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REVIEW

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Cancer-associated fibroblasts: a pivotal regulator of tumor microenvironment in the context of radiotherapy

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Abstract

Background In the course of tumor treatment, radiation therapy (RT) not only kills cancer cells, but also induces complex biological effects in non-malignant cells around cancer cells. These biological effects such as angiogenesis, changes in stromal composition and immune cell infiltration remodel the tumor microenvironment (TME). As one of the major components of the TME, Cancer-associated fibroblasts (CAFs) are not only involved in tumorigenesis, progression, recurrence, and metastasis but also regulate the tumor-associated immune microenvironment. CAFs and tumor cells or immune cells have complex intercellular communication in the context of tumor radiation.

Main content.

Different cellular precursors, spatial location differences, absence of specific markers, and advances in single-cell sequencing technology have gradually made the abundant heterogeneity of CAFs well known. Due to unique radioresistance properties, CAFs can survive under high doses of ionizing radiation. However, radiation can induce phenotypic and functional changes in CAFs and further act on tumor cells and immune cells to promote or inhibit tumor progression. To date, the effect of RT on CAFs and the effect of irradiated CAFs on tumor progression and TME are still not well defined.

Conclusion In this review, we review the origin, phenotypic, and functional heterogeneity of CAFs and describe the effects of RT on CAFs, focusing on the mutual crosstalk between CAFs and tumor or immune cells after radiation. We also discuss emerging strategies for targeted CAFs therapy.

Keywords Cancer associated fibroblast, Radiation therapy, Tumor microenvironment, Immune microenvironment

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Introduction

Over the past few decades, tremendous advances have been made in the comprehensive treatment of tumors. Yet, RT remains the cornerstone of antitumor treatment, with approximately 50% or more of cancer patients requiring the implementation of further RT [1–3]. Ionizing radiation mainly kills tumor cells by damaging DNA, including direct killing of cancer cell DNA and indirect DNA damage caused by free radicals generated by water molecules in tumor tissues [4, 5]. Based on the "4R" theory of radiobiology—Re-repair, cell Repopulation, cell cycle Redistribution, Reoxygenation of hypoxic tumor cells, and the concepts of intrinsic radiosensitivity, RT has been established to control tumors and alleviate symptoms according to the difference in the response of tumor tissue and normal tissue to rays [6]. However, radiation not only acts directly on tumor cells, but also induces biological effects on the stroma, vasculature, and immune components in the TME, which are crucial for tumor treatment [7, 8]. The TME is defined as all cellular and non-cellular components of tumor ecology, among which non-malignant cells include activated fibroblasts, immune cells, inflammatory cells, adipocytes, endothelial cells, and pericytes, and the non-cellular components include the extracellular matrix (ECM) and soluble signals such as growth factors, cytokines, and chemokines [9–11]. RT can not only mediate the DNA damage in tumor cells but also directly affect the TME in which they are located [8, 12]. Since the "bystander effect" and "distant effect" induced by radiation have been proposed, it has been found that RT may promote tumor immunogenicity by facilitating cross-initiation, triggering tumor T-cell response, and releasing inflammatory factors after killing tumor cells, or it may induce chronic inflammation/reflex immunosuppression, thereby inhibiting tumor progression or supporting tumor regeneration [13, 14].

