Crosstalk between cancer-associated fibroblasts and inflammation in tumor microenvironment: A novel perspective in cancer therapy (Review)

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Abstract. Inflammation is a hallmark of cancer, significantly contributing to tumor progression and therapeutic outcomes. Among the diverse cellular components of the tumor microenvironment, fibroblasts have been recognized as key regulators of inflammatory processes. Under tumor-specific conditions, cancer-associated fibroblasts (CAFs) undergo differentiation and promote tumor proliferation, metastasis and immune evasion *via* highly intricate mechanisms. This review provides a comprehensive analysis of the reciprocal interactions between CAFs and inflammation, elucidating the mechanisms by which CAFs induce pro-inflammatory signaling and how inflammatory mediators, in turn, potentiate CAF activation and function. Furthermore, innovative therapeutic strategies, including the inhibition of stromal proteins, hypoxia-inducible factor 1α and metabolic pathways associated with CAFs, as well as the application of nanoparticle-based drug delivery systems, are examined for their potential to impede CAF-mediated tumor progression. Pharmacological agents targeting CAF-associated signaling pathways or inflammatory cytokines show dual efficacy by concurrently modulating inflammatory responses and CAF activity. These approaches frequently demonstrate improved therapeutic efficacy compared to interventions solely directed at CAF surface proteins, highlighting the therapeutic potential of concurrently addressing both inflammation and CAFs to enhance cancer treatment efficacy.

Contents

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1. Introduction

Global cancer statistics from 2022 indicate that ~20 million new cancer cases were diagnosed, with an estimated 9.7 million cancer-related deaths (1). The complexity of the tumor microenvironment (TME) represents a significant obstacle to effective cancer treatment. The TME consists of diverse cellular and non-cellular components that drive tumor progression and therapeutic resistance through intricate molecular interactions (2). Among them, cancer-associated fibroblasts (CAFs) are key regulators of tumor initiation, progression, metastasis and resistance to therapy (3). In certain cancer types, CAFs may comprise up to 60% of the tumor stroma, with an elevated stromal fraction being highly associated with poor prognosis (4,5). Furthermore, inflammation is crucial in tumorigenesis by inducing epithelial mutations, supporting tumor stem cell maintenance and facilitating immune surveillance (6). Tumor cells recruit inflammatory cells *via* chemokine receptors, leading to enhanced cytokine expression and contributing to invasion, metastatic dissemination and suppression of antitumor immune responses (7).

Inflammation and CAFs are inherently interconnected through key signaling cascades, including interleukin-6 (IL-6), transforming growth factor-β (TGF-β) and nuclear factor κβ (NF-κB), which collectively establish a self-sustaining feedback loop that promotes tumor progression and immune evasion. Although these pathways are universally present across various cancers, their activation patterns show cancer-specific distinctions. For instance, in pancreatic and breast carcinomas, IL-1β and IL-6 promote the activation of inflammatory CAFs (iCAFs) (8,9), whereas in lung and colorectal cancers, TGF-β-driven CAFs differentiation enhances immunosuppressive signaling and regulates extracellular matrix (ECM) remodeling (10-12). Considering this complexity, only targeting inflammation may be insufficient to effectively disrupt the CAF-driven pro-tumorigenic microenvironment. Therefore, integrating CAF-targeted therapies with anti-inflammatory interventions is proposed as a more comprehensive strategy for modulating the TME.

Traditional anti-inflammatory drugs, such as aspirin and celecoxib, have been shown to reduce cancer incidence and mortality (13,14). Furthermore, therapeutic strategies aimed at inhibiting IL-6, TGF-β and NF-κB are increasingly being explored for their potential to enhance patient survival in various clinical trials (15-18). However, only targeting inflammatory pathways fails to completely neutralize the tumor-promoting functions of CAFs. For instance, cyclooxygenase-2 (COX-2) inhibitors lower IL-6 and prostaglandin E2 levels (19), yet CAF activity persists through alternative mechanisms, including TGF-β signaling and ECM remodeling. Similarly, IL-6 inhibition suppresses inflammation but does not effectively prevent CAF-mediated immune suppression and fibrosis (20).

Currently, two main immunotherapeutic strategies targeting CAFs are being explored: i) Direct elimination of CAFs by targeting surface markers, e.g., fibroblast activation protein (FAP), and ii) suppression of CAF activation and function *via* the modulation of key signaling molecules, e.g., TGF-β. Although CAF-depleting therapies have demonstrated some efficacy in preclinical animal models, their success in clinical trials remains limited (21), with their development progressing slower than therapies targeting CAF-associated signaling pathways. Some emerging therapies targeting CAF-associated signaling pathways (e.g., TGF-β inhibitors) or inflammatory cytokines (e.g., IL-6 blockade) have demonstrated the ability to regulate both CAF activity and the inflammatory response (9,10). Combining TGF-β inhibitors with gemcitabine and anti-PD-L1 antibodies has proven to yield better anti-tumor efficacy (22-24). Furthermore, tocilizumab, an inhibitor of the IL-6/JAK/STAT3 signaling pathway, has demonstrated the potential to enhance immune responses and improve tumor control (25). These findings indicate that disrupting the crosstalk between CAFs and inflammation may improve therapeutic efficacy by impairing stromal remodeling and alleviating immune suppression.

A deeper understanding of the molecular mechanisms underlying this interaction is essential to optimize such combination strategies. A comprehensive examination of the functions of key signaling pathways-such as IL-6/STAT3, TGF-β and NF-κB-in regulating the inflammatory and stromal components of the TME is crucial for the identification of novel therapeutic targets and the development of rational and effective combinatorial treatment strategies. The following sections examined the intricate bidirectional crosstalk between CAFs and inflammation, emphasizing the signaling mechanisms contributing to tumor progression and therapeutic resistance.

