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Review Articles

Stress-adapted cancer-associated fibroblasts as mediators of immunosuppression and therapy resistance

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ABSTRACT

Cancer-associated fibroblasts (CAFs) are key regulators of the tumor microenvironment (TME), shaping immune surveillance, stromal architecture, metastatic progression, and therapeutic resistance across solid tumors. Although traditionally classified into heterogeneous subtypes, emerging evidence indicates that CAF phenotypes are not fixed lineages, but dynamic stress-adaptive states continuously reshaped by hypoxia, oxidative stress, nutrient deprivation, metabolic pressure, and therapy-induced injury. These pressures reprogram CAFs transcriptional, metabolic, and secretory programs, enabling CAFs to amplify tumor-promoting signals that reinforce immunosuppression, extracellular matrix (ECM) remodeling, metastatic niche formation, and treatment resistance. Viewing CAF biology through this stress-adaptation framework provides a mechanistic explanation for the limited success of indiscriminate stromal depletion strategies and highlights the need for more selective, context-aware therapeutic intervention. In this review, we examine how microenvironmental and therapeutic stress rewires CAF identity and function across tumor progression, integrating insights from single-cell, spatial, and translational evidence. We further discuss emerging strategies aimed at disrupting stress-adaptive CAF programs, including modulation of inflammatory signaling, stromal mechanotransduction, metabolic dependencies, and senescence-associated secretory phenotypes. Reframing CAFs as dynamic stress-responsive hubs rather than static stromal subtypes may provide a conceptual foundation for next-generation stromal-targeted therapies designed to overcome immunosuppression and therapeutic resistance.

1. Introduction

Tumor initiation and progression occur within a dynamic and hostile microenvironment shaped by hypoxia, oxidative stress, nutrient deprivation, therapy-induced injury, and other selective pressures [1–3]. To survive under these constraints, cancer cells undergo adaptive rewiring of metabolic, signaling, and epigenetic programs. However, these stress responses are not confined to malignant cells. They also profoundly remodel the tumor microenvironment (TME), reprogramming stromal and immune compartments in ways that sustain tumor growth, immune evasion, and therapeutic resistance [4,5].

Among stromal populations, cancer-associated fibroblasts (CAFs) are the most abundant and functionally plastic constituents of the TME. Far from serving as passive structural support, CAFs actively shape tumor ecology through extracellular matrix (ECM) remodeling, cytokine and chemokine secretion, metabolic crosstalk, vascular regulation, and immune modulation [6–9]. Yet CAF functions are highly context dependent. In many tumors, CAFs promote malignant progression by establishing fibrotic barriers, reinforcing immunosuppressive niches, and supporting metastatic dissemination. Conversely, specific CAF populations can restrain tumor growth by preserving tissue architecture or facilitating immune infiltration [10,11]. This apparent functional

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duality reflects the dynamic influence of spatially and temporally heterogenous stress signals within the evolving TME.

These features make CAFs attractive therapeutic targets, but clinical efforts aimed at broad stromal depletion or disruption of single stromal pathways have yielded limited success. Such failures underscore a central challenge: CAFs are not fixed cell populations with uniform biological roles, but highly adaptive stromal states that respond continuously to environmental and therapeutic pressures. Emerging evidence suggests that hypoxia, metabolic stress, oxidative injury, and treatment-induced damage actively reprogram CAF identity, function, and intercellular communication, generating context-specific tumor-promoting phenotypes that may represent more tractable therapeutic vulnerabilities than indiscriminate stromal targeting [12].

Although CAF heterogeneity and stromal biology have been extensively reviewed, a key conceptual gap remains: stress has rarely been positioned as the unifying framework that explains CAF plasticity, functional divergence, and therapeutic adaptability [13]. In this review, we examine how microenvironmental and therapy-associated stresses rewire CAF transcriptional, metabolic, and secretory programs across tumor progression, thereby shaping immune suppression, stromal remodeling, metastatic fitness, and therapeutic resistance. By framing CAF biology through the lens of stress adaptation, we propose a mechanistic model that redefines CAFs as dynamic stress-responsive hubs within the tumor ecosystem and highlights new opportunities for precision stromal intervention.

2. Stress-adaptive CAF programs and functional plasticity

Advances in single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and multiplex tissue profiling have fundamentally reshaped our understanding of CAFs, revealing that they do not present a uniform stromal population but rather a spectrum of dynamic cellular states with distinct transcriptional and functional programs. Among the best-characterized CAF populations are myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) [14,15]. However, despite extensive classification efforts, a unified CAF nomenclature remains elusive, reflecting a deeper biological reality: CAF states are not fixed lineages, but adaptive phenotypes continuously shaped by cellular origin, spatial localization, and microenvironmental stress. Within the context of this review, CAF heterogeneity is therefore best understood not as a rigid subtype taxonomy, but as a manifestation of stress-responsive stromal plasticity.

2.1. Dominant CAF programs reflect dominant stress-responsive states

Major CAF populations can be broadly interpreted as dominant stress-adaptive programs aligned with specific microenvironmental cues. myCAFs are primarily associated with TGF-β signaling, mechanical stress, and ECM remodeling, leading to activation of contractile machinery, collagen deposition, and stromal stiffening [16,17]. These programs contribute to desmoplasia, impaired drug delivery, and immune exclusion, while also supporting tumor invasion and survival. In pancreatic ductal adenocarcinoma (PDAC), for example, myCAFs promote epithelial-mesenchymal transition (EMT) and invasive behavior through ECM-associated signaling networks [18].

In contrast, iCAFs emerge under inflammatory conditions dominated by NF-κB and JAK/STAT signaling and are characterized by secretion of cytokines and chemokines that actively shape immune composition and tumor-associated inflammation [19,20]. These CAFs reinforce immunosuppressive microenvironments through recruitment of regulatory and myeloid populations, thereby facilitating immune escape and disease progression [21]. apCAFs, defined by MHC class II expression, represent a distinct immune-interactive state capable of modulating $CD4^+$ T cell responses and contributing to tolerance-promoting stromal niches [22,23].

At the mechanistic level, stress-adaptive CAF plasticity is orchestrated through the integration of multiple stress-responsive signaling pathways that translate environmental cues into distinct functional programs. TGF-β signaling promotes myofibroblastic differentiation through SMAD-dependent transcriptional networks that induce ACTA2 expression, extracellular matrix deposition, and tissue remodeling [24]. In contrast, IL-1-mediated activation of NF-κB and JAK/STAT pathways favors inflammatory CAF states characterized by secretion of IL-6, CXCL chemokines, and other immune-modulatory mediators [25]. Hypoxia further shapes CAF identity through HIF-dependent transcriptional rewiring that promotes angiogenesis, metabolic adaptation, and extracellular matrix remodeling [26]. Mechanical stress and matrix stiffness activate integrin-FAK-YAP/TAZ signaling, reinforcing fibroblast activation and mechanotransduction-dependent gene expression programs [27]. In parallel, nutrient deprivation and metabolic stress alter CAF phenotypes through AMPK-, mTOR-, and redox-sensitive pathways that support cellular adaptation under hostile microenvironmental conditions [28,29]. Together, these signaling networks function as an integrated stress-sensing system that enables CAFs to dynamically adapt to changing tumor microenvironments and transition between distinct functional states [8,13].

Consequently, CAF phenotypes should be viewed as dynamic outputs of convergent stress-responsive signaling networks rather than fixed stromal lineages.

Although common stress-responsive pathways are shared across malignancies, the dominant manifestations of stress-adaptive CAF programs vary substantially across tumor types. In pancreatic ductal adenocarcinoma (PDAC), dense desmoplasia, chronic hypoxia, and nutrient deprivation favor the emergence of matrix-remodeling and metabolically adaptive CAF populations that contribute to immune exclusion and therapeutic resistance [30]. In breast cancer, inflammatory CAF programs characterized by cytokine and chemokine secretion frequently support tumor progression and metastatic dissemination [31,32]. Colorectal cancers often exhibit CAF states linked to inflammatory signaling and extracellular matrix remodeling [33], whereas lung cancers demonstrate pronounced therapy-adaptive CAF responses following chemotherapy, radiotherapy, and targeted therapy exposure [34]. In glioblastoma, CAF-like stromal populations are shaped by profound hypoxia and vascular dysfunction, promoting angiogenesis and immune suppression [35,36]. These observations suggest that stress adaptation represents a conserved organizing principle of CAF biology, while the relative contribution of hypoxic, inflammatory, metabolic, and therapy-induced programs remains highly context dependent.

Collectively, these observations further support the concept that CAF phenotypes represent context-dependent manifestations of stress-adaptive stromal plasticity rather than fixed stromal subtypes.