CAFs, as one of the main components of TME, are inextricably linked to tumorigenesis, progression, recurrence, and metastasis [15]. CAFs not only produce collagen to mediate ECM remodeling to form a physical barrier, indirectly regulating tissue stiffness and matrix tension; but also affect the tumor immune environment through direct cell–cell contact and paracrine effects (growth factors, cytokines, and chemokines) [16, 17]. Early studies have demonstrated the tumor-promoting effects of CAFs, while some studies have also found tumor-suppressive effects. Thus, the abundant heterogeneity of CAFS has attracted extensive attention [18–20]. CAFs in the TME have different subtypes and functions, most of which can induce tumor-promotion effects through paracrine signaling [21, 22]. CAFs can also create immunosuppressive TME by affecting immune cell recruitment, driving immune cells' suppressive function, and inhibiting cytotoxic T lymphocytes (CTL) killing and remodeling the ECM [23, 24], while other CAF subtypes have tumor-suppressive effects. As one of the most abundant stromal cell types, CAFs are inevitably irradiated during RT of tumors. It has been shown that RT can cause persistent DNA damage in CAFs, induce senescence-related phenotypes, and alter specific secretory functions [25–27]. In addition, irradiated CAFs not only increase tumor aggressiveness but also confer RT resistance to tumor cells through the paracrine effect [28, 29]. At the same time, the immunomodulatory functions of irradiated CAFs were also altered, such as cytotoxicity to NK cells, immunosuppression effects on macrophages, and recruitment of monocytes and differentiation into myeloid-derived suppressor cells (MDSCs) [30–34]. In the context of RT, the effects of radiation on CAFs and their interactions with tumor cells and immune cells have become extremely complex.

So far, different RT regimens have different effects on CAFs in existing studies. The interaction mechanism of CAFs or irradiated CAFs with tumor cells and immune cells is still controversial. The cellular markers for CAFs have not yet been unified, and their abundant heterogeneity makes targeting CAFs for anti-tumor therapy extremely challenging. Therefore, in this review, we first introduce the origin and heterogeneity of CAFs, gather available knowledge about the effects of radiation exposure on CAFs, then describe the interaction of CAFs or irradiated CAFs with tumor cells and the immune environment in the context of RT, and finally summarize the current therapeutic strategies related to targeting.

The characteristics of CAFs

Origin heterogeneity of CAFs

In the current definition of CAFs, cells with negative epithelial, endothelial, and leukocyte markers, elongated morphology, and lacking mutations found within cancer cells may be considered CAFs. Therefore, the identification of CAFs needs to be a combination of biomarkers, physical forms, and gene mutations [35, 36]. As a highly heterogeneous population, CAFs can originate from different cell populations. CAFs are mainly induced to differentiate from normal fibroblasts (NFs) or quiescent stellate cells after activation by cytokines, chemokines, and exosomes [37]. CAFs can also acquire a mesenchymal phenotype from epithelial/endothelial cells by epithelial/endothelial mesenchymal transformation (EMT/EndMT). In addition to this, CAFs have less common cellular precursors such as adipocytes, pericytes, mesothelial cells, and some specific macrophages [38–40].

Phenotypic and functional heterogeneity of CAFs

Classic markers found in CAFs in previous studies include α-smooth muscle actin (α-SMA), vimentin, fibroblast-specific protein 1 (FSP1, also known as S100A4), fibroblast activation protein (FAP), and platelet-derived growth factor receptor-α/β (PDGFRα/β), but none of these markers are specific [41]. Due to the absence of specific markers, the existence of partial tumor-suppressive subpopulations and differences in spatial location, researchers have turned to single-cell sequencing technology to identify CAFs subpopulations with distinct markers and functions.

Currently, researchers have identified four CAF subtypes in several tumors such as breast cancer (BC), pancreatic ductal adenocarcinoma (PDAC), endometrial cancer (EC), intrahepatic cholangiocarcinoma (ICC), and oral squamous cell carcinoma (OSCC). They are inflammatory CAFs (iCAFs), stromal CAFs (mCAFs), vascular CAFs (vCAFs), and antigenic presenting CAFs (apCAFs), of which the most widely recognized are mCAFs and iCAFs. A study by Julia et al. revealed the different origins of the two CAF subtypes. iCAFs and mCAFs in BC originate from the transformation of CD26 + NFs and CD26- NFs respectively. CD26 + NFs promote tumor cell invasion by enhancing matrix metalloproteinase (MMP) activity and recruit monocytes in a CXCL12-dependent manner, thereby contributing to the protumorigenic phenotype of iCAFs [42]. In addition, iCAFs and mCAFs exhibited unique transcriptional profiles by single-cell sequencing. Myofibroblast markers such as α-SMA, PDGFRα/β, COL5A1, podoplanin (POSTN), and Decorin (DCN) were significantly up-regulated in mCAFs compared to the other subtypes, whereas inflammatory factors such as secretory leukocyte protease inhibitor (SLPI), insulin-like growth factors-1 (IGF1), CXCL12, and CXCL1 were up-regulated in iCAFs. In terms of signaling pathway activation, mCAFs were associated with ECM formation and promotion of angiogenesis, while iCAFs were related to activation of pro-tumor invasion metastatic pathways and immunomodulation. In terms of spatial location, mCAFs were often adjacent to tumors and played an important role in matrix remodeling and collagen formation, while iCAFs were often located far from the dense stromal region of tumors and played an important role in immunosuppressive TME formation and tumor metastasis through the interaction of cytokines and cytokine receptors [43, 44]. The diverse phenotypes and functional subgroups of CAFs revealed in single-cell sequencing studies can be seen in Table 1.