2. Pro-inflammatory role of CAFs in tumors

Tumorigenesis is intrinsically associated with inflammation, and tumor progression closely parallels the advancement of inflammatory processes. Metabolic changes within the TME, cellular death and microbial existence and their secreted products collectively contribute to the establishment of inflammation (26). Furthermore, conventional cancer therapies such as chemotherapy and radiation have been shown to induce IL-6 expression within tumors, thus promoting chronic inflammation (27). Therefore, CAFs remain a persistent and active component in shaping the inflammatory TME (Fig. 1).

Orchestrating inflammatory cell recruitment. These CAFs play a pivotal role in the recruitment and polarization of inflammatory cells (Fig. 1A). Chemokines secreted by both tumor cells and CAFs facilitate the infiltration of tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs) and lymphocytes into the TME, thus intensifying the inflammatory response (28,29). CAFs contribute to macrophage recruitment by secreting pro-inflammatory cytokines such as IL-1β and IL-6, along with C-X-C motif chemokine ligand (CXCL)1 and -2, exerting these effects even in the absence of tumor cells (30). Furthermore, CAFs produce extra domain A fibronectin variants that bind to macrophage Toll-like receptor 4, consequently inducing M2 macrophage polarization (31). In hepatocellular carcinoma (HCC), cardiotrophin-like cytokine factor 1 secreted by CAFs enhances the production of chemokine ligands CXCL6 and TGF-β in tumor cells, thus promoting tumor cell stemness through an autocrine mechanism while facilitating TAN infiltration and polarization *via* paracrine signaling (32). In lung cancer, CAFs secrete CCL2 and CXCL12, which mediate the recruitment of monocytes and promote their differentiation into myeloid-derived suppressor cells (MDSCs), thus suppressing CD8+ T-cell proliferation and interferon-γ (IFNγ) production (33). In addition, hyaluronic acid (HA)-producing CAFs interact with MDSCs and epithelial tumor cells, leading to HA degradation and the accumulation of pro-inflammatory HA fragments, further exacerbating cancer-associated inflammation. The HA-rich stromal environment promotes the differentiation of tumor-infiltrating hyaluronan 2+ MDSCs into programmed death ligand 1 (PD-L1)+ TAMs, thus establishing an immunosuppressive and tumor-favorable TME (34).

Secretors of inflammatory factors in tumoral inflammation. CAFs play a crucial role in the secretion of inflammatory mediators (Fig. 1B). In response to various stimuli, CAFs directly produce pro-inflammatory cytokines, IL-6, IL-1β, IL-11, leukemia inhibitory factor (LIF) and TGF-β, contributing to tumor-associated inflammation. They can also recognize damage-associated molecular patterns and activate the NOD-, LRR- and pyrin domain-containing protein 3 inflammasome pathway, leading to the induction of pro-inflammatory signaling and the secretion of IL-1β (35). IL-1 binds to its receptor to activate the NF-κB signaling pathway, exerting crucial functions in regulating innate immunity and inflammation (36). A study identified fibroblasts that sustain the activation of STAT3 through the urokinase-type plasminogen activator receptor (uPAR)-dependent focal adhesion kinase (FAK)-Src-JAK2 signaling cascade. Further, uPAR-dependent FAK-Src-JAK2 signaling within tumor-associated fibroblasts regulated the inflammatory component of the TME in a liver cancer model (37). CAFs-secreted IL-1, IL-6 and IL-22 can activate STAT3 signaling and promote the development of inflammation in tumors (38-40). In particular, IL-6 acts as a stromal messenger, triggering JAK/STAT3 and TGFβ signaling in malignant cells to enhance invasion and induce epithelial-to-mesenchymal transition (EMT) (38,41). Tumor and immune cells within the TME can also activate CAFs through paracrine signaling, inducing the production of cytokines and chemokines. Even normal dermal fibroblasts can