Importantly, these categories should not be interpreted as exclusive or permanently fixed. CAF programs can interconvert in response to changing gradients of hypoxia, cytokine exposure, metabolic stress, and matrix stiffness. Similarly, marker-defined populations such as $GPR77^+$, $LRRC15^+$, $PDPN^+$ CAFs likely represent context-specific refinements of broader adaptive programs rather than entirely independent biological populations [34,37,38]. Thus, CAF classification is most useful when viewed as a reflection of dominant signaling inputs and adaptive functional states rather than intrinsic stromal identity. Representative CAF programs and associated markers are summarized in Table 1.

2.2. CAF function is context-dependent rather than subtype-intrinsic

A key implication of the stress-adaptation model is that CAF function cannot be inferred solely from subtype designation. Instead, biological outputs emerge from the interaction between CAF state, tumor context, and prevailing microenvironmental pressures.

This context dependence helps explain why CAFs can exert seemingly contradictory effects across tumor settings. In PDAC, depletion of $\alpha\text{-SMA}^+$ CAFs or pharmacologic inhibition of Hedgehog signaling

Table 1
Representative CAF programs, marker genes, and functional features.

CAF program	Representative markers	Dominant functional features Functions	Key references
myCAFs	ACTA2, TAGLN, MYL9, COL1A1, POSTN	ECM deposition and remodeling, stromal stiffening, desmoplasia, immune exclusion, regulation of tumor invasion and therapeutic response	[16–18, 39]
iCAFs	IL6, CXCL1, CXCL2, CXCL 8, CCL2, PDGFRA	Cytokine/chemokine secretion, immune cell recruitment, immunosuppressive signaling, immunosuppressive niche formation	[14,19,21]
apCAFs	HLA-DRA, HLA-DPA1, CD74	Antigen presentation, $CD4^+$ T-cell interaction, tolerance-promoting immune modulation	[22,40]
vCAFs	VEGFA, MCAM, NOTCH3, EPAS1	Angiogenesis, vascular remodeling, stromal adaptation to hypoxia	[41,42]
dCAFs	SCRG1, SOX9	Developmental programs; Stemness support	[41]
cCAFs	MKI67, TUBA1B	High proliferative activity; Tumor growth support	[41,42]

paradoxically accelerates tumor progression and shortens survival, indicating that subsets of ECM-producing CAFs may exert tumor-restraining functions under specific conditions [39,43]. Similarly, stromal fibroblast-derived SLIT2 suppresses tumor growth and metastatic dissemination in breast cancer models, further illustrating that stromal fibroblasts are not uniformly tumor promoting [44,45].

Even identical signaling pathways may generate opposing biological outcomes depending on CAF state. In colorectal cancer (CRC), activation of NF-κB signaling in $COLVI^+$ CAFs promotes inflammation and tumor progression through IL-6 secretion, whereas disruption of related signaling programs in alternative fibroblast populations enhances stemness-supportive tumor niches [33,46]. These observations indicate that pathway activity is interpreted through a state-dependent transcriptional and epigenetic contexts rather than functioning in a universally predictable manner.

In addition to inflammatory signaling, CAFs also regulate tumor behavior through metabolic, hormonal, and biomechanical mechanisms. CAF-mediated ECM remodeling can generate migration tracks that facilitate collective invasion, while metabolic crosstalk and paracrine signaling further influence stemness, therapeutic response, and tumor plasticity [47–49]. Collectively, these findings support a model in which CAFs function as context-dependent stromal effectors whose biological impact is determined by adaptive state rather than static subtype identity.

2.3. *CAF plasticity evolves across tumor progression*

CAF plasticity is not only spatially heterogeneous but also temporally dynamic across tumor evolution. Rather than representing a linear maturation process, CAF transitions reflect stage-specific adaptations to progressively changing stress landscapes (Fig. 1).

During early tumorigenesis, inflammatory and progenitor-like

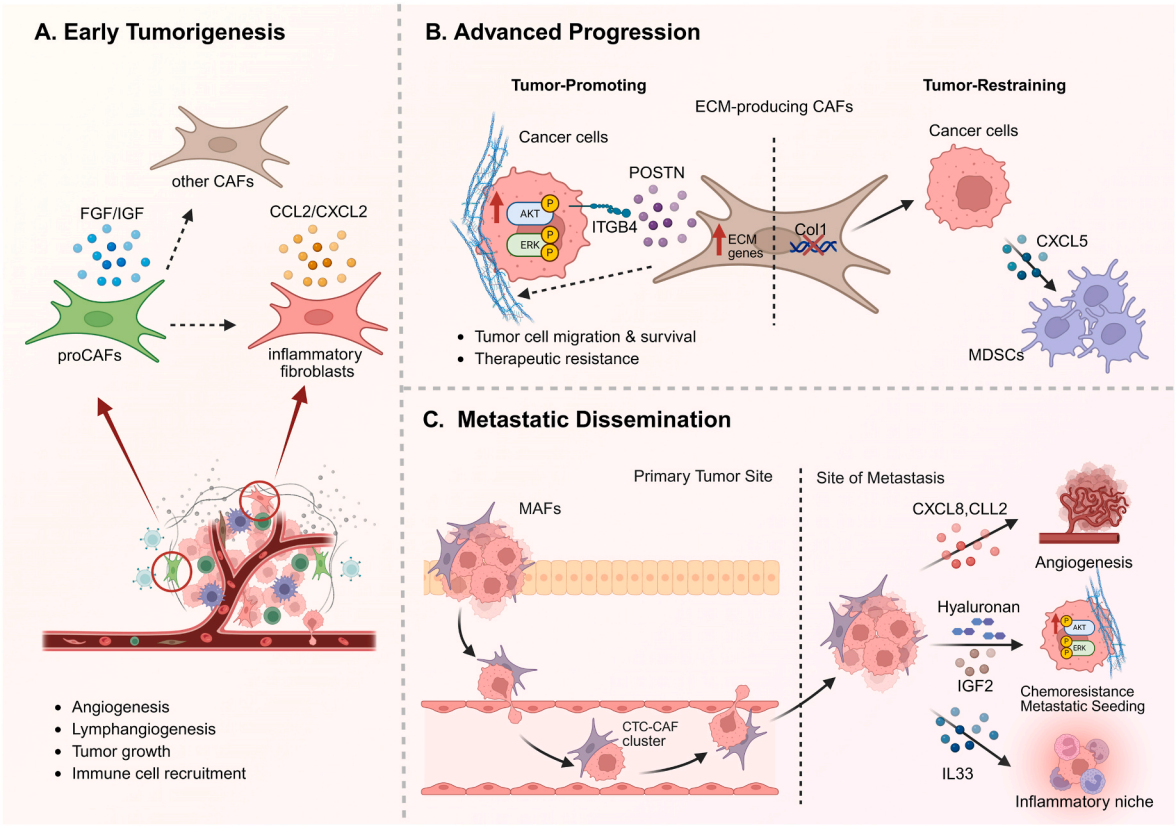

Fig. 1. Stage-specific evolution of stress-adaptive CAF programs during tumor progression. **A.** During early tumorigenesis, inflammatory and progenitor-like fibroblast programs predominate in response to tissue injury, oncogenic signaling, and immune activation, promoting stromal expansion, immune cell recruitment, and early vascular remodeling. **B.** During advanced tumor progression, sustained hypoxia, TGF-β signaling, and mechanical stress drive ECM-producing and contractile CAF programs associated with desmoplasia, stromal stiffening, immune exclusion, impaired drug delivery, and therapy resistance, while also exerting context-dependent tumor-restraining effects. **C.** At metastatic sites, MAFs, including CAFs associated with circulating tumor cell clusters, remodel stromal, vascular, and immune niches through ECM remodeling, growth factor signaling, angiogenic programs, and inflammatory reprogramming to support metastatic colonization and therapeutic resistance.

fibroblast programs predominate, driven by tissue injury, oncogenic signaling, and immune activation [21,50–53]. These early adaptive states promote stromal expansion, inflammatory signaling, vascular remodeling, and establishment of tumor-supportive niches (Fig. 1A).

As tumors progress, sustained hypoxia, TGF-β signaling, and mechanical stress drive CAFs toward ECM-producing and contractile phenotypes that reinforce desmoplasia, restrict immune infiltration, impair therapeutic delivery, and support invasive growth (Fig. 1B) [16,25,54]. However, these same stromal programs may also preserve structural constraints that partially restrain tumor expansion, highlighting the biological complexity of indiscriminate stromal targeting [43,55,56].

At metastatic sites, fibroblasts undergo further adaptation into metastasis-associated CAFs (MAFs), which remodel organ-specific stromal, vascular, and immune niches to support metastatic colonization (Fig. 1C) [57–64]. Emerging evidence also suggests that CAFs may physically accompany circulating tumor cells, enhancing resistance to mechanical stress and facilitating metastatic seeding, although mechanistic understanding of these interactions remains incomplete [63–65].

