACKR3 (immune, endothelial)	Immune cells, endothelial cells	Myeloid and T _{reg} cell recruitment, immunosuppression, vessel maturation	iCAF gene signature correlates with immunosuppression; paradoxically some respond better to immune checkpoint blockade	33,35,36
	IL-6, LIF, OSM	IL-6R, LIFR (immune cells)	Immune cells	Drives macrophage polarization, immunosuppression	Predictive of immunotherapy response but promotes immunosuppression	35
	CSF1, IL-34	CSF1R (macrophages)	Macrophages	M2 macrophage polarization, immune evasion	M2 polarization linked to tumor progression	35
	LGALS1	PTPRC (CD45, T cells)	T cells	Induces T cell exhaustion and apoptosis	Immune evasion, worse prognosis	35
	CCL2, CCL8	CCR2, CCR4 (T _{reg} cells, monocytes)	T _{reg} cells, monocytes	Recruitment of immunosuppressive cells	Immunosuppressive microenvironment	36
	ANXA1	FPR1 (neutrophils)	Neutrophils	Neutrophil recruitment, vascular remodeling	Supports immunosuppressive niche	33
	VEGFA, VEGFB, VEGFC	FLT1, KDR, NRP1 (endothelial)	Endothelial cells	Angiogenesis induction	Angiogenic CAFs linked to worse prognosis	35,39
	FN1, laminins (LAMB1, LAMC1), collagens (COL1A1, COL6A1)	Integrins (ITGA6, ITGB1, ITGA1)	ECM CAFs, endothelial cells	ECM deposition stabilizes vessels and niches	ECM rich, linked with immune evasion and poor outcomes	35,38
	ANGPTL4, ANGPT2	CDH5, integrins	Endothelial cells	Controls vascular permeability and angiogenesis	vCAFs contribute to tumor progression	38
	JAG1	NOTCH1, NOTCH4	Endothelial cells	Angiogenic sprouting regulation	Supports vascular niche	38
(3) TLSs (apCAF)	CCL19, CCL21	CCR7 (T cells, B cells)	T cells, B cells	Immune cell recruitment and TLS formation	apCAF signature correlates with improved survival and better immunotherapy response	33,39
	HLA-DR, CD74	CD4 ⁺ T cell antigen receptor (helper T cells)	CD4 ⁺ T cells	Antigen presentation, T cell activation	Promotes adaptive immunity	33,36
	JAG1	NOTCH2 (B cells)	B cells	B cell support, plasma cell homeostasis	Supports TLS function	33
	LGALS9	CD47 (immune checkpoint)	T cells	Immune inhibition	Immunosuppressive checkpoint molecule expression	33
	AXL	IL-15RA (T cells)	T cells	T cell survival and homeostasis	Supports TLS and adaptive immune responses	33

Table 1 (continued) | Summary of CAF subtypes parsed by niches and drivers of heterogeneity

Tumor niche	Ligand (sender cell)	Receptor (target cell)	Cell types involved	Functional consequence	Survival/outcome correlation	Source
(4) Perineural (neuron–CAF) niche	IL-1 α (Schwann cells)	IL-1R1 (CAFs)	Schwann cells, CAFs	Induces iCAF phenotype	Nerve-associated iCAFs potentiate tumor progression	52
	MDK (Schwann cells)	ALK, LRP1 (tumor cells)	Schwann cells, tumor cells	Promotes cancer proliferation and migration	Schwann cell proximity predicts poor outcome	52
	CXCL5 (Schwann cells)	CXCR2 (tumor cells)	Schwann cells, tumor cells	Promotes EMT, invasion	Associated with aggressiveness	50
	CCL2 (Schwann cells)	CCR2 (macrophages)	Schwann cells, macrophages	M2 macrophage polarization	Immunosuppression microenvironment	50
	CXCL12 (Schwann cells)	CXCR4 (immune cells)	Schwann cells, immune cells	M2 macrophage polarization and immunosuppression	Pro-tumoral immunosuppression	50
	IL-1 β (monocytes)	IL-1R1 (enteric glia)	Monocytes, enteric glia	Drive enteric glia to pro-tumorigenic phenotype	Modulates stromal-immune niche in colon cancer	49
	IL-6 (enteric glia)	IL-6R (monocytes/macrophages)	Enteric glia, monocytes	Drives pro-tumor macrophage differentiation	Supports tumor-promoting immune niche	49
	SLPI (tumor cells)	Sensory nociceptor neuron	Tumor cells, sensory neurons	Activates nociceptors leading to neurogenic inflammation	Promotes immunosuppression via CGRP release	51
	CGRP (nociceptor neurons)	RAMP1 (CD8 ⁺ T cells)	Sensory neurons, CD8 ⁺ T cells	Induces CD8 ⁺ T cell exhaustion and immune evasion	Enhances tumor growth via immunosuppression	51

subpopulation of CAFs characterized by the expression of angiogenic factors⁷⁰, which were termed vascular CAFs (vCAFs). This study also identified three other CAF populations termed matrix CAFs (mCAFs), cycling CAFs (cCAFs) and developmental CAFs, and all subsets except cCAFs were found to be spatially and functionally distinct⁷⁰. vCAFs and mCAFs were subsequently also identified in cervical squamous cell carcinoma⁷¹.

Complementary CAF subtypes have been identified with immunomodulatory potential. Two recent studies documented CAFs in breast and pancreatic cancer with senescence-associated gene signatures, and these senescent CAFs functionally mediated immunosuppression in both organs but with tissue-specific impacts on immune contexture^{20,72}. Other examples include metabolic CAFs (meCAFs) and reticular-like CAFs (rCAFs). First identified in human PDAC tissue as showing high expression of metabolism-related genes such as *PLA2G2A* and *CRABP2* (ref. 73), meCAFs were also found in colorectal cancer and were linked to immunosuppressive functions⁷⁴. rCAFs are a rare subset found in human breast cancer and express lymphoid reticular fibroblast markers such as *CCL21* and *CCL19* (ref. 37). Future studies will hopefully elucidate the mechanistic drivers of these CAF states and their functional importance in cancer.