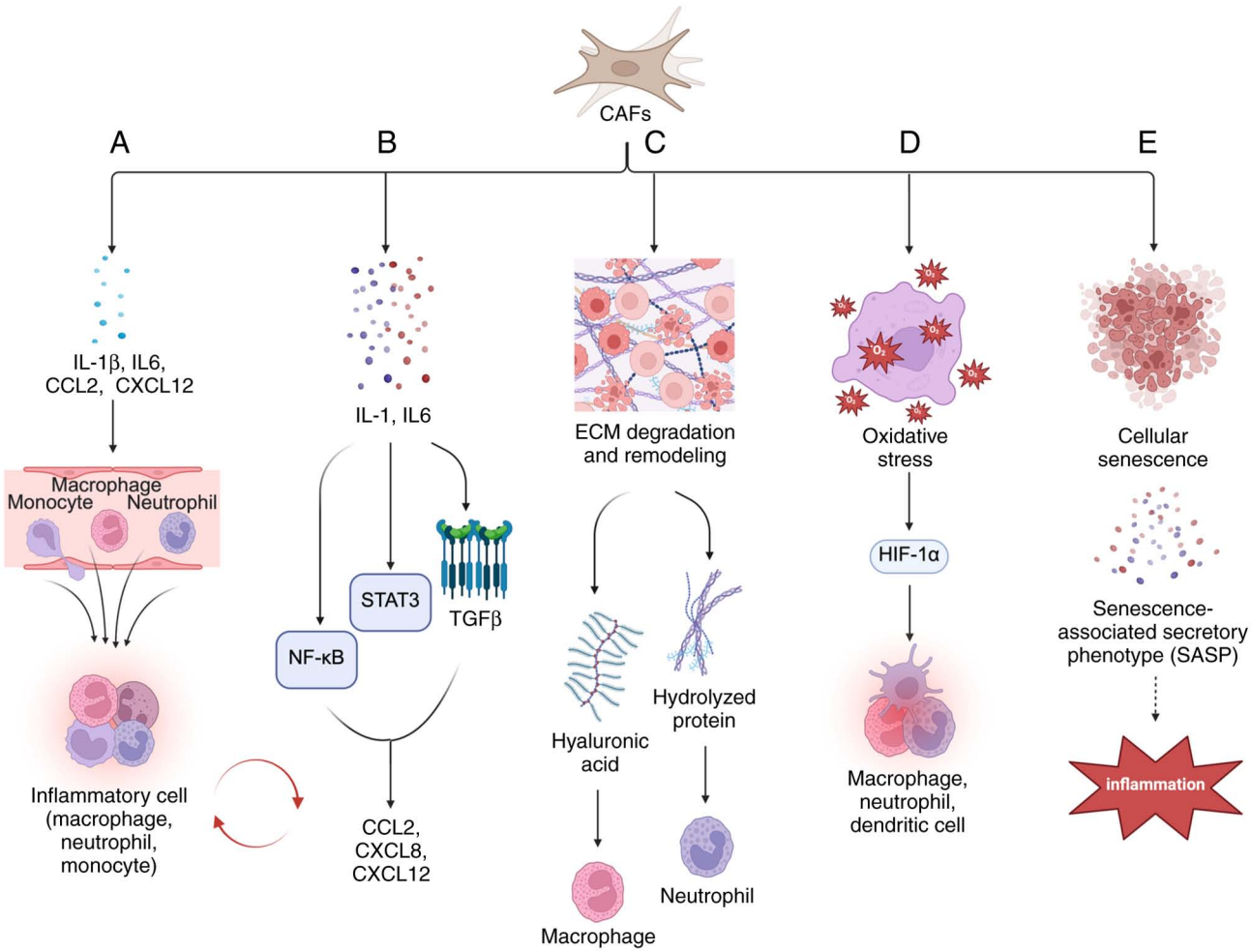

Figure 1. Pro-inflammatory role of CAFs in tumors. (A) CAFs recruit inflammatory cells activating inflammatory pathways. (B) CAFs also release inflammatory factors, further activating inflammatory pathways. These two processes influence each other, creating a feedback loop. (C) CAFs exacerbate inflammation by remodeling the ECM and promoting its degradation. (D) CAFs further intensify the hypoxic microenvironment, which in turn promotes inflammation. (E) CAFs participate in cellular senescence, a process that is associated with the onset and accumulation of inflammation (created with Biorender.com). CAF, cancer-associated fibroblast; IL-1β, interleukin-1β; ECM, extracellular matrix; HIF, hypoxia-inducible factor; CCL2, C-C motif chemokine ligand 2; CXCL12, C-X-C motif chemokine ligand 12.

be affected by cancer cells to upregulate pro-inflammatory gene expression (30). IL-1α and IL-1β released by pancreatic cancer cells and TAMs are key regulators of thymic stromal lymphopoietin (TSLP) secretion by CAFs. This secretion is pivotal in facilitating TSLP-mediated modulation of type 2 T-helper cell immune responses (42). The paracrine inflammatory mediator TNF-α, originating from immune cells or tumor cells, induced CAFs to express IL-6 and chemokine CCL2 in colorectal metastatic and liver metastatic cancers, along with pro-angiogenic CXCL8/IL-8 expression in an NF-κB-dependent manner (43-45). Meanwhile, CAFs possess the ability to undergo self-activation through autocrine signaling. In breast cancer, TGF-β and stromal cell-derived factor (SDF)-1α/CXCL12 secreted by CAFs initiate autocrine signaling loops that maintain their differentiation and tumor-promoting phenotypes. However, the specific *in vivo* molecular signals that activate these inflammatory pathways in CAFs remain unidentified (46).

Shaping the stroma for the inflammatory cascade. CAFs are the main cellular components of the stroma and are the primary source of connective tissue and proteolytic enzymes within the ECM (Fig. 1C). The production of ECM by CAFs modifies and engages multiple signaling pathways from the cell surface to the nucleus, resulting in alterations in gene expression and cellular behavior. CAFs promote ECM degradation and remodeling by secreting cytokines, chemokines and other effector molecules (TGF-β, CXCL2), various matrix proteins (fibronectin and type I collagen) and MMPs (47,48). ECM deposition is intricately associated with TGF-β, a relationship mediated by CAFs through the production of activin A, which promotes epithelial cell migration and induces EMT (49). These fibroblasts synthesize significant amounts of laminin, which binds to α6β4 integrin receptors on malignant cells, thus enhancing their migration potential (50). They are also the primary source of HA, a crucial stromal-derived component that facilitates the recruitment of TAMs, which are predominantly concentrated within the HA-rich tumor stroma (51). A single-cell RNA-sequencing study revealed that CAFs interact with a tumor-specific keratinocyte subpopulation that shows significant EMT features, with the pleiotropic growth factor Midkine being upregulated in primary CAFs (52).

The ECM is a crucial component of the TME, providing structural support and regulating the microenvironment and cellular interactions. Changes in its composition, density and rigidity are closely associated with tumor progression. Increased ECM rigidity influences cellular behavior by altering mechanotransduction pathways, thus affecting the capacity of cells to perceive and respond to external mechanical stimuli. The ECM also activates T cells and promotes their differentiation through integrin-mediated complexes to regulate immune cells (53). TGF-β plays a significant role in regulating ECM stiffness, while MMPs promote ECM degradation and remodeling, both of which are essential for tumor cell invasion. TGF-β is predominantly secreted and deposited within the ECM as latent complexes (54). Pathological upregulation of TGF-β induces EMT, promotes ECM deposition and drives the activation of CAFs, ultimately contributing to fibrotic diseases and cancer progression (16). MMP is the most relevant protease for primary tumors, regulating various physiological processes and signal transduction events (55). The most well-known function of MMP is to cleave ECM proteins to regulate ECM remodeling. Certain hydrolyzed protein fragments of the ECM are chemotactic, recruiting neutrophils, increasing their chemotactic activity and exacerbating tumor inflammatory responses (56). The interaction between the tumor and ECM activates the Notch1 pathway through pro-inflammatory signaling, leading to the induction of CXCL8, which promotes tumor metastasis (57). Several proteins associated with inflammation, stromal remodeling, TGF-β receptor signaling and angiogenesis have been identified within the stromal microenvironment (58).