Taken together, CAF evolution across tumor progression is best understood as a dynamic process of stress adaptation rather than simple subtype succession. Recognizing these temporally evolving stromal programs is essential for designing "context-aware" therapeutic strategies that selectively target tumor-promoting CAF functions while preserving protective stromal constraints.

3. Stress-driven CAF reprogramming and altered tumor-stroma crosstalk

Rapid tumor expansion, aberrant vasculature, excessive ECM deposition, and therapeutic intervention collectively generate a hostile TME characterized by hypoxia, oxidative stress, nutrient deprivation, metabolic pressure, and therapy-associated injury [66–70]. These stresses not only challenge tumor-cell survival but also profoundly reprogram CAFs, altering their transcriptional states, metabolic behaviors, and intercellular communication. As central stromal integrators of environmental stresses, CAFs dynamically reshape tumor interactions with immune populations, vasculature, and the ECM, thereby promoting invasion, metastatic progression, and therapeutic resistance. An overview of how diverse microenvironmental stressors reprogram CAFs and reshape tumor-stroma crosstalk is illustrated in Fig. 2.

3.1. Nutrient deprivation and metabolic stress

Nutrient deprivation and metabolic stress are persistent features of solid tumors, where rapid proliferation frequently outpaces vascular nutrient delivery. Under these constraints, CAFs exhibit substantial metabolic plasticity that enables stromal survival and tumor adaptation.

A central feature of this response is metabolic coupling between CAFs and cancer cells. Under nutrient-limited conditions, CAFs engage adaptive programs such as autophagy and macropinocytosis to preserve intracellular homeostasis while sustaining stromal function [71–75]. In PDAC, inhibition of macropinocytosis alters CAF state composition, shifting myofibroblastic programs toward inflammatory phenotypes while increasing immune infiltration and therapeutic responsiveness [74], highlighting the functional plasticity of stress-adaptive metabolic programs.

Beyond self-preservation, CAFs actively buffer metabolic stress within the TME through reciprocal metabolite exchange. CAF-derived

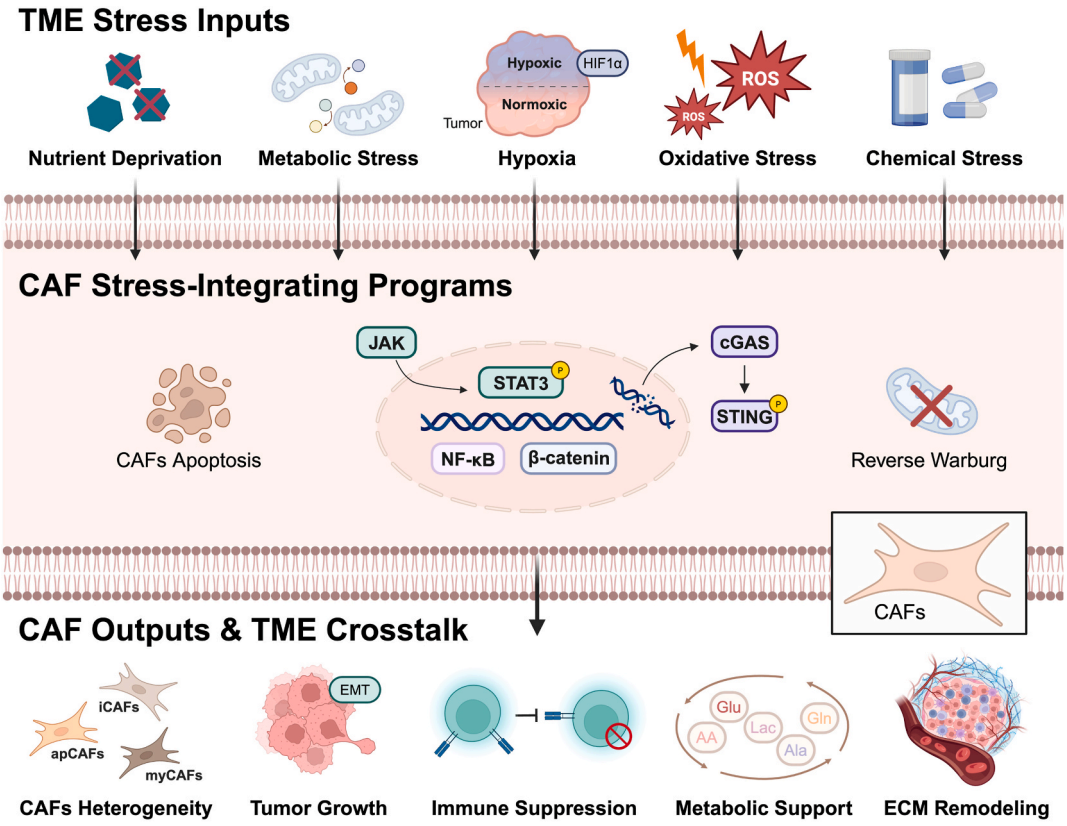

Fig. 2. Stress-driven reprogramming of CAFs and altered tumor-stroma crosstalk. Diverse microenvironmental stressors, including nutrient deprivation, metabolic stress, hypoxia, oxidative stress, and therapy-associated injury, dynamically reprogram CAFs. These stress signals are integrated through transcriptional, inflammatory, metabolic, and stress-response pathways that reshape CAF cellular states and functional programs. Stress-adapted CAFs subsequently alter tumor-stroma interactions by promoting immunosuppression, metabolic support, ECM remodeling, and tumor-supportive signaling, thereby contributing to tumor progression and therapeutic resistance. This schematic highlights CAFs as central integrators of tumor microenvironmental stress and key mediators of adaptive stromal reprogramming.

amino acids, nucleotides, and other biosynthetic intermediates support tumor-cell survival under nutrient scarcity [76]. In pancreatic cancer, stromal adaptation to tumor-derived lactate through MCT1-dependent uptake increases tricarboxylic acid (TCA) cycle activity and promotes IL-6 production, reinforcing immunosuppressive and fibrotic microenvironments through NF-κB/STAT3-associated signaling [77]. CAFs also recycle tumor-derived metabolites, including lactate and glutamate, into bioavailable substrates such as glutamine, thereby sustaining anabolic tumor metabolism [78]. Similarly, pancreatic stellate cell-derived CAFs provide alanine and other nonessential amino acids that fuel oxidative metabolism in nutrient-deprived cancer cells [28].

Lipid metabolic rewiring represents an additional adaptive dimension of CAF-mediated tumor support. Stress-adapted CAFs can enhance tumor stemness and metastatic fitness through transfer of unsaturated lipids and lipid-derived metabolites [79–81]. In hepatocellular carcinoma, $CD36^{+}$ CAFs activate lipid peroxidation-associated signaling program that promote recruitment of immunosuppressive myeloid populations and resistance to immunotherapy [82]. Under severe metabolic stress, CAF-derived lysophosphatidylcholine (LPC) can further support membrane homeostasis and tumor-cell survival during combined nutrient and oxygen deprivation [83].

Collectively, metabolic stress reprograms CAFs into dynamic nutrient-buffering and metabolically supportive stromal partners that sustain tumor growth while reinforcing immune suppression and therapeutic resistance.

Metabolic stress reprograms CAFs through nutrient-sensing pathways that coordinate cellular adaptation to energy deprivation and altered metabolite availability. AMPK activation promotes metabolic flexibility and survival under nutrient-limited conditions, whereas mTOR signaling integrates growth factor, amino acid, and energy signals to regulate biosynthetic activity and stromal function. In parallel, autophagy provides an additional adaptive mechanism that enables CAFs to recycle intracellular components and sustain tumor-supportive metabolic crosstalk during periods of metabolic stress [28,84].

3.2. Hypoxia

Hypoxia is a defining feature of solid tumors and a major driver of aggressive disease behavior, treatment resistance, and poor clinical outcomes [85,86]. CAFs are highly responsive to hypoxic stress, undergoing HIF-dependent transcriptional reprogramming that alters stromal architecture, metabolism, immune regulation, and tumor-stroma communication [87,88].

One major consequence of hypoxic CAF adaptation is ECM remodeling. Under low oxygen conditions, fibroblasts acquire activated CAF phenotypes characterized by sustained expression of fibroblast activation protein (FAP), α-SMA, and collagen-associated programs [89]. Hypoxia promotes matrix deposition, collagen cross-linking, and stromal stiffening through HIF-mediated upregulation of collagen synthesis enzymes such as P4HA and PLOD, thereby enhancing tumor invasion while restricting immune-cell infiltration and therapeutic penetration [90,91]. Matrix remodeling further impairs perfusion and oxygen diffusion, reinforcing hypoxic stress in a self-amplifying stromal feedback loop.