Cell-of-origin-based CAF heterogeneity

Various cell types give rise to CAFs in response to tumor-derived cues as established through in vitro experiments, bone marrow transplantation, intravital imaging and fate mapping studies in mice^{23,75–77}. Lineage tracing models are particularly valuable in this context. However, important caveats of this method are the need for cell-type-restricted markers to lineage trace specific cell populations and the challenge of validating such findings in human cancer evolution.

Although other cell types have CAF-forming potential, perhaps the most documented cellular origins for CAFs are tissue-resident fibroblasts (TRFs)^{23,78–82}, mural cells such as pericytes^{38,70,77,83}, and mesothelial cells^{45,84,85} (Fig. 2b). TRFs are mesenchymal cells with homeostatic functions during quiescence and wound healing and repair

functions during injury and inflammation⁷⁸. In response to paracrine cues from the tumor, TRFs are activated to form CAFs. Subpopulations of resident fibroblastic cells can be found within the same tissue, each with distinct CAF-forming potential per lineage tracing. For example, both lipid-storing stellate cells and periductal fibroblasts give rise to CAFs during formation of intrahepatic cholangiocarcinoma, with notable differences in transcriptional profiles across cellular origins^{80,82}. Similarly, stellate cells and resident fibroblasts that express GLI1 give rise to CAFs in PDAC^{23,79}, unlike HOXB6-expressing TRFs. This may indicate a noncanonical role for these fibroblasts in wound healing and regeneration. Similarly, Cre-based lineage tracing revealed that En1⁺ dermal fibroblasts, unlike En1[−] fibroblasts, are the primary source of fibrosis in a model of cutaneous melanoma⁸¹. Other mesoderm-derived cell types, such as endothelial cells⁸⁶, mesenchymal stem cells^{76,87,88} and adipocytes⁸⁹, may give rise to CAFs via activation or transdifferentiation. Some lineage-associated transcriptional profiles and functions have been documented, such as for stellate cell-derived CAFs in liver tumors⁸⁰, and the extent to which distinct mesenchymal origins translate to origin-specific versus shared CAF functions remains under investigation.

Mural cells surrounding blood vessels, such as pericytes, and mesothelial cells lining organs and body cavities also give rise to distinct populations of CAFs. Human PDGF-BB staining and lineage tracing in NG2-CreERT2 mice showed that pericytes transdifferentiate into CAFs in multiple cancer types⁷⁷. Two recent studies described tumor-associated pericytes as defined subpopulations in the TME, with some transcriptional and functional features of CAFs^{38,83}. A pan-cancer scRNA-seq and spatial transcriptomics analysis identified two populations of tumor-associated pericytes, inferred to originate from FABP4-expressing pericyte progenitors across tissues. One of these populations, fibrogenic pericytes, expressed ECM components and remodeling enzymes, whereas the other, vascular pericytes, expressed angiogenic factors and components of interleukin signaling³⁸. An independent study used computational and experimental approaches across four cancer types (breast, pancreas, ovary and prostate) and

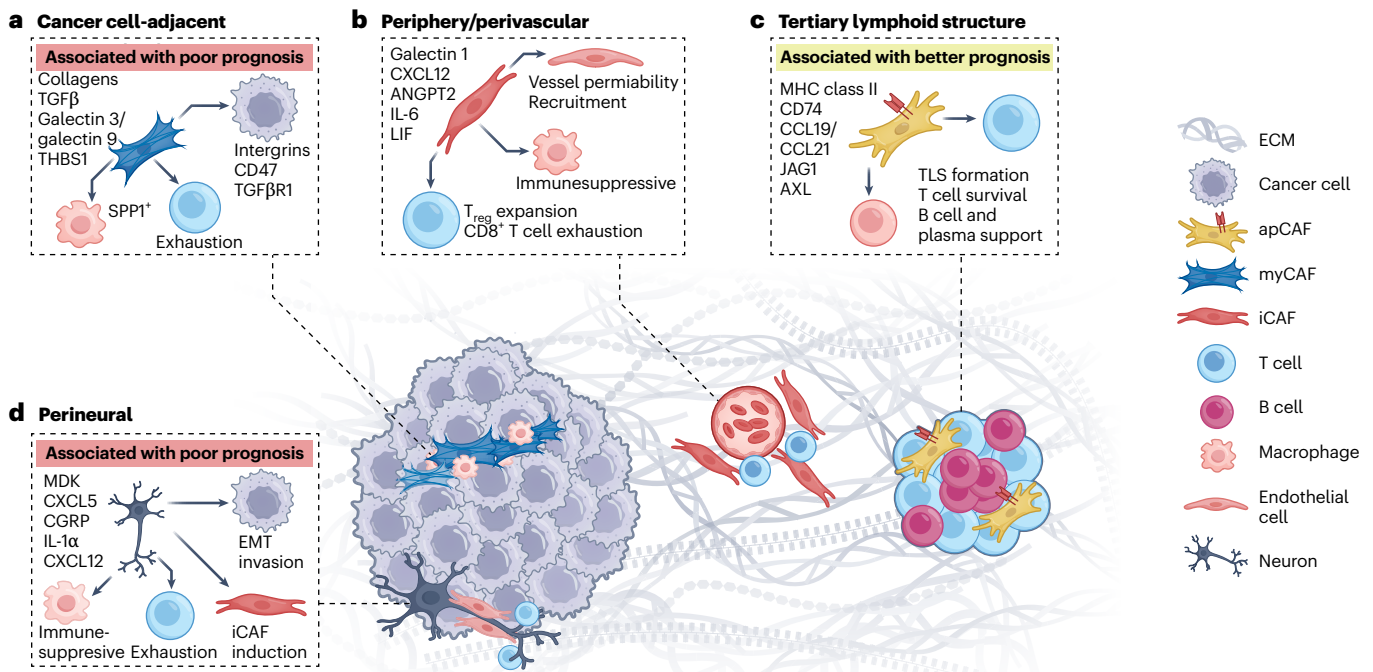


Fig. 1 | Defined CAF niches within heterogeneous TMEs. Within TMEs, recurrent heterocellular niches have been identified across organ sites, with consistent CAF states found in these spatially defined niches. These include cancer cell-adjacent regions (a), tumor periphery or the perivascular space (b), TLSs (c) and perineural niches (d).