After clarifying the phenotypes and functions of different CAF subtypes, it was found that depletion or targeting a particular type of CAF subtype alone could not yield the expected results. Therefore, the focus of research gradually shifted from specific CAF subtypes to biological processes related to CAF subtypes. A Japanese study in 2024 about BC patients identified multiple distinct cell clusters in subpopulations of iCAFs and myCAFs, respectively. They were IL-iCAFs, Detox-iCAFs, IFNγ-iCAFs, Wound myCAFs, TGFβ-myCAFs and ECM-myCAFs. The results of the study showed that myCAFs were associated with elevated TGF-β signaling, but genes regulating TGF-β immunosuppression function were upregulated in IFNγ-iCAF, suggesting an interaction between the subpopulations of myCAFs and iCAFs [45, 46]. Du et al. found that PDPN + CAFs could inhibit NK cell-mediated ADCC in BC tissues, thereby causing tumor resistance to trastuzumab [47]. Cao et al. also found that a kind of lipid-rich CAFs in SETD2-deficient PDAC promoted mitochondrial oxidative phosphorylation by providing lipids, which in turn promoted tumor growth [48]. These findings revealed the complex biological processes of different CAF subpopulations in TME and also opened up new perspectives for subsequent therapies targeting CAF subpopulations.

Effect of Radiation on CAFs

Altered CAF gene expression after radiation

To understand the changes in gene expression experienced by tumor stromal tissue as a result of ionizing radiation, researchers attempted to perform genome-wide studies through microarray gene technology [67–71]. A total of 680 differentially expressed genes were found in the irradiated CAFs sample group (1 × 18 Gy) obtained from NSCLC tissues, of which 127 genes were downregulated and 553 genes were upregulated in transcripts. Data analysis revealed that the expression of genes related to cell cycle regulation and repair, oxidative stress, and apoptosis pathways such as ANAPC2, ACAD10, and BAG3 were upregulated in irradiated CAFs. These findings were further validated by polymerase chain reaction (PCR) and in vitro experiments. Therefore, the authors concluded that ionizing radiation caused severe genotoxic stress in cells, subsequently altered the expression of genes involved in biological processes such as DNA repair, cell proliferation, cell cycle, apoptosis, and the p53 pathway [69]. Similarly, transcriptional upregulation of cell cycle regulators and apoptosis-related genes such as GADD45A and CDKN1A were observed in primary human fibroblasts and fibroblasts from BC patients [70, 71].

Effects of RT on behaviors and functions of CAFs

Limited research findings have delineated the impact of RT on the behavior of CAFs. After exposure to a single dose of 18 Gy radiation, the proliferative, invasive, and migratory capacities of CAFs were assessed. The results

Table 1 The diverse phenotypes and functional subgroups of CAFs revealed in single-cell sequencing studies