Hypoxia also drives metabolic rewiring in CAFs. Through reverse Warburg-like programs, hypoxic CAFs increase glycolysis and release metabolites including lactate, pyruvate, amino acids, and fatty acids that support tumor-cell growth and metabolic adaptation [28,80,92]. In pancreatic cancer, CAF-derived lactate contributes to specialized metabolic niches that facilitate aggressive behaviors such as perineural invasion [93]. Emerging evidence also suggests that stromal HIF-2α contributes to lineage-specific CAF reprogramming, promoting angiogenic and metabolic adaptation in metastatic settings [94].

Beyond stromal remodeling and metabolic support, hypoxic CAFs actively shape immune suppression. HIF-dependent signaling enhances secretion of VEGF, CXCL12, IL-6, and TGF-β, limiting $CD8^{+}$ T-cell infiltration while promoting recruitment of immunosuppressive myeloid populations [95–98]. Hypoxia also alters extracellular vesicle-mediated communication; for example, HIF-1α/miR-21 signaling promotes release of CAF-derived vesicles that enhance cancer stemness and chemoresistance in pancreatic cancer [99]. Together, these observations position hypoxic CAFs as central mediators linking oxygen deprivation to stromal remodeling, immune escape, and therapeutic resistance.

Mechanistically, hypoxia-driven CAF reprogramming is primarily mediated through stabilization of hypoxia-inducible factors (HIF-1α and HIF-2α), which activate transcriptional programs governing angiogenesis, extracellular matrix remodeling, glycolytic metabolism, and immune regulation. HIF signaling induces expression of VEGF, CXCL12, LOX family members, and matrix-remodeling enzymes, thereby promoting vascular dysfunction, stromal stiffening, and immune exclusion [100]. In addition, HIF-dependent metabolic rewiring enhances glycolysis and lactate production, reinforcing adaptive interactions between CAFs and tumor cells under oxygen-limited conditions [101,102].

3.3. Oxidative stress

Oxidative stress is another pervasive hallmark of the TME, arising from tumor metabolism, inflammatory infiltrates, stromal signaling, and therapeutic intervention. ROS function not only as metabolic byproducts but also as signaling mediators that drive CAF activation, metabolic rewiring, and immune modulation.

ROS promote CAF differentiation through multiple convergent pathways. Oxidative stress enhances TGF-β activation, matrix metalloproteinase activity, and redox-sensitive signaling that facilitate fibroblast-to-CAF conversion [103–106]. Among these pathways, Nox4-dependent signaling has emerged as a major regulator of stromal redox adaptation, sustaining CAF activation, survival, and tumor-promoting functions [103,106,107]. CAF simultaneously activate antioxidant buffering programs, including glutathione synthesis and cystine transport, enabling survival under sustained oxidative stress while preserving matrix-remodeling activity [108].

ROS-driven CAF reprogramming also reinforces stromal remodeling and immune exclusion. Oxidative stress increases secretion of matrix-remodeling enzymes, growth factors, and inflammatory mediators that support tumor invasion, angiogenesis, and metastatic progression [109–112]. In immunotherapy-responsive models, suppression of stromal ROS signaling reduces CAF abundance, alleviates stromal barriers, restores $CD8^{+}$ T-cell infiltration, and improves checkpoint blockade efficacy [113,114]. These findings suggest that redox adaptation directly contributes to immune-resistant stromal niches.

Persistent oxidative stress additionally drives senescence-associated CAF phenotypes. Sustained ROS accumulation activates DNA damage responses and engages NF-κB and mTOR-associated signaling, enforcing senescence-associated secretory phenotype (SASP) despite cell-cycle arrest [115]. These senescent CAFs remain metabolically active and secrete cytokines, chemokines, matrix-remodeling enzymes, and immunoregulatory mediators that promote EMT, stemness, angiogenesis, and immune suppression [116–122]. CAF associated Fas ligand (FasL) signaling can further induce apoptosis in T cells and NK cells, reinforcing immune escape [123].

Thus, oxidative stress converts CAFs into durable stromal amplifiers of tumor progression, coupling redox adaptation to stromal remodeling, senescence, and immunosuppressive microenvironmental evolution.

At the molecular level, oxidative stress drives CAF reprogramming through activation of multiple redox-sensitive signaling pathways. ROS activate NF-κB, p38/MAPK, and TGF-β signaling, leading to enhanced inflammatory cytokine production, extracellular matrix remodeling, and fibroblast activation. In addition, NRF2 functions as a central regulator of oxidative stress adaptation by inducing antioxidant and cytoprotective programs, including HO-1, NQO1, glutathione metabolism enzymes, and other redox-buffering molecules, thereby maintaining redox homeostasis and supporting CAF survival under chronic

oxidative stress conditions [124,125]. The balance between ROS-driven activation and NRF2-mediated stress buffering is increasingly recognized as an important determinant of CAF phenotype and function [126].

3.4. Therapy-associated stress

Anticancer therapies impose an additional layer of stress on an already adaptive stromal ecosystem. Chemotherapy, radiotherapy, and targeted therapies not only damage tumor cells but also reprogram CAF composition, secretory activity, and functional states, with major consequences for therapeutic response [115,127].

A recurring consequence of therapy-associated stress is activation of paracrine resistance programs. DNA damage responses in stromal fibroblasts can trigger secretion of survival-promoting mediators that protect neighboring tumor cells from cytotoxic injury. For example, therapy-induced NF-κB activation promotes WNT16B secretion, enhancing tumor-cell survival and weakening chemotherapy efficacy [128]. In neuroendocrine prostate cancer (NEPC), cisplatin-induced cGAS-STING activation in CAFs drives senescence and CCL5 secretion, which promotes CCR5-dependent tumor survival and DNA repair [129]. Similarly, cisplatin-treated CAFs in lung adenocarcinoma upregulate IL-11, activating STAT3-mediated anti-apoptotic signaling in cancer cells [130]. These observations illustrate how therapy-adapted CAFs actively transmit stress-resistance signals rather than serving as passive bystanders.

Therapeutic stress can also reshape CAF population states. In PDAC, cytotoxic treatment has been associated with expansion of iCAF programs characterized by stress-adaptive transcriptional signatures [131]. Neoadjuvant therapy (NAT) can additionally generate distinct immunomodulatory CAF states with complement-associated features, suggesting that therapy-induced stromal remodeling may occasionally support immune activation rather than universal immune suppression [132]. These findings reinforce the context-dependent plasticity of CAF responses to therapeutic injury.

A central mechanism underlying therapy-driven stromal adaptation is therapy-induced senescence (TIS) accompanied by persistent SASP. Although senescence can initially suppress cellular proliferation, persistence of senescent CAFs often promotes tumor adaptation, immune evasion, and treatment resistance. SASP-associated CAFs secrete IL-6, IL-8, CCL5, and other mediators that reinforce tumor stemness, inflammatory signaling, and immunosuppressive niche formation [16,133]. In non-small cell lung cancer (NSCLC), radiotherapy-induced senescence-like CAFs promote tumor growth and radioresistance through JAK/STAT signaling, whereas senolytic clearance restores treatment sensitivity [134].

Collectively, therapy-associated stress converts CAFs into dynamic mediators of adaptive resistance, highlighting senescent and stress-rewired stromal programs as actionable therapeutic targets.

At the mechanistic level, therapy-induced CAF reprogramming is mediated in part through activation of DNA damage response (DDR) pathways, including ATM, ATR, and p53 signaling, which coordinate cellular adaptation to chemotherapy- and radiotherapy-induced stress [135]. Persistent activation of these pathways can promote senescence-associated phenotypes characterized by acquisition of a SASP, resulting in sustained production of inflammatory cytokines, growth factors, and matrix-remodeling mediators. These adaptive responses contribute to stromal-mediated therapeutic resistance and tumor recurrence following treatment [16,128].

3.5. Integrated stress network governing CAF reprogramming

Although hypoxia, oxidative stress, metabolic stress, and therapy-associated injury are often discussed as distinct drivers of CAF reprogramming, growing evidence indicates that these stressors function as an integrated network rather than isolated inputs [136–138]. Within this framework, CAFs are not merely responders to environmental stress but active amplifiers that sustain and redistribute stress signals throughout the tumor microenvironment. To conceptualize how these interconnected stress pathways converge to sustain CAF activation and tumor-promoting stromal adaptation, the integrated stress circuitry is summarized in Fig. 3.