Induction of inflammation via hypoxic microenvironment. Inflammatory fibroblasts (iCAFs) exhibit hypoxia-associated gene expression and biochemical profiles. These cells are predominantly localized in hypoxic regions of pancreatic cancer, whereas myofibroblasts (myCAFs) are largely absent. Hypoxia further enhances cytokine-induced iCAF phenotypes, contributing to tumor progression (59). The transcriptional target of hypoxia-inducible factor (HIF)-1α, the G-protein estrogen receptor, establishes a feed-forward loop in which IL-1β secretion by fibroblasts enhances IL1R1 expression in breast cancer cells. Furthermore, IL-1β present in the conditioned medium of triple-negative breast cancer cells under hypoxic conditions reinforces the invasion of fibroblasts (Fig. 1D) (60). MyCAFs deficient in caveolin-1 activate HIF and NF-κB transcription factors, generating oxidative stress that promotes aerobic glycolysis and inflammation, thus creating a pseudo-hypoxic state. This phenomenon drives the 'reverse Warburg effect' within the TME, where aerobic glycolysis occurs predominantly in tumor-associated fibroblasts rather than malignant cells, facilitating metastasis (61,62). The lactate-NAD+ axis further activates CAFs by downregulating p62, which enhances tumorigenesis through inflammation and metabolic reprogramming in both *in vitro* and *in vivo* models (63). Furthermore, the dense ECM exerts mechanical pressure on blood vessels, inducing hypoxia, with collagen deposition contributing to the expression of hypoxia-related aberrant factors (64).

The association between hypoxia and inflammation is well established, with inflammatory diseases frequently showing severe hypoxic conditions. Malignant tumor cell clones consume substantial amounts of oxygen, inducing persistent hypoxia that sustains chronic inflammation. This process is driven by the release of reactive oxygen species (ROS) and nitric oxide alongside NF-κB activation, which plays a pivotal role in the induction of HIF. Elevated levels of HIF further promote the production of multiple pro-inflammatory mediators, reinforcing the inflammatory state within the TME (65,66). HIF-1α can interact with p53 to inhibit its activity, thus reducing p53-induced apoptosis and promoting tumor cell survival and metastasis (67). The inactivation of the tumor suppressor p53 results in the upregulation of NF-κB, a key positive regulator of inflammatory signaling, thus fostering a pro-inflammatory microenvironment conducive to tumor metastasis (68). HIF-1α modulates various immune functions, including the polarization of M1 macrophages, the maturation and migration of dendritic cells, and the formation and survival of neutrophil extracellular traps. In comparison, another transcription factor, HIF-2α, promotes M2 macrophage polarization by inducing the expression of M2-associated markers, e.g., arginase 1 (69). HIF-1α has been shown to influence the differentiation and function of different T-cell subsets under both hypoxic and normoxic conditions (70,71). HIF-2α is also expressed in TAMs and its depletion in TAMs impairs the expression of chemokine receptors and the migration and infiltration of TAMs (69).

Fueling inflammation by aging cells. Cellular senescence is characterized by progressive mitochondrial dysfunction, resulting in elevated production of ROS, such as H_2O_2, which increases the risk of carcinogenesis (72). Studies suggest that alterations in senescence-associated secretory phenotype (SASP) gene expression in senescent CAFs facilitate malignant tumor proliferation (73). In tumor tissues, H_2O_2-activated CAFs interact with tumor cells to produce H_2O_2, mimicking the behavior of immune cells like macrophages and neutrophils, driving local and systemic inflammation through the innate immune response, mainly *via* NF-κB activation (Fig. 1E) (74). Pro-inflammatory cytokines mediate the epigenetic modification of H3K27me3 in CAFs, thus sustaining the SASP and promoting peritoneal tumor formation in gastric cancer by activating the JAK/STAT3 signaling pathway (75).

Cellular senescence is distinguished by a reduced proliferative potential, the activation of anti-apoptotic pathways and the secretion of pro-inflammatory cytokines, chemokines and interleukins (IL-6, IL-1α and IL-1β). It also involves releasing growth factors, proteases and their inhibitors, angiogenic factors and insoluble components (fibronectin, collagen and laminin). Other inflammatory mediators, including growth differentiation factor-15, TGFβ1 and IFNγ, also contribute to this secretory profile, collectively called the SASP (76). Senescent cells demonstrate high oxidative metabolism and ROS production (76). The complex interaction among the SASP, oxidative stress and inflammation highlights the intrinsic association between cellular senescence and the initiation and progressive accumulation of inflammatory responses (77).