Type of cancer	Subtype of CAFs	Spatial position	Function	Markers	Refe-rence
CRC	CAF-A CAF-B	- -	ECM Myofibroblast activation	MMP2, DCN, COL1A2 ACTA2, TAGLN, PDGFA	[49]
BC	vCAFs mCAFs dCAFs cCAFs	Adjacent blood vessel Resident fibroblasts Malignant cells of EMT -	Vascular development and angiogenesis ECM and EMT Tissue development Proliferation of vCAFs	Nidogen-2、PDGFRb PDGFRa、PDGFRb SCRG1、PDGFRb Ki-67	[50]
ICC	vCAFs mCAFs iCAFs apCAFs eCAFs lipofibroblast	Tumor core aggressive part of the tumor nest - - - adjacent tissues	tumorigenesis tumor invasion immunoregulation antigen presentation EMT Lipid metabolism and processing	CD146, IL-6, CCL8 COL5A1, POSTN, DCN IGFl, CXCL1, SLPI CD74, MHC-II KRT19, KRT8, SAA1 APOA2, FABP1/4, FRZB	[51]
LUAD	TAF TCF	Tumor margin Tumor core	Induce EMT in cancer cells Promote cancer cell invasion	α-SMA, FAP low express α-SMA, FSP1	[52]
PDAC	myCAFs iCAFs apCAFs	- - -	ECM Cytokine and cytokine receptor interaction Antigen processing presentation	ACTA2, MYL9 IL6, CXCL12 CD74, MHC-II	[53]
NSCLC	Meflin + CAFs	Fibroinflammatory matrix	Inhibition of ECM and tumor growth	Meflin	[54]
EC	mCAFs iCAFs vCAFs apCAFs	- - - -	ECM Leukocyte migration and chemotaxis MYH11, GJA4, ESAM Muscles contract, tissues migrate immune regulation	PDPN, COL12A1, MMP2 SLPI, IGF1, CD24, CXCL12 CD74, MHC-II	[55]
OSCC	iCAFs apCAFs myCAFs	Residual tumor, tumor bed Residual tumor Residual tumor	immune regulation antigen presentation ECM	CXCL1, CXCL14, IGF1 CD74, MHC-II PDPN, COL1A1	[56]
BLCA	irCAFs	tumor tissue	Promote tumor cell stemness	SLC14A1, WNT5A, IFN	[57]
Pan-cancer	myoCAFs inflaCAFs adiCAFs	- - -	Tumorigenesis, angiogenesis immune regulation EMT	ACTA2 FAP、TGFB1 CFD	[58]
OC	CAF_c1 CAF_c2	Adjacent cancer cell -	immune activation cell proliferation	CCDC80, SFRP2, VCAN RGS5, NOTCH3	[59]
GC	GPC3 (+) CAFs	Deep tumor tissue	Greater developmental potential	Glypican-3	[60]
BC	PDPN + CAFs	Trastuzumab resistant cancer	Inhibition of NK cell-mediated ADCC	TDO2, IDO1	[47]
BC	COL1A1 + CAFs	Adjacent cancer cell	Inhibit immune cell infiltration	COL1A1	[61]
BMC	Collagen I (+) CAFs	-	The formation of type I collagen ECM-mediated brain metastases	COL1A1, COL1A2, PDGFRB	[62]
LC	POSTN CAFs PLA2G2A CAFs	progress after targeted therapy Remission after targeted therapy	Immune regulation, collagen secretion, tumor promotion Signal transduction and immunoactivity, tumor suppression	CTHPC1, COL10A1, POSTN SCARA5, PLA2G2A	[63]
Chordoma	ERS-CAFs	Tumor adjacent tissue	Promote tumorigenesis and progression	HSPA1A/B, CCL2, DNAJB1, HSPA6, HIF1A, BAG3	[64]
NSCLC	myCAFs iCAFs apCAFs	- Brain metastases Bone metastases	Promote tumor angiogenesis Promote invasion and metastasis Activate cancer stem pathways	MMP13, MMP11, ACTA2 APOD, PTGDS, MET-HGF SPP1, MHC II	[65]
PDAC	lipid-laden CAFs	-	Provide lipids, promote tumor growth	ABCA8a	[66]
ICC	LUM + CAFs	Tumor adjacent tissue	Promote tumor proliferation and migration	LGALS1, CCR2, ADAM15, β-integrin	[48]