At the center of this network lies a self-reinforcing ROS-hypoxia-ECM feedback circuit (Fig. 3). Hypoxia stabilizes HIF-1α, promoting glycolytic rewiring, lactate accumulation, and mitochondrial dysfunction that increase intracellular and extracellular ROS levels [139,140]. In turn, ROS further reinforce HIF signaling while activating redox-sensitive pathways including NF-κB, p38/MAPK, and TGF-β, thereby sustaining CAF activation and inflammatory outputs. Simultaneously, hypoxia and ROS drive excessive ECM deposition and remodeling through induction of collagen synthesis enzymes (e.g., P4HA, PLOD) and matrix-modifying proteases (e.g., MMPs) [90,141]. Progressive matrix stiffening and vascular compression then impair perfusion and oxygen delivery, further aggravating hypoxia and oxidative stress.

Metabolic stress is tightly integrated into this circuitry. Nutrient deprivation, altered metabolite fluxes (e.g., lactate, glutamine, lipids), and redox imbalance reinforce ROS production and hypoxic adaptation, while CAF-derived metabolites support tumor cell survival under hostile conditions [76]. Adaptive programs such as autophagy and antioxidant buffering enable CAFs to withstand these stresses while preserving tumor-supportive functions [108]. Thus, metabolic adaptation not only sustain CAF viability but also reinforce immunosuppressive and pro-invasive stromal states.

Therapy-associated stress further amplifies this network. Chemotherapy and radiotherapy induce ROS accumulation, DNA damage responses, and senescence-associated signaling that intensify inflammatory secretion, matrix remodeling, and immune evasion [115,133]. In some contexts, therapeutic injury may transiently generate immunostimulatory stromal states, but persistent therapy-adapted CAF programs more commonly reinforce adaptive resistance [132].

Taken together, these observations support a unified model in which CAFs function as central hubs of stress integration and propagation. The dynamic coupling of hypoxia, oxidative stress, metabolic adaptation, ECM remodeling, and therapy-associated injury creates a self-sustaining stress network that drives tumor progression, immune escape, and therapeutic resistance. Consequently, targeting individual stress pathways in isolation may yield limited benefit, whereas disrupting key regulatory nodes or feedback circuits may offer more effective strategies for stromal reprogramming and durable therapeutic control.

4. Therapeutic targeting of stress-adapted CAF programs in cancer

As central regulators of the TME, CAFs orchestrate stromal remodeling, immune suppression, and adaptive resistance across solid tumors. Importantly, many tumor-promoting CAF functions are not fixed intrinsic properties, but dynamic phenotypes induced or reinforced by hypoxia, metabolic stresses, oxidative injury, and therapy-associated damage. This stress-adaptive plasticity helps explain the inconsistent outcomes of indiscriminate stromal depletion strategies and argues for more selective, context-aware therapeutic intervention. Rather than broadly eliminating fibroblasts, emerging strategies increasingly aim to intercept stress-rewired CAF programs that sustain immune exclusion, matrix remodeling, metabolic support, and residual disease persistence. Major therapeutic approaches targeting these adaptive stromal vulnerabilities are summarized in Fig. 4.

4.1. Inhibiting stress-induced CAF activation pathways

Stress-induced CAF activation is sustained by interconnected inflammatory and profibrotic signaling pathways, making these programs attractive therapeutic targets (Fig. 4A–Table 2); Among these, TGF-β

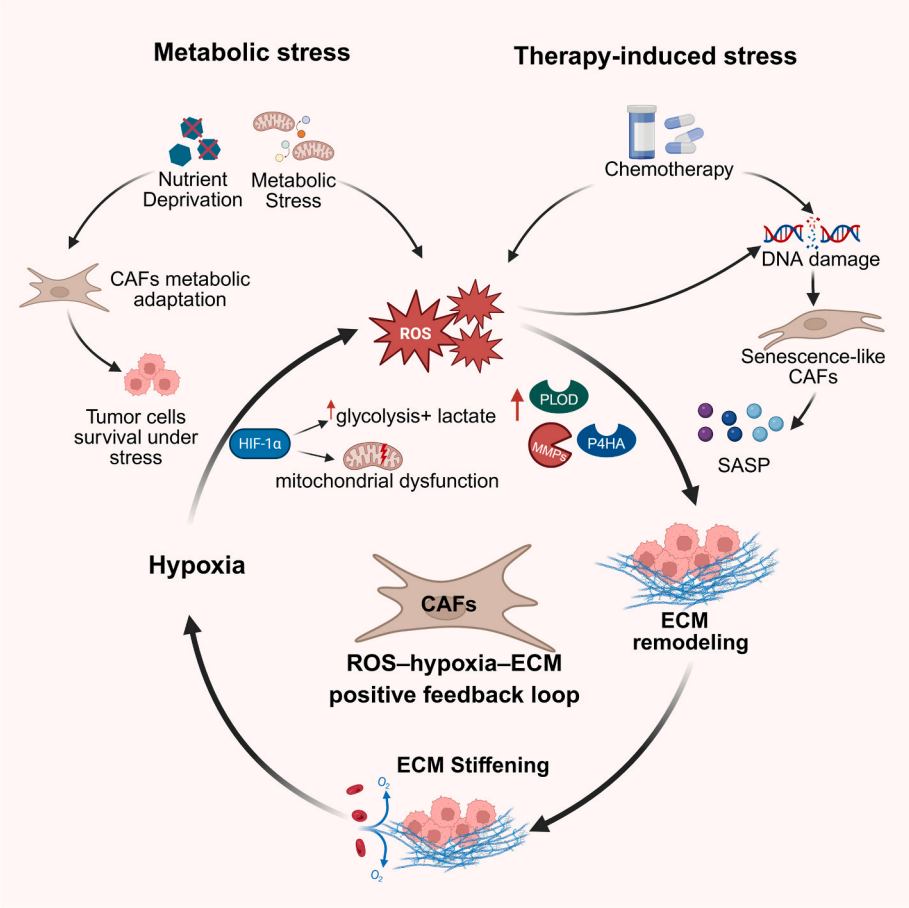

Fig. 3. Integrated-stress network governing CAF reprogramming. Hypoxia, oxidative stress, metabolic pressure, and therapy-associated injury converge to form an interconnected stress network that drives CAF reprogramming. At the core of this circuitry, a ROS-hypoxia-ECM positive feedback loop links HIF-1α-mediated metabolic adaptation, ROS accumulation, matrix remodeling, and vascular dysfunction. Metabolic stress and therapeutic injury further amplify this network through autophagy, redox buffering, DNA damage responses, and SASP. As central stress integrators, CAFs propagate these signals to sustain immunosuppression, tumor progression, and therapeutic resistance.

remains the most clinically advanced stromal-targeting axis, given its central role in myofibroblastic activation, ECM deposition, and desmoplastic remodeling.

However, the translational record of TGF-β inhibition highlights the complexity of CAF targeting. Agents such as galunisertib and bifunctional PD-L1/TGF-β traps have demonstrated activity in selected settings, yet broader efficacy remains limited by pathway pleiotropy, compensatory signaling, and context-dependent tumor-suppressive roles of TGF-β [145,146]. These limitations illustrate a recurring challenge in stromal intervention: pathways that drive tumor-promoting CAF programs may also participate in tissue homeostasis or tumor restraint.

Hedgehog signaling represents another important regulator of CAF biology and stromal homeostasis. Early preclinical studies suggested that Hedgehog inhibition could reduce desmoplasia, improve vascular perfusion, and enhance drug delivery, particularly in pancreatic cancer [144]. However, subsequent investigations revealed a more complex and context-dependent role for Hedgehog signaling within the tumor microenvironment. In several models, stromal Hedgehog inhibition unexpectedly accelerated tumor progression, increased vascular density, and promoted the emergence of more aggressive tumor phenotypes, suggesting that certain stromal compartments may exert tumor-restraining functions [147,148]. These findings highlight the dualistic nature of CAF-targeted therapies and underscore the importance of selective stromal reprogramming rather than indiscriminate pathway suppression. Consequently, therapeutic modulation of Hedgehog signaling should be approached cautiously and may require biomarker-guided patient selection and combination strategies to maximize benefit while minimizing unintended stromal disruption.

Inflammatory CAF activation pathway present additional opportunities but have similarly produced mixed results. JAK/STAT signaling contributes to inflammatory CAF maintenance, while IL-1 acts as an upstream regulator of cytokine-rich iCAF programs [25,142,149,150]. Although preclinical models support the rationale for disrupting these pathways, clinical outcomes remain inconsistent, likely reflecting CAF heterogeneity, cytokine redundancy, and inadequate biomarker-guided patient selection.

Collectively, these findings suggest that suppressing stress-induced CAF activation is mechanistically rational but unlikely to succeed through single-pathway inhibition alone. More effective strategies will likely require biomarker-guided patient stratification, rational combination therapy, and targeting of dominant upstream regulatory nodes rather than isolated downstream effectors.