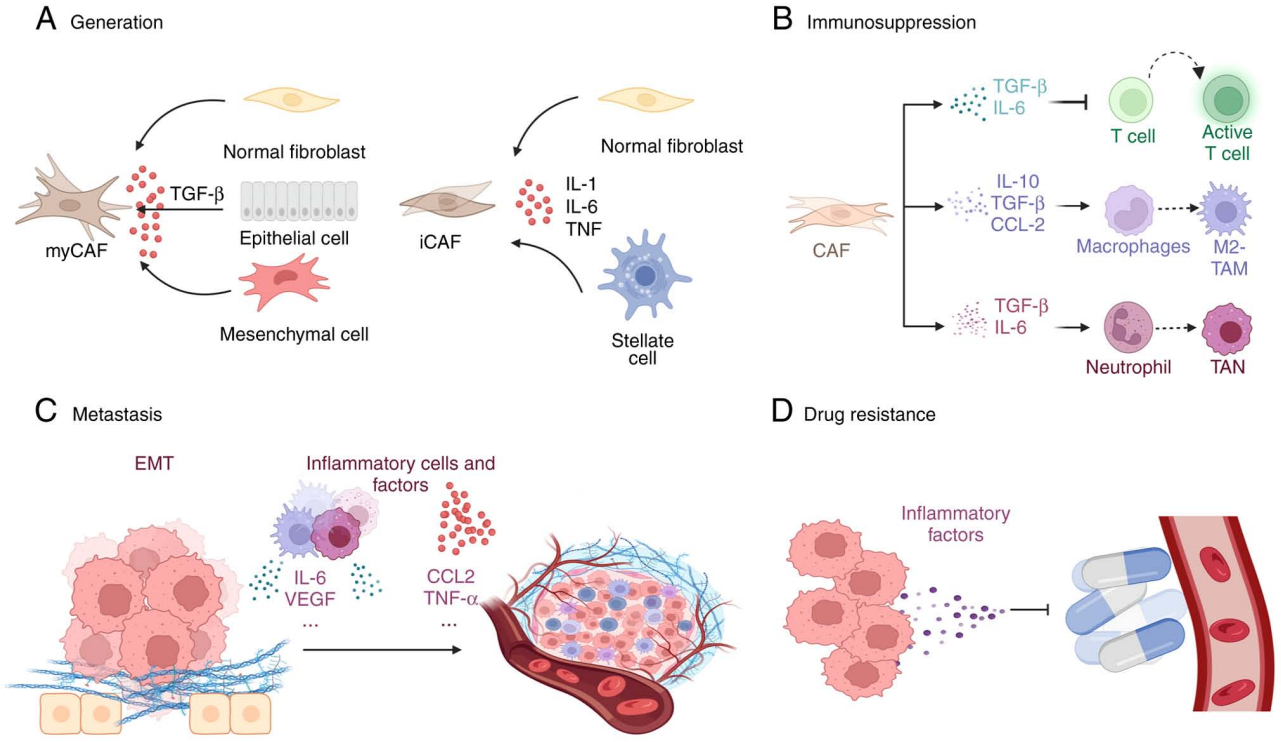

Figure 2. Effect of tumor inflammation on CAFs. (A) Multiple inflammatory signaling pathways activate different CAF precursors into CAFs. (B) CAFs secrete various inflammatory cytokines and chemokines interacting with immune cells, promoting their polarization into an immunosuppressive state. (C) Inflammatory cells and factors play a crucial role in EMT and contribute to tumor invasion and metastasis. (D) CAFs secrete inflammatory cytokines that drive drug resistance, protecting cancer cells from drug-induced apoptosis (created with Biorender.com). CAF, cancer-associated fibroblast; iCAFs, inflammatory CAFs; myCAFs, myofibroblasts associated with cancer; EMT, epithelial-mesenchymal transition; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; CCL2, C-C motif chemokine ligand 2.

3. Effect of tumor inflammation on CAFs

These CAFs represent a heterogeneous population with distinct origins, phenotypic characteristics and functional properties, contributing significantly to the complexity of the TME-their heterogeneity results in particular functions for different types of CAF. For instance, myCAFs, which show elevated expression of α-smooth muscle actin (αSMA), promote fibrosis and contribute to ECM remodeling to support tumor growth (21). However, iCAFs, characterized by low expression of αSMA and the secretion of IL-6 and other pro-inflammatory mediators, contribute to immune evasion and resistance to chemotherapy (21). Furthermore, antigen-presenting CAFs, distinguished by the expression of major histocompatibility complex class II genes, function as decoy receptors to promote immune suppression (78). Inflammation plays a crucial role in shaping both the phenotype and functional properties of CAFs (Fig. 2).

Inflammation promotes CAF production. MyCAFs originate from various cell types, including fibroblasts, smooth muscle cells and epithelial cells. Their activation is primarily driven by inflammatory signals and tissue injury (Fig. 2A). These cells functionally resemble contractile fibroblasts involved in wound healing. TGF-β is a key regulator of myCAF differentiation, inducing their activation from multiple cell types. Upon activation, TGF-β binds to its receptor, leading to the phosphorylation of Smad2/3, which then form a complex with Smad4 and translocate into the nucleus to regulate gene transcription (12); TGF-β promotes CAF formation primarily through the Smad-dependent signaling pathway, where Smad2/3 phosphorylation leads to CAF differentiation with high expression of αSMA and SDF1/CXCL12 (79-81). The upregulation of microRNA-21 (miR-21) in CAFs, mediated by the TGF-β signaling pathway, enhances their CAF-like morphology and migratory capacity (82). Smad7, a negative feedback regulator that antagonizes receptor/Smad signaling, plays a complementary role in modulating this pathway. Either depletion of Smad7 or increased expression of miR-21 contributes to the sustained activation of CAFs, ultimately promoting tumor progression (82). The EMT process with increased expression of FAP, α-SMA and vimentin, primarily driven by TGF-β, further facilitates the differentiation of myCAFs, contributing to fibrosis and metastasis (83,84). In addition to Smad signaling, TGF-β activates non-Smad pathways, including PI3K/AKT and MAPK/ERK, which collectively control fibroblast proliferation, contractility and ECM deposition (85). Furthermore, macrophage recruitment can activate hematopoietic stem cells, maintained by TNF and IL-1, which promote myCAFs activation *via* ROS and NF-κB-dependent pathways (39,86). MyCAFs are contractile and ECM-remodeling cells that highly express αSMA, transgelin, periostin and collagen-related genes (21). They play a crucial role in modulating the mechanical and structural properties of the tumor stroma. By promoting desmoplasia, myCAFs increase tissue stiffness and contribute to the formation of a dense ECM that acts as a physical barrier, thereby limiting immune cell infiltration and reducing the efficacy of drug delivery.

Compared to myCAFs, iCAFs are directly activated by pro-inflammatory cytokines (Fig. 2A). TNFα and IL-1 play a central role in the activation mechanism of iCAFs. These cytokines promote the transformation of mesenchymal stem cells (MSCs) and pancreatic stellate cells into iCAFs, characterized by elevated expression of FAP, reduced αSMA levels, enhanced proliferative capacity and upregulated expression of CCR2, CCR5 and CXCR1/2 (8,87). TNFα, secreted by neutrophils, binds to TNFR2 on the cell membrane, leading to the overproduction of CXCL1, a feedforward factor that polarizes iCAFs and induces T-cell dysfunction (88). Similarly, IL-1β signaling through the P53/NF-κB pathway results in the secretion of IL-6, which activates CAF-tumor cell IL-6/STAT3 signaling pathways, further enhancing the inflammatory CAF phenotype (9,89). ICAFs secrete high levels of inflammatory cytokines and chemokines, such as IL-6, IL-11, CXCL1, CCL2 and LIF, which can recruit immunosuppressive cells, promoting tumor-associated inflammation (21).