found two conserved cancer-associated pericyte states with CAF-like features. These included *matriPer*, associated with the matrisome and wound-healing processes, and *musclePer*, enriched in contractility pathways⁸³. CAFs can also originate from mesothelial cells, marked by expression of genes such as *Wtl* and *Msln*. Lineage tracing mesothelial cells using *Wtl*-CreERT2 in an orthotopic model of PDAC revealed that they give rise to CAFs expressing CD74 and MHC class II, as well as other immunomodulatory molecules⁴⁵. Functionally, these MHC class II-expressing apCAFs promoted tumor growth by promoting T_{reg} cell differentiation and an immunosuppressive TME. As apCAFs are found in multiple tissue sites, mesothelial cells may play broad roles in CAF biology or may be organ-specific contributors to immunomodulatory CAF populations. Indeed, mesothelial cells lining the peritoneal cavity are thought to be major contributors to CAFs in peritoneal metastases⁸⁴ and give rise to CAFs in primary ovarian cancer⁸⁵, yet similarities and differences among mesothelial cell-derived CAFs across organ sites remain to be investigated in depth.

In addition to these tissue-resident CAF sources, various bone marrow transplantation studies in humans and mice have shown that bone marrow-derived cells can migrate to different tumor sites and give rise to CAFs^{75,90,91}. For instance, sex mismatched bone marrow transplantation in individual cases of invasive breast cancer, hepatocellular carcinoma and squamous cell carcinoma revealed the presence of CAFs with chimeric genetic material, indicative of recipient bone marrow origin. These cells were found to have increased α -SMA expression⁹⁰. Similarly, allogeneic bone marrow transplantation of green fluorescent protein-positive (GFP⁺) cells in KPC mice revealed that PDAC CAFs are partially derived from bone marrow-derived hematopoietic cells and promote invasion of cancer cells⁷⁵.

Cellular marker-based heterogeneity

CAF are most often categorized on the basis of marker expression, although underlying functions associated with these markers may shift with tumor progression or therapy. α -SMA-expressing CAFs are

broadly considered myCAFs⁹, associated with TGF β signaling and ECM remodeling, yet this category includes diverse subsets. For example, leucine-rich repeat containing 15-positive (LRRC15⁺) myCAFs regulate immunosuppression and response to immune checkpoint blockade in PDAC^{10,53}, whereas epidermal growth factor receptor-positive (EGFR⁺) myCAFs promote metastasis in PDAC⁹² and are also found in breast and lung cancer. FAP⁺ CAFs represent another myCAF subset⁹³ but have also been classified as iCAFs across cancer types^{94,95}, driving metastatic spread and immunosuppression^{96,97}, including via T cell suppression in human breast cancer^{98,99}. α -SMA is also expressed by pericytes, suggesting a potential pericyte origin for some myCAFs³⁷. In addition to FAP expression, iCAF subsets can also be associated with the expression of lymphocyte antigen 6 complex locus C1 (ref. 69), IL-6 (ref. 67) or clusterin (Clu)¹⁰⁰ depending on tissue context. MHC class II molecules at the surface of apCAFs reflect their immunomodulatory functions in the TME. Although not strictly aligned with an iCAF or apCAF identity, a defined population of PDAC CAFs expresses the synaptic protein NetG1 on the cell surface and promotes both immunosuppression and the metabolic needs of neighboring PDAC cells¹⁰¹. Although CAFs are often defined in part by the lack of markers of other cellular compartments of the TME, some CAFs express markers of other mesoderm lineages. For example, endoglin (CD105), typically associated with endothelial cells, distinguishes two CAF populations in several solid tumor types. In PDAC, CD105⁺ CAFs were found to be tumor supportive, whereas CD105⁻ CAFs restrain PDAC growth through adaptive immunity²².

In addition to cellular markers that define specific CAF subpopulations, some pan-CAF markers are useful in cell sorting or validation of fibroblast purity. However, there is some heterogeneity in the expression of these markers on the basis of tumor type and context. For example, podoplanin (PDPN) is generally considered a broad CAF marker, and, although it does mark most CAFs in multiple cancer types^{67,102,103}, it only marks certain subsets of CAFs in breast cancer and squamous cell carcinoma. In breast cancer, iCAFs and myCAFs, but not apCAFs,