4.2. *Disrupting stress-induced CAF secretome signaling*

Stress-adapted CAFs reshape the TME not only through structural remodeling but also through secretion of cytokines, chemokines, and angiogenic mediators that reinforce immune suppression, vascular dysfunction, and therapeutic resistance (Fig. 4B–Table 2). Compared with direct stromal depletion, targeting soluble CAF-derived signaling networks offers a potentially more selective and clinically tractable

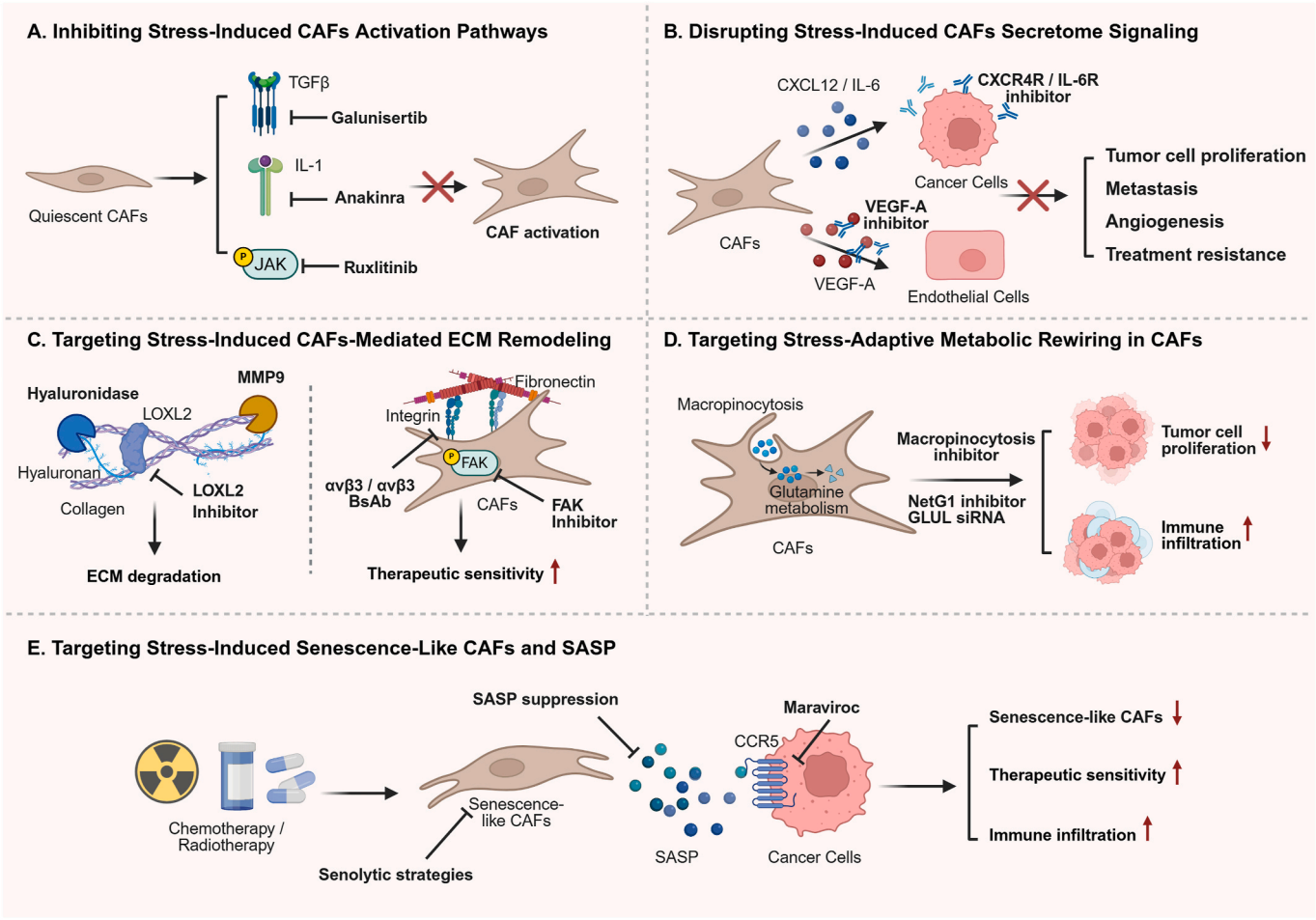

Fig. 4. Therapeutic strategies targeting stress-adapted CAF programs. Schematic overview of emerging therapeutic approaches designed to intercept CAF programs induced or reinforced by microenvironmental and therapy-associated stresses. **A.** Inhibition of stress-induced CAF activation through targeting inflammatory and profibrotic signaling pathways, including TGF-β, IL-1, and JAK/STAT signaling. **B.** Disruption of CAF-derived secretome signaling, including cytokine, chemokine, and angiogenic mediators that promote tumor progression and immune suppression. **C.** Modulation of CAF-mediated ECM remodeling and mechanotransduction to alleviate fibrosis, immune exclusion, and impaired drug delivery. **D.** Targeting stress-adaptive metabolic programs, including nutrient scavenging and glutamine-dependent metabolic crosstalk. **E.** Elimination or functional suppression of senescence-like CAFs and SASP to overcome therapy-associated stromal resistance.

strategy.

Among these pathways, the CXCL12-CXCR4 axis represents one of the most compelling approaches for overcoming CAF-mediated immune exclusion. FAP^{+} CAFs are a major source of CXCL12, which restricts immune-cell trafficking and promotes immunosuppressive niche formation [30,151]. Early clinical studies suggest that CXCR4 blockade may enhance immune infiltration and improve responses when combined with immunotherapy (e.g., pembrolizumab), although monotherapy activity remains limited [152]. These findings reinforce the broader principle that stromal signaling pathways are often most vulnerable in rational combination settings rather than as standalone interventions.

Similarly, IL-6/STAT3 signaling represents a major inflammatory axis linking CAFs to tumor-cell survival, immune dysfunction, and therapy resistance. While IL-6 pathway blockade (e.g., tocilizumab) has demonstrated encouraging preclinical activity, clinical efficacy remains inconsistent, likely due to cytokine redundancy and compensatory inflammatory circuitry [153,154].

Anti-angiogenic strategies targeting VEGF remain the most clinically established but least CAF-specific examples of secretome-directed intervention. Although vascular normalization can transiently improve treatment delivery, adaptive stromal remodeling and alternative angiogenic programs frequently limit durability [143,155].

Beyond CXCL12 and IL-6 signaling axes, iCAFs secrete a broader repertoire of cytokines and chemokines that contribute to tumor progression and immune suppression. Among these, IL-6 represents a central mediator that promotes STAT3 activation in both tumor and immune cells, supporting tumor growth, stemness, and resistance to therapy [156,157]. Additional chemokines such as CXCL8 (IL-8) and CCL2 facilitate recruitment of immunosuppressive myeloid populations, enhance angiogenesis, and reinforce chronic inflammatory signaling within the tumor microenvironment [158,159]. These observations have stimulated the development of therapeutic strategies targeting IL-6/STAT3 signaling, CXCL8-driven inflammatory programs, and CCL2-mediated myeloid recruitment pathways. Although clinical efficacy remains variable, combinatorial strategies that simultaneously disrupt multiple inflammatory networks may provide a more effective means of overcoming CAF-mediated immunosuppression and therapeutic resistance [160].

Taken together, secretome-targeted strategies may be particularly effective when dominant immune-exclusion or inflammatory circuits are clearly defined. Their clinical success will depend less on target availability alone and more on biomarker-guided identification of stress-adapted stromal states that remain dependent on specific paracrine signaling axes.

Table 2
Therapeutic strategies targeting CAF signaling and secretome.