Growing evidence suggests that the IL-6/STAT3 and TGF-β signaling pathways interact synergistically, forming a positive feedback loop that sustains inflammation-driven activation of CAF. IL-6, a pro-inflammatory cytokine, activates the JAK/STAT3 pathway, which in turn enhances TGF-β signaling by promoting the phosphorylation of Smad3, a key mediator of TGF-β-induced transcriptional responses (90). Treatment with IL-6 increased the expression of TGF-β type I receptor in A549, NCI-H358 and NHLF cells, thus enhancing TGF-β signaling and fibroblast activation (91). However, certain findings indicate that the simultaneous presence of cytokines may lead to TGF-β-mediated suppression of IL-6-induced proliferative effects, highlighting more intricate regulatory dynamics (92,93).

Inflammation and its contribution to the immunosuppressive function of CAFs. The immunosuppressive properties of CAFs are modulated by inflammatory signaling cascades, cytokines and chemokines (Fig. 2B). IL-6 and TGF-β are crucial mediators through which CAFs suppress cytotoxic T lymphocyte infiltration, and blocking IL-6 has been shown to enhance T-cell function (94,95). The CXCL12-CXCR4 signaling axis promotes the interaction between CAFs and monocytes, inducing the reprogramming of monocytes into an immunosuppressive phenotype (96). Furthermore, CAFs also promote the recruitment of monocytes and their differentiation into M2-TAMs by secreting IL-8, IL-10, TGF-β and CCL2, thus impairing effector T-cell responses and inducing immunosuppression within the TME (97). CAFs also mediate neutrophil chemotaxis and activation of TANs through the IL-6/STAT3/ERK1/2 axis (98). IL-6 stimulation activates the STAT3 signaling pathway in TANs, suppressing T-cell activity and inducing immune tolerance *via* PD-L1 expression (99). In melanoma and colorectal cancer, CXCL5 facilitates the upregulation of PD-L1 expression on tumor cells *via* a PI3K/AKT-dependent mechanism, thus enhancing immune tolerance and promoting tumor immune evasion (100).

Inflammation as a driver of CAF invasiveness. Inflammation is pivotal in enhancing the invasive properties of CAFs (Fig. 2C). Exposure of breast cancer cells to TNFα or IL-1β, in co-culture with MSCs or CAFs, leads to a significant upregulation of CXCL8, CCL2 and CCL5 expression. This observation underscores the contribution of tumor-stroma-inflammation interactions in driving tumor aggressiveness (57,101). M2-type macrophages can also drive EMT progression by secreting soluble factors such as IL-6 and SDF-1 (102). *In vitro* co-culture studies analyzing the interaction between TAMs and CAFs have revealed that macrophages significantly enhance the invasive potential of both tumor cells and CAFs (103). Similarly, TANs secrete VEGF, CCL17 and MMP9, which induce tumor angiogenesis, remodel the ECM in the TME and promote tumor invasion and metastasis (104). Inflammation-activated iCAFs show elevated expression of inflammatory genes and chemokines, facilitating tumor metastasis by activating Ras and GαI proteins (8). Inhibition of the Notch1-Jagged1/NF-κB (p65) signaling pathway downregulates key factors associated with CAF activity, leading to ECM remodeling and reduced tumor metastasis, even under TNF-α stimulation (105). Similarly, knockout of the G protein-coupled receptor 30 suppresses IL-6 secretion and attenuates the invasive potential of CAFs (106).

Inflammation drives CAF-mediated drug resistance. The ECM, comprising structural components such as collagen and HA, plays a pivotal role in tumor chemoresistance by establishing a dense matrix that serves as a physical barrier, thus hindering the effective penetration of therapeutic agents (107). CAFs contribute to this resistance by secreting cytokines, chemokines, growth factors and exosomes, which engage their respective signaling pathways, ultimately protecting cancer cells from apoptosis induced by therapeutic interventions (Fig. 2D).

Inflammation plays a crucial role in tumor formation. During tumor treatment, a reduction in the neutrophil-to-lymphocyte ratio induces the reprogramming of iCAFs, leading to a marked decrease in IL-6/STAT-3 expression and enhancing chemotherapy sensitivity in preclinical models of pancreatic cancer (9). Hypoxia within the TME, driven by COX-2 secretion from CAFs, M2 macrophages and cancer cells, and its positive interaction with Yes-associated protein 1 and anti-apoptotic mediators, fosters cancer cell resistance to chemotherapy (14). Furthermore, exosomal miRNA-20a secreted by CAFs inhibits the phosphatase and tensin homolog/PI3K-AKT pathway, promoting non-small cell lung cancer progression and inducing resistance to cisplatin (108).

4. Current and emerging therapeutic strategies

Multiple therapeutic strategies targeting CAFs and their role in tumor-associated inflammation have been explored in preclinical and clinical research (Table I). For instance, inhibition of TGF-β receptor 1 (300 mg/day) has been associated with prolonged patient survival in phase II clinical trials for pancreatic cancer and HCC (22,23). However, considering the functional heterogeneity of CAFs, broad inhibition of TGF-β may inadvertently induce immunosuppressive effects. To overcome this bottleneck, combination approaches, such as co-administering TGF-β inhibitors with immune checkpoint blockade therapies (e.g., anti-PD-L1 antibodies), have demonstrated superior anti-tumor immune responses compared to monotherapy (24). Similarly, in a phase I clinical trial, IL-6 inhibitors (1, 2, 4 or 8 mg/kg intravenously, every 4 weeks) have been shown to stimulate CD8+ T-cell activation and

Table I. Representative panel of interventions targeting CAFs.