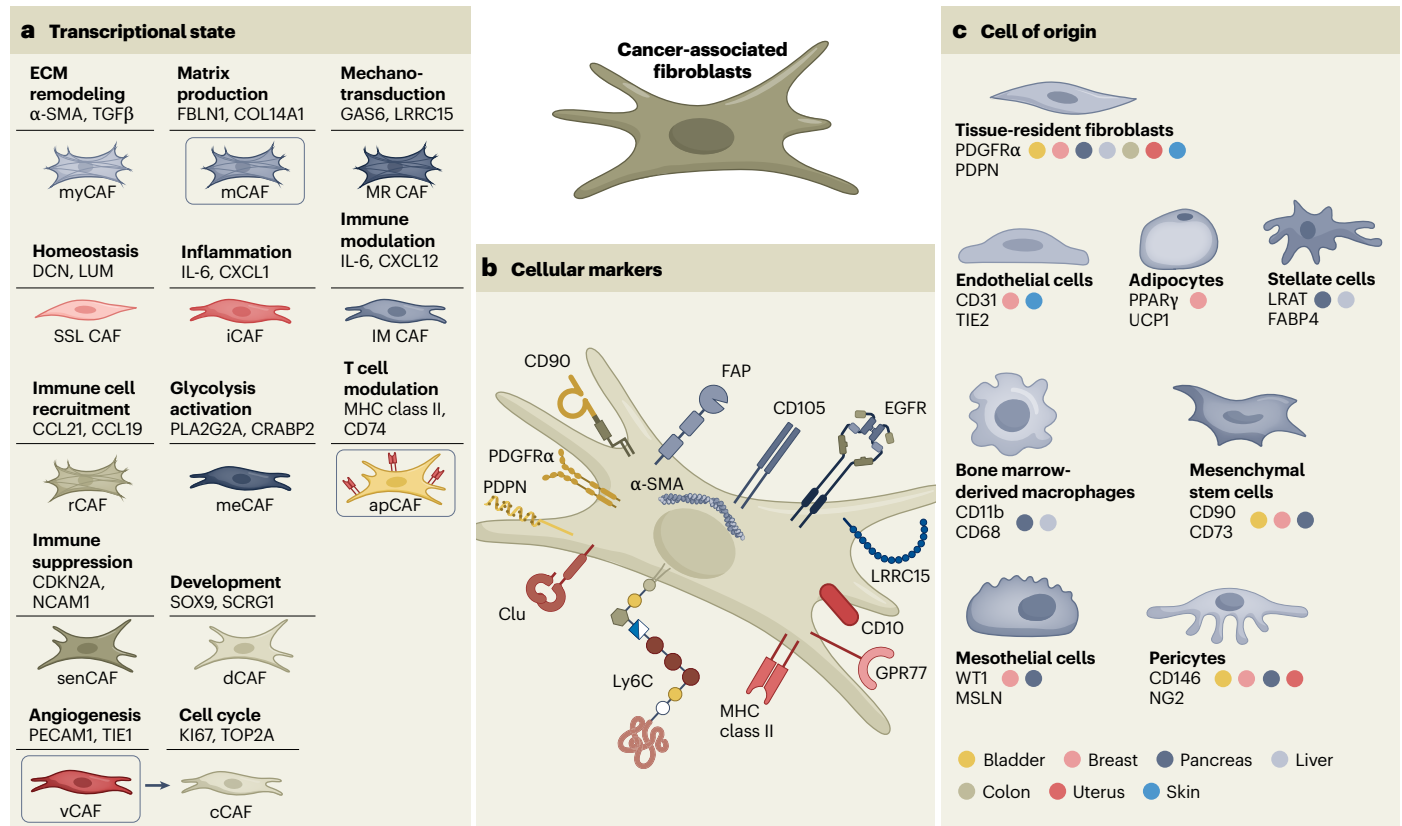


Fig. 2 | CAF heterogeneity in the primary TME. CAFs may be classified by transcriptional state (a), cellular markers (b) and cell of origin (c). Transcriptionally distinct CAFs include myCAFs, mCAFs, mechanoresponsive CAFs (MR CAFs), steady-state-like CAFs (SSL CAFs), iCAFs, immunomodulatory CAFs (IM CAFs), rCAFs, meCAFs, apCAFs, senescent CAFs (senCAFs), developmental CAFs (dCAFs), vCAFs and cCAFs. CAFs express cellular markers

such as PDPN, PDGFR α , thymus cell antigen-1 (CD90), FAP, endoglin (CD105), EGFR, LRRC15, α -SMA, neprilysin (CD10), G-protein-coupled receptor 77 (GPR77), MHC class II, lymphocyte antigen 6 complex locus C1 (Ly6C) and Clu. Cell types that form CAFs are TRFs, stellate cells, pericytes, mesothelial cells, endothelial cells, adipocytes, mesenchymal stem cells (MSCs) and bone marrow-derived macrophages (BMDMs).

express PDPN, and PDPN expression is linked with worse overall prognosis⁶⁹. PDPN marks the reticular subset of dermal fibroblasts linked to tumor invasion and epithelial-to-mesenchymal transition (EMT) in squamous cell carcinoma¹⁰⁴ and lymphatic endothelial cells in angiosarcomas¹⁰⁵. CD90, encoded by *Thy1*, is not fibroblast specific but is pervasively expressed by CAFs in several tumor tissues, including pancreas, breast and soft tissue sarcomas^{22,63,106}, and may be useful for CAF isolation across organ sites. Similarly, platelet-derived growth factor receptor- α (PDGFR α) is often used as a pan-CAF marker^{23,66,79,107}, but it has also been cited as an iCAF marker⁶⁷ and is expressed by quiescent TRFs in various organs⁶⁶. Another such marker is S100A4 or FSP1, which is expressed mostly by CAFs⁶⁹ but also by immune cells, healthy fibroblasts and even certain cancer cells^{108–110}. Finally, single-cell fate mapping work revealed that the universal fibroblast markers PII6 and COL15A1, which are expressed by nearly all PDGFR α ⁺ fibroblasts in healthy tissues isolated from different organs, show heterogeneous levels of expression when fibroblasts transition to CAFs⁶⁶. However, it is important to note that this study assessed the transcriptional profiles of fibroblasts and CAFs and thus cannot be compared to other studies that measure protein expression. Overall, CAF heterogeneity based on cellular markers is highly context dependent and variable but also conserved across cancers, to a certain extent (Fig. 2c).

Drivers of CAF heterogeneity and plasticity

Although targeting specific tumor-supportive CAF functions may be a productive route to stroma-targeted cancer therapies, to fully explore the potential of targeting CAFs in cancer, one must understand the mechanisms that drive CAF heterogeneity and plasticity (Table 1).

Drivers of CAF plasticity in the immediate TME

Recent efforts have identified mutational status, subtype-specific paracrine cues and metabolic states that program heterogeneous CAF phenotypes and/or enable their plasticity in the dynamic TME. A link between mutational status and CAF heterogeneity has been particularly well-established in breast cancer, in which, compared to *BRCA*-wild-type tumors, *BRCA*-mutant tumors harbor many fewer PDPN^{hi} CAFs, a CAF population identified in a mouse model of triple-negative breast cancer to have putative immunosuppressive function⁶⁹. In PDAC, *BRCA* mutations in cancer cells were associated with an expansion of Clu⁺ iCAFs compared to the *BRCA*-wild-type context¹⁰⁰. This was mediated by activation of transcription factor heat shock factor 1 (HSF1) in the stroma of *BRCA*-mutant tumors. Given the pervasive stress and HSF1-associated transcriptional signatures observed across human cancers⁸³, these results warrant further investigation into the link between *BRCA* status and stromal heterogeneity. Subtypes or cancer cell states and mutational status have been further linked to CAF states in PDAC. Several studies that incorporated preclinical models and spatial analyses of clinical samples show a broad association of the basal-like subtype of PDAC with myCAFs, which are often found in direct proximity of basal-like PDAC cells, suggesting that these two cell states may mutually regulate one another^{111,112}. PDAC specimens also revealed a link between p53 status and CAF heterogeneity: CAF states differ in the context of *TP53*-mutant (R172H in mice) versus *TP53*-null somatic mutations in the epithelial compartment^{23,113}. In the *TP53*-mutant setting, CAFs take on a transcriptional profile rich in specific matrix components, such as perlecan, which promote metastasis and chemoresistance.