Key targets	Representative agents	Indication	Development stage	Efficacy summary	Limitations/challenges	References
TGF-β	Galunisertib Bintrafusp alfa (M7824, SHR-1701, PM8001)	PDAC NSCLC Colorectal Cancer Biliary tract cancer	Phase I-III clinical trials	Partial efficacy; improved responses in selected subsets; stromal modulation observed	Pathway redundancy; compensatory signaling; context-dependent CAF functions	NCT02734160 NCT04297748 NCT03436563 NCT03833661
JAK/STAT	Ruxolitinib	Ovarian Cancer Classical Hodgkin lymphoma	Phase I-II clinical trials	Limited efficacy; no statistically significant improvement in PFS or OS	Heterogeneous patient responses; limited patient stratification	NCT02713386 NCT03681561
IL-1	Anakinra	PDAC	Preclinical	Reduced inflammatory CAF signaling; improved immune balance	Cytokine redundancy; incomplete pathway suppression	[25,142]
CXCL12/ CXCR4	Plerixafor (AMD3100); Motixafortide (BL-8040)	Lymphoma PDAC	Phase I-II clinical trials	Enhanced immune infiltration; encouraging activity in combination settings	Chemokine redundancy; compensatory signaling; limited monotherapy efficacy	NCT00694590 NCT02826486
IL-6/STAT3	RO7172508 Tocilizumab	Advanced Melanoma NSCLC Urothelial Carcinoma	Phase I-II clinical trials	Inconsistent clinical efficacy; primarily evaluated in combination settings	Cytokine redundancy; lack of biomarkers; limited monotherapy efficacy	NCT04940299 NCT03539484
VEGF	Bevacizumab	Multiple cancers	FDA-approved across multiple solid tumors	Established clinical efficacy; improves outcomes mainly in combination regimens	Non-CAF-specific; transient efficacy; adaptive resistance	[143]
Hedgehog signaling	Vismodegib; Sonidegib; IPI-926 (Saridegib)	PDAC; Solid tumors	Phase I-II clinical trials	Reduced stromal density and improved drug delivery in preclinical models; limited clinical benefit observed	Context-dependent effects; potential loss of tumor-restraining stroma; limited biomarkers	[144]

4.3. Targeting stress-induced CAF-mediated ECM remodeling

Under chronic hypoxic and oxidative stress, CAFs drive excessive ECM deposition, collagen cross-linking, and biomechanical remodeling that collectively promote immune exclusion, impaired drug delivery, and invasive tumor progression. Representative therapeutic strategies targeting CAF-mediated ECM remodeling and stromal mechanotransduction are summarized in Table 3. This has made stromal matrix targeting an attractive therapeutic strategy, but clinical experience has been sobering.

The repeated failure of ECM-depletion approaches including hyaluronan degradation, LOX/LOXL2 inhibition, and MMP-targeted therapies suggests that the limitations of stromal targeting do not simply reflect inadequate drug selection, but rather an oversimplified view of stromal biology (Fig. 4C) [161,164,165]. The ECM is not a passive physical barrier; it is a dynamic structural and signaling network governed by biomechanical feedback, compensatory remodeling pathways, and context-dependent interactions between tumor-promoting and tumor-restraining stromal program.

This complexity helps explain why depletion of individual ECM components has rarely produced durable clinical benefit, despite strong preclinical rationale. Broad stromal disruption may also inadvertently eliminate protective matrix constraints or destabilize tissue architecture in ways that accelerate tumor adaptation.

Accordingly, emerging strategies increasingly focus on stromal normalization rather than indiscriminate matrix depletion. Mechanotransduction pathways such as focal adhesion kinase (FAK) represent attractive targets because they modulate CAF survival, matrix organization, immune exclusion, and stromal stiffness simultaneously [162,166,167]. Similarly, targeting upstream matrix assembly programs, including fibronectin-integrin interactions, may offer a more controlled strategy to disrupt CAF-mediated stromal architecture while avoiding the liabilities of blunt ECM degradation [163,168].

Thus, future ECM-directed therapies will likely require systems-level modulation of stromal mechanics and CAF plasticity rather than isolated depletion of matrix components.

Table 3
Therapeutic strategies targeting CAF-mediated ECM remodeling and mechanotransduction.

Key targets	Representative agents	Indication	Development stage	Efficacy summary	Limitations/challenges	References
Hyaluronan (HA)	PEGPH20	PDAC	Phase III (failed)	Improved drug delivery; benefit observed in HA-high tumors in early-phase studies; no survival benefit in phase III	Stromal targeting alone insufficient; tumor-restraining ECM functions; compensatory resistance mechanisms	[161]
LOX/LOXL2	Simtuzumab	Colorectal cancer	Phase II (failed)	No improvement in PFS, OS, or ORR	ECM pathway redundancy; lack of biomarker selection	NCT01479465
MMPs (e.g., MMP9)	Andecaliximab (GS-5745)	Gastric cancer	Phase III (failed)	Improved response rates; no survival benefit in phase III trials	Lack of survival benefit; no biomarker selection; context-dependent MMP9 biology	NCT02545504
FAK signaling	FAK inhibitors	PDAC	Phase I clinical trials	Reduces tumor fibrosis; modulates immune infiltration	Limited monotherapy efficacy; systemic toxicity; broad signaling effects	[162] NCT00787033 NCT02546531
Integrin α5β1/ αvβ3	bispecific α5β1/ αvβ3 antibody	PDAC	Preclinical	Disrupts fibronectin-collagen assembly; impairs CAF-driven matrix organization; enhances therapeutic sensitivity	Species specificity; limited in vivo validation; translational uncertainty	[163]

4.4. Targeting stress-adaptive metabolic rewiring in CAFs

Nutrient deprivation and metabolic stress drive CAFs to adopt adaptive nutrient-scavenging and metabolite-exchange programs that sustain tumor survival under hostile microenvironmental conditions. These stress-adaptive metabolic dependencies represent an emerging and mechanistically distinct therapeutic vulnerability (Fig. 4D). Representative therapeutic strategies targeting CAF-mediated nutrient scavenging and stress-adaptive metabolic vulnerabilities are summarized in Table 4.

Among these approaches, inhibition of macropinocytosis has attracted growing interest as a means of disrupting CAF-mediated nutrient buffering. In preclinical PDAC models, blockade of CAF macropinocytic nutrient scavenging reprogrammed stromal states, reduced desmoplasia, enhanced immune infiltration, and improved therapeutic responsiveness [72,169]. These findings suggest that metabolic targeting may reshape stromal biology more dynamically than conventional structural depletion strategies.

Glutamine metabolism represents another key adaptive axis. Stress-adapted CAFs can sustain tumor growth through glutamine synthesis, nutrient exchange, and immunosuppressive metabolic support. Disruption of the CAF surface protein Netrin-G1 (NetG1)-dependent glutamine support circuits or dual targeting of tumor-stromal glutamine flux has demonstrated encouraging preclinical efficacy [170,171], further supporting metabolic rewiring as a tractable stromal vulnerability.

Another important metabolic vulnerability involves monocarboxylate transporter (MCT)-mediated lactate exchange between CAFs and tumor cells. Under hypoxic and oxidative stress conditions, stress-adapted CAFs frequently upregulate MCT4 to export lactate generated through glycolytic metabolism, whereas tumor cells can utilize MCT1 to import lactate as an alternative carbon source for oxidative phosphorylation and TCA cycle fueling. This metabolic coupling supports redox homeostasis, metabolic flexibility, and tumor survival under nutrient-restricted conditions [173]. Emerging therapeutic strategies targeting MCT1/4-mediated lactate transport seek to disrupt stromal-tumor metabolic symbiosis and may enhance the efficacy of immunotherapy and conventional anticancer treatments [172,174,175]. However, the widespread physiological roles of lactate transporters and the metabolic redundancy of the tumor microenvironment remain important translational challenges.

However, enthusiasm should be tempered by important translational limitations. Most metabolic CAF-targeting strategies remain preclinical, and currently available inhibitors often lack specificity, raising concerns regarding systemic toxicity and interference with normal nutrient homeostasis [176,177]. Moreover, tumor metabolism is inherently adaptive, making compensatory nutrient-scavenging pathways a predictable resistance mechanism.

Nevertheless, compared with static ECM-depletion approaches, targeting stress-adaptive metabolic dependencies may offer a more dynamic route to stromal reprogramming. Future progress will depend on biomarker-guided identification of metabolically vulnerable CAF states and rational integration with cytotoxic or immunotherapeutic regimens.

4.5. Targeting stress-induced senescence-like CAFs and SASP

A distinct population of senescence-like CAFs emerges under therapy-associated and oxidative stress, representing one of the most therapeutically compelling stress-adapted stromal states. Rather than functioning as passive damaged fibroblasts, these cells actively reshape the TME through persistent SASP, promoting tumor plasticity, immune suppression, and adaptive resistance (Fig. 4E). Representative therapeutic approaches targeting senescence-like CAFs and SASP are summarized in Table 5.

Two major therapeutic strategies have emerged: selective elimination of senescent CAFs (senolysis) and functional suppression of SASP signaling.

Senolytic strategies are conceptually attractive because they directly remove therapy-adapted stromal populations that sustain residual disease. Preclinical studies using FOXO4-DRI, navitoclax, and engineered stromal-targeting nanoplatforms demonstrate that senescent CAF depletion can reduce fibrosis, restore treatment sensitivity, and reverse immunosuppressive stromal remodeling [178–180]. However, these approaches remain largely preclinical, and systemic senolysis raises concerns regarding toxicity, incomplete selectivity, and disruption of physiologic senescence programs.

An alternative strategy is suppression of SASP-mediated signaling without eliminating the cells themselves. Because inflammatory SASP outputs often represent the biologically dominant tumor-promoting feature of senescent CAFs, targeting downstream chemokine or cytokine circuits may provide a more controlled therapeutic approach. Disruption of the CCL5-CCR5 axis, for example, has shown promise in reversing therapy-associated stromal resistance [129].