Therapy	Target	Dose	Combination therapy	Effects	Disease	Testing stage	(Refs.)
Galunisertib	TGF-β	80 or 150 mg, bid	No	Enhances overall survival	Hepatocellular carcinoma	Phase 2	(22)
		300 mg, qd	Gemcitabine	Enhances overall survival with minimal added toxicity	Pancreatic cancer	Phase 2	(23)
		37.5, 75 or 150 mg/kg bid	Anti-PD-L1 immunotherapy	Enhances anti-tumor immunity; inhibits tumor cell growth	Colon carcinoma	Preclinical	(24)
Tocilizumab	IL-6	1, 2, 4 or 8 mg/kg	Carboplatin and doxorubicin	Enhances anti-tumor immunity	Epithelial ovarian cancer	Phase 1	(25)
IL-6$^{loxP/loxP}$	IL-6	/	Gemcitabine and anti-PD-L1 immunotherapy	Enhances anti-tumor immunity and the efficacy of immune checkpoint blockade	PDAC	Preclinical	(109)
^{177}Lu-BiOncoFAP	FAP	15 or 70 MBq/mouse, i.v.	No	Enhances anti-tumor efficacy	Fibrosarcoma	Preclinical	(110)
[^{18}F]AlF-FAPI-74	FAP	5x10^{6} CAR^{+} FAP CAR-T2A-mCherry T cells, i.v.	No	Monitors changes in FAP expression	Mesothelioma and lung adenocarcinoma	Preclinical	(111)
PEGPH20	Hyaluronic acid	3.0 μg/kg, q2w or qw	Gemcitabine and nab-paclitaxel	Enhances objective response rate	Pancreatic cancer	Phase 3	(112)
Zebularine	HIF-1α	100 or 700 mg/kg, qd	Oxaliplatin	Enhances the efficacy of chemotherapies	Colorectal cancer	Preclinical	(113)
Dasatinib	ECM	8 mg/kg, qod	Anti-PD-1 immunotherapy	Enhances anti-tumor immunity	Breast cancer	Preclinical	(116)
Anti-WNT2 monoclonal antibody (3C4)	SOCS3/ p-JAK2/ p-STAT3	200 μg, qd	Anti-PD-1 immunotherapy	Enhances anti-tumor immunity	Oesophageal squamous cell carcinoma and colorectal cancer	Preclinical	(117)
Celecoxib	COX-2	400 mg, bid	Carboplatin and pemetrexed, carboplatin and gemcitabine	No significant differences	Non-small-cell lung cancer	Phase 3	(118)
Celecoxib, TG4-155 and ONO-AE3-208	COX-2/ PGE2/ EP2-4	Derived from pharmacokinetic studies	Anti-PD-1 and anti-NK1.1 immunotherapy	Inhibits tumor-promoting inflammation and enhances anti-tumor immunity	Melanoma	Preclinical	(119)
NT157/MF63/DPI	IRS-1/ mPGES-1/ NOX2	NT157 (15 mg/kg), MF63 (30 mg/kg) and DPI (1 mg/kg), qd	No	Inhibits tumor-promoting inflammation and enhances anti-tumor immunity	Melanoma	Preclinical	(120)
IL-1R antagonist	IL-1β	5 mg/kg, qod	No	Inhibits tumor growth and metastasis	Breast cancer	Preclinical	(121)

Table I. Continued.

Therapy	Target	Dose	Combination therapy	Effects	Disease	Testing stage	(Refs.)
28H1-700DX	FAP	50 μg, i.v.	No	Depletes FAP expression	PDAC	Preclinical	(122)
PDPN-targeted NIR-PIT	PDPN/gp38	100 μg, i.v.	No	Enhances anti-tumor immunity	Head and neck squamous cell carcinoma and colon adenocarcinoma	Preclinical	(123)

i.v., intravenous; IL-6loxP/loxP, interleukin-6 gene knockout; PEGPH20, pegvorhyaluronidase alfa; 177Lu-BiOncoFAP, Lutetium-177-labeled bispecific OncoFAP;[18F]AlF-FAPI-74, aluminum fluoride-18-labeled fibroblast activation protein inhibitor-74; NIR-PIT, near-infrared photoimmunotherapy; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; NK1.1, natural killer cell protein 1.1; CAR-T, chimeric antigen receptor T-cell; WNT2, wingless-type MMTV integration site family member 2; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; IRS-1, insulin receptor substrate 1; mPGES-1, microsomal prostaglandin E synthase-1; ECM, extracellular matrix; HIF, hypoxia-inducible factor; PDPN/gp38, podoplanin/glycoprotein 38; PDAC, pancreatic ductal adenocarcinoma.

increase levels of anti-tumor effectors, such as IFN-γ and TNF-α (25). In a dual recombinase-driven model of pancreatic ductal adenocarcinoma (PDAC), the knockdown of IL-6 on αSMA+ CAFs markedly enhanced the efficacy of gemcitabine, whereas its deletion from FAP+ CAFs did not yield a similar effect (109). Furthermore, although IL-6 blockade failed to demonstrate synergy with anti-PD-1 immunotherapy, it significantly accelerated gemcitabine-induced tumor suppression, ultimately prolonging survival in PDAC mouse models (109). These findings highlight the intricate and context-dependent roles of CAF-derived IL-6 in tumor progression and therapeutic resistance.