Niche factors, including secreted molecules and nutrient levels, intersect with genetic features to drive CAF heterogeneity and plasticity. For example, TGF β signaling has been implicated in myCAF programming whereas IL-1 signaling drives iCAF states^{53,60}, and in vitro studies revealed that cultured CAFs can readily transition between iCAF and myCAF states depending on TGF β and IL-1 signaling intensity^{53,60}, implicating signaling gradients as key regulators of CAF plasticity. These same paracrine cues also program apCAF formation from a mesothelial origin⁴⁵, underscoring the relevance of both signaling gradients and stromal lineage heterogeneity in establishing CAF complexity. Studies of metabolic states of tumor tissues, which exhibit clear heterogeneity across the microenvironments of solid tumors, implicate nutrient and oxygen levels as major drivers of CAF plasticity. Several studies have demonstrated a causal role for hypoxia and downstream HIF-2 α activity to the iCAF state^{114,115}, with hypoxic tumor niches showing a greater proportion of iCAFs out of total CAFs than relatively well-perfused regions. Furthermore, the combination of glutamine deprivation and nutrient scavenging via macropinocytosis enforces the myCAF state, while metabolic stress resulting from macropinocytosis inhibition drives myCAF-to-iCAF transitions and reduced immunosuppression¹¹⁶. Finally, the oxidative stress response is preferentially activated in iCAFs versus myCAFs and in the musclePer versus matriPer subset of cancer-associated pericytes⁸³. These results suggest that the metabolic heterogeneity across the TME may support spatial heterogeneity in CAF subtypes and may enable CAF plasticity as metabolite abundance changes during tumor evolution. Overall, these established links from gradients of paracrine cues and metabolites to CAF heterogeneity and plasticity provide a mechanistic basis for intratumoral and intertumoral CAF heterogeneity within a given anatomic site.

Drivers of CAF plasticity in the metastatic TME

Similar to the primary TME, distant metastatic organs also possess a niche encompassing a complex interplay of various cell types¹¹⁷, including CAFs. CAFs in these metastatic niches have a similar range of functions as their primary tumor counterparts, promoting ECM remodeling, inflammation, immunosuppression, angiogenesis, tumor proliferation, migration and EMT phenotypes^{118–123}. Despite these similarities, it is fairly well understood that within an individual organism, CAFs in the primary and metastatic microenvironments are functionally distinct¹²⁴. These differences can be attributed to anatomic region-specific cell of origin¹²⁵ and exposure to various tumor-secreted cues^{118,121}. As discussed previously, different quiescent cell populations are capable of forming CAFs in each organ with lineage-restricted functions in tumor progression^{23,45,76,77,89,90,126}.

Additionally, during and after the metastatic cascade, tumors secrete unique cues (distinct from those secreted in early tumor stages) that drive the activation of CAFs and other nonmalignant cells at the metastatic site, contributing to the divergent functions of CAFs observed between primary and metastatic tumors^{127,128}. For instance, CAFs from liver, bone, lung and skin metastases of individuals with breast cancer, termed mCAFs, were found to have a more pro-tumorigenic effect on triple-negative breast cancer cell lines than CAFs isolated from primary tumor sites¹¹⁸. mCAFs were also found to promote breast cancer growth and metastasis when coimplanted with MDA-MB-436 cells in the mammary fat pad of nude mice compared to CAFs isolated from primary tumor sites¹¹⁸. Another study that explored the differences in CAFs from primary breast cancer and brain metastases found that metastatic site CAFs produced higher amounts of CXCL12 and CXCL16 than primary tumor CAFs, which resulted in more potent tumor cell migration¹²³. Similarly, CAFs in colorectal cancer liver metastases promote increased angiogenesis compared to their counterparts in primary colorectal cancer through upregulation of ECM-remodeling genes¹¹⁹. A recent study that explored the primary PDAC TME and liver-metastatic TME found

increased expression of genes associated with inflammation, angiogenesis, metabolism and ECM signaling in liver-metastatic CAFs compared to primary PDAC CAFs, resulting in an immunosuppressive metastatic microenvironment¹²⁰.

Furthermore, there is growing evidence that CAF precursors at the metastatic site can be exposed to systemic cues such as extracellular vesicles from the tumor before dissemination from the primary site, driving the formation of a tumor-permissive, premetastatic niche^{121,122}. Exosomes derived from a lung-trophic breast cancer cell line are taken up by fibroblasts in the lung, promoting premetastatic niche formation¹²⁹. Likewise, ITGBl-1-rich extracellular vesicles derived from primary colorectal tumors increase the expression of pro-tumor factors such as IL-6, TGF β and CXCL12 in CAFs in liver and lung metastatic sites compared to normal extracellular vesicle-treated mice, indicating a role in establishing a premetastatic niche¹²² (Table 1). In addition to affecting CAFs at distant metastatic sites, secreted factors from primary or disseminated tumor cells can also affect the host as a whole¹²⁸.

Finally, there is some evidence suggesting that CAFs can circulate systemically, indicating that CAFs from the primary site may disseminate and metastasize with cancer cells^{130–132}. One study engrafted red fluorescent protein⁺ (RFP⁺) lung adenocarcinoma cells subcutaneously into mice with GFP⁺ skin and found metastatic colonies in the lung containing both GFP and RFP expression¹³². Furthermore, using a microfilter capture process, FAP⁺ and α -SMA-coexpressing CAFs have been identified in the peripheral blood of individuals with metastatic breast cancer¹³⁰. This marks an added source of CAF heterogeneity in the metastatic microenvironment.