Despite strong mechanistic rationale, major uncertainties remain. Senescence can exert both tumor-suppressive and tumor-promoting effects depending on timing, tissue context, and therapeutic setting. Consequently, indiscriminate senescence targeting may produce unintended biological consequences.

Thus, successful therapeutic exploitation of senescence-like CAFs will require precise temporal intervention, improved stromal selectivity, and integration with broader therapeutic strategies aimed at preventing therapy-driven microenvironmental adaptation.

5. Conclusion and future perspectives

CAFs have traditionally been viewed as heterogeneous stromal populations that influence tumor progression through diverse

Table 4
Therapeutic strategies targeting stress-adaptive metabolic vulnerabilities in CAFs.

Key targets	Representative agents	Indication	Development stage	Efficacy summary	Limitations/challenges	References
Macropinocytosis (Na^+/H^+ exchanger)	EIPA	PDAC	Preclinical	Reprograms myCAFs toward inflammatory states; reduces fibrosis; enhances immune infiltration	Limited clinical applicability; non-specific inhibition; dependence on tumor context	[169]
NetG1 signaling (p38/FRA1, AKT/4E-BP1 pathways)	NetG1 neutralizing antibody (mAb)	PDAC	Preclinical	Disrupts CAF-mediated glutamine support; reduces tumor growth and immunosuppression	Mechanistic complexity; unclear biomarker selection; compensatory metabolic pathways	[170]
ASCT2/GLUL axis	FH-V9302-siGLUL-NDs	Melanoma	Preclinical	Dual targeting of tumor glutamine uptake and CAF-mediated glutamine synthesis; suppresses tumor growth and metabolic support	Preclinical evidence only; murine model dependence; challenges in systemic delivery and targeting specificity	[171]
MCT1/MCT4-mediated lactate transport	AZD3965 (MCT1 inhibitor); Syrosingopine	Multiple solid tumors	Phase I/ Preclinical	Disrupts lactate-fueled stromal-tumor metabolic coupling; impairs metabolic flexibility and tumor growth	Metabolic redundancy; systemic toxicity; compensatory metabolic pathways	[172]

Table 5
Therapeutic strategies targeting senescence-like CAFs and SASP.

Key targets	Representative agents	Indication	Development stage	Efficacy summary	Limitations/challenges	References
FOXO4-p53 interaction	FOXO4-DRI	NSCLC	Preclinical	Selectively eliminates senescent CAFs; suppresses JAK/STAT3 signaling; reduces fibrosis and myofibroblast activation	Preclinical evidence only; context-dependent effects; potential activation of alternative SASP-related pathways	[178]
FAP-targeted delivery	FAP-targeted nanoplatforms (e.g., FAP-CAR-CM@PLGA-ABNPs)	Radioresistant Breast Cancer	Preclinical	Eliminates both activated and senescent CAFs; reverses immunosuppressive microenvironment; enhances antitumor immunity	Complex engineering; limited scalability; challenges in clinical translation	[179]
BCL-2 family	navitoclax	Colorectal cancer	Preclinical	Depletes senescent CAFs; reduces SASP factors (e.g., IL-6)	Off-target toxicity; senescence heterogeneity; limited selectivity	[180]
CCR5/CCL5 axis	Maraviroc	Multiple cancers	Preclinical	Inhibits SASP-mediated chemokine signaling; restores therapeutic sensitivity; disrupts tumor-stroma communication	Limited CAF-specific validation; compensatory chemokine networks	[129]

mechanisms [8,181]. However, the evidence synthesized in this review supports a conceptual shift from a static, subtype-based taxonomy toward a stress-adaptive framework, in which CAFs are better understood as dynamic regulators continuously shaped by microenvironmental and therapeutic stress. Within this model, CAF heterogeneity reflects not only lineage diversity but also context-dependent activation of stress-responsive programs that drive functional plasticity across tumor stages and anatomical niches.

This perspective helps explain the limited success of prior CAF- or ECM-targeted therapies. Rather than simply reflecting failure of individual targets, these outcomes likely arise from the inherent robustness of stress-adaptive stromal network. Redundant signaling pathways, spatial compartmentalization of CAF states [15], and compensatory reprogramming under therapeutic pressure enable tumors to preserve stromal support even when specific pathways are disrupted. Consequently, effective therapeutic strategies will require moving beyond indiscriminate stromal depletion [147] or single-pathway inhibition toward selective destabilization of tumor-promoting CAF programs while preserving or reprogramming protective stromal functions.

Future progress will depend on improved resolution of CAF dynamics across spatial and temporal scales. Single-cell and spatial multi-omics technologies are beginning to define stress-conditioned CAF niches and their interactions with tumor and immune populations in situ, while biomarker-guided precision oncology frameworks increasingly provide translational opportunities for context-aware stromal intervention [182]. Complementing these approaches, artificial intelligence (AI)-driven integrative modeling may help decode adaptive stromal circuitry [183,184], predict treatment-induced CAF transitions, and identify rational combinatorial therapeutic targets. These advances could accelerate the translation from descriptive CAF classification toward predictive modeling of stromal adaptation and therapeutic response.

Despite these opportunities, important challenges remain. It remains unclear when stress-adaptive CAF programs represent true therapeutic dependencies versus reversible, adaptive states. The temporal kinetics and reversibility of CAF reprograming under treatment are poorly understood, and clinical translation will require overcoming barriers in biomarker-guided patient stratification, drug delivery, and real-time monitoring of stromal responses [185].

An important challenge for clinical translation is the identification of robust biomarkers capable of distinguishing stress-adaptive CAF states in patient samples. Emerging evidence suggests that hypoxia-adapted CAFs may be associated with HIF-1α-regulated signatures and extracellular matrix remodeling markers [140], whereas inflammatory CAF programs are characterized by expression of cytokines and chemokines such as IL-6, CXCL12, and related inflammatory mediators [42]. Myofibroblastic CAF states are commonly linked to α-SMA (ACTA2), FAP, and extracellular matrix-associated proteins including POSTN [186], while markers such as LRRC15 and GPR77 have been associated with distinct tumor-promoting stromal phenotypes in specific tumor contexts [34,38]. Advances in spatial transcriptomics, multiplex imaging, single-cell multi-omics profiling, and circulating stromal biomarkers are beginning to enable high-resolution characterization of CAF heterogeneity in clinical specimens [42,184]. Future integration of these approaches may facilitate patient stratification, biomarker-guided therapeutic selection, and real-time monitoring of stromal reprogramming during treatment [8,187].

In summary, we propose that CAFs should be conceptualized as dynamic, stress-adaptive hubs within the tumor ecosystem, rather than static stromal subtypes. This perspective reframes therapeutic targeting from broad stromal depletion toward precision reprogramming of stress-adaptive networks. Integrating stress biology with spatial multi-omics, systems modeling, and rational therapeutic design may ultimately enable more effective strategies to disrupt tumor-promoting stromal programs while preserving tissue homeostasis.

CRediT authorship contribution statement

Yali Hu: Conceptualization, Data curation, Investigation, Software, Visualization, Writing – original draft. **Jingyao Ge:** Conceptualization, Data curation, Investigation, Software, Visualization, Writing – original draft. **Meiqi Xin:** Conceptualization, Data curation, Investigation, Software, Visualization, Writing – original draft. **Runqi Guo:** Conceptualization, Data curation, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Chengsheng Wu:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Wenxue Ma:** Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AI	Artificial intelligence
apCAFs	antigen-presenting CAFs
CAFs	Cancer-associated fibroblasts
CRC	Colorectal cancer
CTC	Circulating tumor cell
DDR	DNA damage response
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
FAK	Focal adhesion kinase
FAP	Fibroblast activation protein
FasL	Fas ligand
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
iCAFs	inflammatory CAFs
IGF	Insulin-like growth factor
LAP	Latent-associated protein
LPC	Lysophosphatidylcholine
MAFs	Metastasis-associated CAFs
MDSCs	Myeloid-derived suppressor cells
mesCAFs	mesothelial CAFs
MMPs	Matrix metalloproteinases
myCAFs	myofibroblastic CAFs
NAT	Neoadjuvant therapy
NEPC	Neuroendocrine prostate cancer
NSCLC	Non-small cell lung cancer
PDAC	Pancreatic ductal adenocarcinoma
POSTN	Periostin
PPP	Pentose phosphate pathway
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
scRNA-seq	single-cell RNA sequencing
TAM	Tumor-associated macrophage
TCA	Tricarboxylic acid
TIS	Therapy-induced senescence
TME	Tumor microenvironment
TSLP	Thymic stromal lymphopoietin
VEGF	Vascular endothelial growth factor

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