Abbreviations: *CRC* Colorectal cancer, *LUAD* Lung adenocarcinoma, *NSCLC* Non-Small Cell Lung Cancer, *BLCA* Bladder cancer, *OC* Ovarian cancer, *GC* Gastric carcinoma, *BMC* Brain metastatic carcinoma, *LC* Lung carcinoma, *ADCC* Antibody-dependent cell-mediated cytotoxicity, *ERS* Endoplasmic reticulum stress, *TAF* Tumor-adjacent-fibroblasts, *TCF* Tumor core fibroblasts

demonstrated that the irradiated CAFs entered a state of growth arrest due to the premature induction of cellular senescence, accompanied by a significant reduction in their invasive and migratory capabilities [25]. Subsequently, the researchers further investigated the effects of CAFs exposed to ablative doses of radiation on tumor growth and angiogenesis. The data revealed that the CM from CAFs before and after radiation showed no significant changes in the proliferative and migratory capacities of tumor cells. However, irradiated CAFs downregulated the release of angiogenic factors, thereby reducing the migratory ability of human umbilical vein endothelial cells [26]. Tommelein et al. exposed CAFs isolated from CRC tissue to different RT regimens, which were respectively received clinically relevant fractionation schedules of 1.8 Gy over 1 day, daily fractions of 1.8 Gy each over 5 days with a cumulative dose of 9 Gy or daily fractions of 1.8 Gy each over 10 days with a cumulative dose of 18 Gy. CAF showed minimal morphologic changes, and α-SMA expression and collagen contraction capacity of CAFs were not affected by any radiotherapy regimens. However, cumulative doses of 9 Gy and 18 Gy induced growth delay of CAFs in long-term culture [72].

Radiation has a certain effect on the paracrine function of CAFs, the expression levels of many growth factors, chemokines, and integrins were changed after radiation of CAFs [72–74]. In two studies of NSCLC-associated CAFs, exposure to at an ablative dose (1 × 18 Gy) resulted in downregulation of the release of angiogenic molecules, such as stromal cell-derived factor-1 (SDF-1) and thrombospondin-2 (TSP-2); up-regulation of the release of basic fibroblast growth factor and integrin; and unaffected of expression of hepatocyte growth factor (HGF), IL-6, IL-8, IL-1β and TNF-α. The increased expression of integrin may be responsible for the decreased motility of irradiated CAFs [25, 26]. In addition, ionizing radiation enhanced α-SMA expression for CAFs activation by inducing rapid and sustained activation of TGF-β signaling. The increase in CAFs quantity and the release of bHGF and vascular endothelial growth factor (VEGF) from CAFs following radiation-induced vascular growth subsequently promoted tumor progression [75, 76]. In contrast, Aboussekhra et al. observed inhibition of CAFs secretion and synthesis of various cancer-related cytokines in the breast stroma after high-dose X-ray radiation [77]. The altered secretory function of CAFs after radiation has shown variable results in different studies. And this phenomenon seems to be related to different tumor ligands, radiation doses, and co-culture modes.

Unique radioprotective properties of CAFs

Many observations have shown that CAFs exposed to ionizing radiation, although subjected to sustained DNA damage, can escape cell death to acquire a senescence associated secretory phenotype (SASP) accompanied by reduced proliferative and invasive capacities [25, 78]. Domogauer et al. observed that lung-derived CAFs exhibited greater resistance to the DNA-damaging effects of γ-rays when co-cultured with breast, prostate, lung, or brain cancer cells, whereas this resistance was not observed in CAFs co-cultured with epithelial cells. They then explored the underlying mechanisms of this cancer cell-dependent radioresistance of CAFs and found that increased antioxidant potential and enhanced ability to repair DNA damage contribute to its radioresistance [79], which is consistent with previous findings [80, 81]. In addition to this, radiation also endowed cellular radiotolerance by inducing cytokine expression in the TME. In mouse prostate cancer, it was demonstrated that radiation increased the expression of TGF-β and inhibition of TGF-β enhanced radiation-induced DAN damages [82]. Inhibition of IL-6 was also shown to enhance radiation sensitivity in prostate cancer [83]. Interestingly, a recent study on breast CAFs revealed that low-dose radiation (5 Gy) inhibited the proliferative capacity and activity of CAFs, while high-dose radiation (16 and 50 Gy) promoted their senescence. However, this senescence was not accompanied by the SASP. Instead, it was associated with a reduction in the synthesis/secretion of various cancer-related cytokines [77]. CAFs obtained from diverse tissues have different resistance to radiation and vary in their ability to protect against different types and doses of radiation. Whether RT can induce the SASP in CAFs appears to be controversial and may vary depending on the type of cancer. At present, there are few studies have been conducted on this aspect, and more in-depth explorations of the potential radioresistance mechanism of CAFs are still needed.