Systemic drivers of CAF heterogeneity and plasticity

In addition to tumor-derived cues, both primary and metastatic, it is increasingly clear that systemic features of the host, such as aging, obesity and cancer-associated cachexia, profoundly influence fibroblast behavior both before and during tumor progression. In aged hosts, fibroblasts exhibit hallmarks of cellular senescence, including increased SASP activity, altered ECM production and chronic inflammation. In melanoma, aged dermal fibroblasts have been shown to promote tumor progression via secretion of sFRP2, which reduces melanoma cell differentiation and enhances resistance to oxidative stress¹³³. In PDAC, aged fibroblasts secrete different factors than young fibroblasts, including increased growth/differentiation factor 15, which promotes cancer¹³⁴. Finally, two recent studies identified a subset of senescent myCAFs in mouse models and in the clinic, which limit natural killer cell cytotoxicity and promote immunosuppressive macrophage functions in turn driving tumor growth in breast cancer and PDAC^{20,72}.

Similarly, obesity alters the metabolic and inflammatory landscape of the host, influencing both resident fibroblasts and the evolving CAF population. Histopathological analysis of breast tissue from women with obesity versus women who are lean revealed an enrichment in myfibroblasts and stiffness-promoting ECM components even in cancer-free tissue, and mouse models showed that these myfibroblasts most likely arise from adipose stem cells¹³⁵. In a different study, a high-fat diet led to the transition of colonic mesenchymal stem cells into CAFs, which displayed increased energy metabolism and promoted tumorigenic properties in colon organoids¹³⁶.

In the setting of cancer-associated cachexia, particularly in PDAC, colon cancer and hepatocellular carcinoma, CAFs have been proposed to act as both local effectors and systemic amplifiers of catabolic signaling. CAFs contribute to the cachectic phenotype by enhancing ECM production, leading to fibrosis and desmoplasia, and by secreting IL-6 and other cytokines that act both locally and on distant tissues, including skeletal muscle and adipose depots, perpetuating systemic wasting¹³⁷.

Overall, various factors regulate CAF heterogeneity between primary and metastatic microenvironments, and, although the primary TMEs of many cancers are extensively studied, more emphasis must

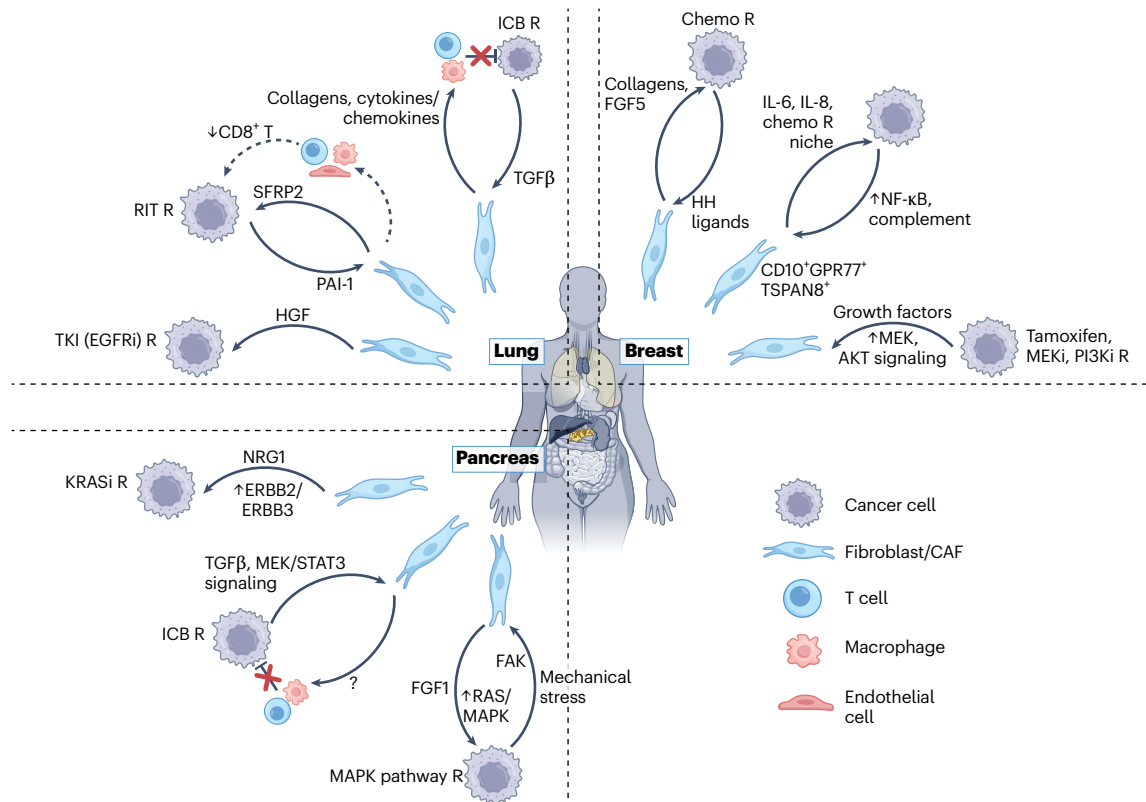


Fig. 3 | Fibroblast interactions that promote resistance to anticancer therapies. Across multiple tumor types, including breast, lung and pancreatic tumors, fibroblasts functionally interact with cancer cells and the immune microenvironment to impact adaptation and resistance to therapy. Relevant mechanisms include paracrine activation of the therapy-targeted pathway

and may be active in the untreated CAF state or acquired during the evolving response to therapy; R, resistance; ICB, immune checkpoint blockade; RIT, radioimmunotherapy; TKI, tyrosine kinase inhibitor; EGFRi, EGFR inhibitor; KRASi, KRAS inhibitor; HH, Hedgehog; MEKi, MEK inhibitor; PI3Ki, PI3K inhibitor.

be given to studies that assess the metastatic microenvironment or compare primary and metastatic sites. Leveraging single-cell and spatial transcriptomic and proteomic technologies to characterize various metastatic microenvironments and systemic or host-driven processes is important to further our understanding of late-stage disease and therapy.