Both *in vivo* and *in vitro* studies further illustrate the complexity of targeting CAFs. FAP, a widely expressed marker on these cells, has been identified as a promising therapeutic target within the TME. Radioligand therapy using FAP-targeting agents has demonstrated potential in delivering localized radiation to tumor sites, offering a targeted approach to cancer treatment. ^{177}Lu-BiOncoFAP is a promising candidate for radioligand therapy of cancer, featuring a favorable tumor-to-organ distribution ratio and low renal uptake (110). FAP-targeted CAR-T cells have been designed to selectively deplete FAP+ CAFs in solid tumors. An emerging study has used positron emission tomography imaging with [^{18}F] AlF-FAPI-74, a radiolabeled FAP inhibitor, to evaluate FAP expression and monitor chimeric antigen receptor T-cell (CAR-T) response *in vivo* (111). This strategy holds promise for enhancing CAR-T cell therapies by optimizing treatment timing, refining therapeutic approaches and identifying patients most likely to benefit from FAP-targeted interventions. The clinical implementation of CAF-targeted therapies remains complex due to off-target toxicities and the heterogeneous nature of CAF populations across different cancer types. Furthermore, inconsistencies in dosing regimens-resulting from variations in tumor models, treatment combinations and pharmacokinetics-highlight the necessity for standardized dosage optimization in future clinical trials. Considering these challenges, a more effective therapeutic strategy may involve combining CAF-targeted therapies with immunotherapy or chemotherapy to overcome resistance, enhance treatment efficacy and improve clinical outcomes.

Recent therapeutic strategies increasingly emphasize the role of stromal proteins and HIF-1α in mediating the crosstalk between inflammation and CAFs. Structural proteins within the tumor stroma, such as collagen and fibronectin, contribute to forming a fibrotic ECM that facilitates tumor progression and immune evasion. Targeting these stromal components offers a promising approach to modulating CAF activity and suppressing inflammation. The findings from a phase III clinical trial demonstrated that integrating stromal protein-targeting agents with gemcitabine and paclitaxel prolonged patient survival and reduced adverse effects associated with treatment (112). Similarly, HIF-1α, a key mediator of hypoxia and inflammation, has emerged as a dual-action therapeutic mediator. Inhibiting HIF-1α disrupts the tumor-promoting functions of CAFs and enhances immune responses, underscoring its clinical potential (113,114).

Nanoparticle-based drug delivery systems have become effective platforms for improving drug penetration within tumors. However, CAFs pose substantial challenges to the

efficacy of nanomedicine by establishing physical and biochemical barriers within the TME. To overcome these obstacles, researchers have designed CAF-targeted nanoparticle delivery systems capable of either modulating CAF activity to enhance drug diffusion or directly transporting therapeutic agents to the tumor stroma, thus improving treatment efficacy (115). A sequential nanomedicine approach using dasatinib to remodel the ECM and enhance epirubicin penetration has demonstrated promising results in breast cancer models. This strategy effectively reduces ECM deposition, facilitates improved drug delivery, enhances anti-tumor immune responses and works synergistically with anti-programmed death-1 therapy. Thus, it significantly inhibits tumor growth and prevents lung metastasis while minimizing systemic toxicity (116).

Based on the existing methods, the combined therapies are becoming increasingly prevalent. These strategies target CAFs while addressing inflammation or immune suppression, aiming to interfere with multiple tumor-supportive mechanisms and strengthen anti-cancer immunity. For instance, the combined administration of TGF-β, WNT, COX, PD-1/PD-L1 inhibitors and cytotoxic chemotherapy have demonstrated enhanced therapeutic efficacy (24,117-119). Such multifaceted approaches provide a comprehensive framework for overcoming tumor resistance and optimizing therapeutic efficacy.

5. Limitations and future perspectives

This review provides a comprehensive analysis of the involvement of CAFs in tumor progression and therapy resistance, with a particular focus on recent therapeutic advancements. However, the findings presented are predominantly derived from preclinical models and early-phase clinical trials, with limited long-term clinical validation of multiple CAF-targeted therapies (120-123). Furthermore, the heterogeneity of CAFs across different tumor types suggests that certain findings may not be universally applicable. Future research should prioritize adding data from large-scale clinical studies and patient-derived models to refine the understanding and optimization of CAF-targeted therapeutic approaches.

Understanding the intricate crosstalk between CAFs and inflammation is crucial for identifying precise therapeutic targets and enhancing treatment efficacy. Inflammation is a basic regulator of CAF-mediated tumor progression; however, current therapeutic strategies often address these factors independently, potentially limiting their effectiveness. Dual-targeted approaches that simultaneously modulate CAF-associated signaling pathways and inflammatory cytokines may lead to improved clinical outcomes. Specifically, pathways such as IL-6/STAT3 and TGF-β, which regulate inflammatory responses and CAF activation, represent promising targets for more effective anti-tumor interventions. In addition, further investigation into the roles of hypoxia, oxidative stress and cellular senescence in modulating CAF behavior may uncover novel therapeutic opportunities.

Targeting the stromal microenvironment also holds significant therapeutic promise. Stromal proteins and HIF-1α, as key mediators of the crosstalk between inflammation and CAFs, represent promising therapeutic targets. Expanding clinical trials to evaluate inhibitors of these pathways, either as monotherapies or in combination with chemotherapy and immunotherapy, will be necessary for translating preclinical insights into clinical applications. Furthermore, identifying reliable biomarkers associated with the CAF-inflammation axis could enable more precise patient stratification, facilitating the development of personalized treatment strategies.

Further advancements in therapeutic strategies should integrate innovations in nanoparticle-based drug delivery, metabolic modulation and the design of combination therapies. Incorporating these approaches into clinical trials will optimize therapeutic efficacy while minimizing adverse effects. Therefore, developing strategies targeting the CAF-inflammation axis will improve cancer treatment outcomes and facilitate the emergence of more personalized and effective therapeutic modalities.

6. Conclusion

This review synthesizes the bidirectional interplay between CAFs and inflammatory processes, demonstrating how CAFs drive pro-inflammatory signaling while inflammatory mediators reinforce CAF activation. The study highlighted novel therapeutic approaches targeting stromal elements and employing nanotechnologies to disrupt CAF-tumor crosstalk. Notably, pharmacological interventions simultaneously addressing CAF signaling and inflammatory cytokines exhibit enhanced antitumor effects compared to mono-targeted therapies. The present analysis underscores the critical advantage of dual-pathway strategies that concurrently modulate both CAF functionality and inflammatory microenvironments, proposing this combined targeting approach as a promising paradigm for optimizing cancer therapeutics.

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Competing interests

The authors declare that they have no competing interests.

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