CAFs and therapy

In this section, we will discuss the influence of CAFs on therapy response and resistance and their targeting.

Roles and responses of CAFs under therapy

Innate and acquired drug resistance present major barriers to successful treatment of individuals with cancer. After much focus on cancer cell-autonomous mechanisms of therapy resistance, a series of discoveries over the last 15 years has implicated CAFs as key mediators of resistance to anticancer therapies (Fig. 3). Although relevant CAF populations and molecular mechanisms vary across tumor sites and therapeutic modalities, the links between CAF function and therapy resistance generally relate to their evolutionarily conserved roles in wound healing, mediated by production of secreted factors that promote epithelial cell growth or suppression of immune responses. Pioneering work demonstrated a critical role for mechanisms only found *in vivo* in resistance to anticancer therapy¹³⁸, but the cellular mediators long remained unknown. Coculture experiments later implicated breast CAFs in resistance of cancer cells to tamoxifen¹³⁹, together with paracrine induction of MEK and AKT signaling and increased resistance to MEK and PI3K inhibitors. Soon after, experiments in lung cancer xenografts implicated hepatocyte growth factor (HGF)-producing CAFs in resistance to tyrosine kinase inhibitors, specifically EGFR

inhibitors¹⁴⁰. These studies motivated efforts to incorporate stromal cells in drug screening. Two such screening efforts, which combined diverse sources of fibroblasts with cancer cell lines from multiple tissue sites, illustrated broad CAF-induced chemoresistance in cancer cells from solid tumors and hematologic malignancies^{141,142}. Chemoresistance is associated with secretion of HGF and with paracrine induction of gene signatures associated with poor outcomes, including RAS, AKT, NF- κ B and HIF-1 α signatures. More recently, in triple-negative breast cancer, production of Hedgehog ligands by cancer cells promoted a chemoresistant niche driven by CAF production of collagens and growth factors such as FGF5, motivating a clinical trial that tested combination treatment with docetaxel chemotherapy and inhibition of the Hedgehog/Smoothed pathway¹⁴³. Similarly, analysis of CAF signatures among individuals with non-small cell lung cancer revealed a strong association between targeted therapy resistance and a CAF subtype that expresses high levels of HGF and FGF7 (ref. 144). These studies fostered further efforts to understand mechanisms by which CAFs modulate innate and acquired resistance to cancer treatments, as potential targets for combination therapy.

Accumulating evidence shows that CAFs change in response to radiation therapy and in turn promote radiotherapy resistance. For example, radiotherapy induces the expression of PAI-1 by cancer cells and subsequent changes in the CAF secretome that limit the abscopal effect, a clinically desirable but rare effect involving tumor shrinkage beyond the irradiated field¹⁴⁵. In human PDAC, comparing treatment-naïve tumors to those receiving neoadjuvant chemotherapy and radiotherapy uncovered treatment-enriched CAF signatures, including therapy-induced IL-6 expression by CAFs that functionally promoted chemoresistance in *ex vivo* CAF-tumoroid coculture studies^{146,147}. These spatial transcriptomic analyses further identified

pervasive changes in ligand–receptor pairs in response to treatment, potentially implicating diverse mechanisms of tumor–stroma cross-talk in adaptation and resistance to therapy.

Defined CAF subtypes have also been implicated in resistance to cytotoxic chemotherapy. CAFs expressing CD10 and G-protein-coupled receptor 77 promoted chemoresistance in coculture and patient-derived xenograft studies by the secretion of factors, including IL-6 and IL-8, that promoted a cancer stem cell-like niche, leading to poor prognosis for individuals with chemoresistant breast and lung cancers¹⁴⁸. This CAF state was driven by complement and NF- κ B signaling, pointing to potential targets for combination therapy. An independent study in breast cancer identified a TSPAN8-expressing senescence-like CAF subset that secretes IL-6 and IL-8 to promote chemoresistance and correlates with chemoresistance and poor prognosis¹⁴⁹. These CAF populations may be present in some tumors before treatment or may represent an adaptive population that arises or expands during the course of treatment resistance.

CAF and CAF subtypes function via defined, secreted factors to promote resistance to targeted therapies across anatomic sites. Although hormone-sensitive prostate cancer harbors a substantial population of iCAF, androgen deprivation therapy induces a switch from iCAF to SPPI-expressing myCAF¹⁵⁰. This stromal phenotype switching fosters resistance to anti-androgens via paracrine SPPI–ERK signaling, illustrating a specific feature of tumor–stroma coevolution implicated in treatment resistance. In PDAC, mechanosignaling downstream of FAK leads to the production of FGF1 and paracrine hyperactivation of RAS–MAPK signaling in cancer cells, promoting resistance to both cytotoxic and MAPK pathway-targeted therapies^{151,152}. Combination treatment with chemotherapy and inhibitors of FAK and MAPK signaling led to tumor regressions and prolonged survival in PDAC mouse models. A role for CAFs in acquired resistance to the suite of recently available KRAS inhibitors warrants investigation, particularly in light of evidence in preclinical models that specific CAF-derived factors such as NRG1 can stimulate survival pathways that enable bypass of KRAS signaling¹⁵³. These studies linking CAF state markers to mechanistic mediators of treatment resistance highlight specific opportunities to test combination therapeutic strategies and motivate similar studies in other tumor types.

Consistent with their immunosuppressive roles in inflammation and cancer, activated fibroblasts also limit efficacy of immunotherapies. This occurs via cross-talk to both cancer cells and neighboring immune cells. TGF β promotes immunosuppression in multiple solid tumors, and dual inhibition of TGF β and PD-1 or PD-L1 showed anti-tumor responses superior to those of single-agent treatment in preclinical models of several solid tumors, including lung, colorectal and ovarian cancer^{12,154–160}. However, translating these results to the clinic successfully remains a challenge. With that said, the consistent association between TGF β signaling and resistance to immunotherapy, as well as the anatomically conserved emergence of interferon-licensed and potentially immunomodulatory CAF states in response to TGF β inhibition¹⁶⁰, motivates further mechanistic study to identify additional, functionally relevant targets. For example, a recent clinical trial testing immune checkpoint blockade in individuals with clear cell renal cell carcinoma identified the TGF β -driven myCAF state associated with primary resistance to immunotherapy¹⁶¹. These myCAFs also strongly correlated with mesenchymal-like cancer cells, suggesting a role for these myCAFs in the epithelial-to-mesenchymal cancer cell state gradient associated with immunotherapy resistance. Consistent with this notion, defined clusters of FAP⁺ CAFs characterized by ECM signatures and TGF β signaling associate with immunotherapy resistance in human breast cancer¹⁶².

In addition to these adaptive mechanisms, CAFs have the potential to restrict immunotherapy efficacy from the start, potentially by spatial restriction of T cells from cancer cell-adjacent regions. Single-cell and spatial transcriptomics of treatment-naive basal cell carcinoma

samples from the clinic identified a peritumoral niche harboring CAFs with an activin A signature associated with local exclusion of T cells and resistance to immune checkpoint blockade¹⁶³. IL-17-secreting CAFs in the skin also restrict T cell infiltration into the TME and resistance to anti-PD-L1 treatment¹⁶⁴. Furthermore, a TGF β -dependent CAF population marked by LRRC15 associated with T cell exclusion and immune checkpoint blockade resistance across tumor sites, and its targeting fostered immunotherapy efficacy in mouse PDAC^{10,53}. Suggesting this can be harnessed pharmacologically, treatment of mouse PDAC with combined inhibition of MEK and STAT3 reprogrammed CAFs from the LRRC15⁺ myCAF state to a less differentiated phenotype¹⁶⁵. This CAF plasticity is associated with macrophage remodeling, as well as with potent anti-tumor responses to PD-1 blockade.

Importantly, CAFs may promote adaptive resistance to cancer therapies not only via CAF-intrinsic mechanisms but also by promoting plasticity among neighboring cancer cells, as was inferred from a recent study of human small cell lung cancer¹⁶⁶. Similar results were observed from a large-scale screening effort wherein CAFs promoted plasticity and chemoprotection among patient-derived organoids from colorectal cancer specimens¹⁶⁷. Increasing attention to the dynamics of the TME during the course of therapy may yield new treatments that restrict plasticity of both tumor and stroma.

Targeting CAFs

The genomic similarity between CAFs and normal fibroblasts and their remarkable heterogeneity and plasticity make selective targeting difficult without inducing toxicity. Early efforts to broadly deplete CAFs have proven unsuccessful^{168,169}. More nuanced approaches have shown greater promise (targeting IL-6 in α SMA⁺ CAFs but not in FAP⁺ CAFs improved gemcitabine efficacy¹¹⁰, and adding recombinant PEGPH20A to degrade hyaluronic acid in the ECM improved treatment response to anti-PD-1 and FAK inhibitor combination in PDAC mouse models¹⁷⁰). These findings suggest that selective targeting of pathogenic CAF subsets may offer a more effective path toward stromal-directed cancer treatment. Such selectivity could be guided by distinct functional roles (for example, ECM production), unique surface markers (for example, LRRC15 (ref. 53)) or spatial localization (for example, CAFs restricted to metastatic sites). Specificity may also be achieved through rational combination therapies, such as pairing PARP inhibitors for *BRCA*-mutated cancer cells with compounds targeting iCAFs, which have been associated with *BRCA*-mutated tumors¹⁰⁰.

Alongside the quest for specificity, defining broad markers across organs could expand the therapeutic repertoire. As highlighted in this Review, many CAF subsets, markers and functions are conserved across tumor types and anatomical sites. Therefore, targeting pan-cancer CAF populations represents a promising strategy for developing more widely applicable, stroma-directed cancer therapies.

Concluding remarks

Powered by single-cell and spatial technologies, alongside sophisticated mouse models and three-dimensional culture systems, our understanding of CAF heterogeneity has greatly expanded. Although much of the earlier work focused on CAFs within primary tumors, revealing their diverse states, functions and interactions, these tools have broadened our view to include the tumor macroenvironment and the systemic factors that shape both primary and metastatic TMEs.

Recent advances in spatial profiling technologies have unlocked new insights into the *in vivo* organization of CAFs and their interactions with neighboring cells. To mechanistically dissect these interactions and screen for ways to perturb them, it is important to develop sophisticated and tractable *in vitro* models, including coculture systems, organoids and engineered microenvironments that can faithfully recapitulate the spatial, mechanical and immunological complexity of the native TME. These three-dimensional models are particularly promising for studying how distinct CAF populations interact with

other tumor components and could serve as powerful tools for functional analysis and drug screening. This is not a trivial task; the genomic stability, low proliferative capacity and plasticity of CAFs make them challenging to study *in vitro*.

This Review has focused mainly on carcinomas, with some reference to melanoma, in which CAFs are well studied. However, the principles of fibroblast biology extend beyond epithelial tumors. In sarcomas, fibroblast-like mesenchymal cells are the malignant compartment, blurring the line between stroma and cancer¹⁷¹. Meanwhile, in hematologic malignancies such as lymphomas and leukemias, stromal fibroblasts in lymphoid organs and bone marrow contribute substantially to tumor survival, immune evasion and therapeutic resistance¹⁷². These contexts underscore the broader relevance of fibroblast plasticity and highlight the need to study CAF-like populations across diverse tumor ecosystems.

Understanding CAF heterogeneity was crucial; identifying unifying principles and functional archetypes is essential to translate findings into clinically actionable strategies. As we move toward integrating high-resolution spatial data with functional models and systemic context, the field is well positioned to translate foundational insights into strategies that selectively modulate CAF function. Doing so will require both nuanced understanding of CAF diversity and a focus on shared, targetable features that transcend tumor type or anatomical location.

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