Interactions between CAFs and cancer cells

Usually supporting disease progression through nutritional and immune mechanisms, CAFs are strongly associated with all stages of cancer progression, including metastasis [84]. The main mechanism of action is to promote tumorigenesis, invasive phenotype formation, and resistance to therapy through cell–cell contact, paracrine signaling, or ECM [85]. CAFs are inevitably irradiated during RT, so the interactions between CAFs/ irradiated CAFs and tumor cells are crucial for tumor development and tumor responsiveness to therapy. Therefore, we enumerate the inter-crosstalk between CAFs (Table 2) /irradiated CAFs (Table 3) and tumor cells in recent years (Fig. 1).

Table 2 The underlying mechanism of CAFs in regulating tumor development during RT

Effect of CAFs		Fibroblasts source	Underlying mechanisms	Results	Refe-rence
Tumorigenesis and Proliferation		PDAC	Activation of both proliferation-related (Erks) and survival-related (Akt) pathways	Promoted invasion and metastasis	[88]
	CSCC		Reduced the levels of GADD45 and BTG2, two major radiation-induced genes, and inhibited the phosphorylation of p38	Promoted the proliferation and survival	[89]
	LC, MM		IGF1/2, CXCL12, and β-HB produced by CAFs increase the level of ROS in cancer cells after radiation, thereby enhancing PP2A activity and inhibiting mTOR activation	Promote tumor regeneration and proliferation	[90]
	BC, PC		FAK-depletion in CAFs increased chemokine production, which activates PKA via CCR1/CCR2 on cancer cells	Enhanced growth and glycolysis	[91]
Invasion and metastasis	ESAC		CAFs-derived IL-6	activated EMT, migratory capacity, and clonogenicity	[92]
	LUAD		O-glycosylation regulates the CDK4–pRB axis in TAFs and modulates the anticancer properties of CDK4/6 inhibitors	Promoted tumor invasion and EMT	[52]
	Py-Dll1^{wt} tumor; HR + BC		Dll 1 + BC cells recruited CAFs in an IL6-dependent manner, driving Wnt/β-catenin to increase Dll1 + CSC function	Promoted metastasis	[94]
	GC		CAFs-derived SLIT2 increased CTTN expression and functional activity via NEK9	Promoted cytoskeletal reorganization and GC metastasis	[95]
	ESCC		FAP + CAFs transferred exosomal lncRNA AFAP1-AS1 to enhance DNA damage repair in ESCC cells	promoted radioresistance	[93]
ECM remodeling	PDAC		increased Type I collagen synthesis	Promoted the proliferation	[97]
	PDAC		through β1-integrin–FAK signaling	Enhanced radioresistance	[98]
Angiogenesis	BC		SDF-1 secreted by CAFs acted through the CXCR4 receptor expressed by tumor cells	Promoted tumor growth, angiogenesis	[22]
	NSCLC		The level of tumor neovascularization and inflammatory cell infiltration increased	Promoted tumor angiogenesis	[99]
Resistance to radiotherapy	ESCC		CAFs-secreted CXCL1 increased ROS accumulation following radiation and activated of Mek/Erk pathway	Enhanced radioresistance	[107]
	ESCC		CAFs promoted the expression of DNM3OS through PDGFβ/PDGFRβ/FOXO1 signaling pathway	Enhanced radioresistance	[100]
	CRC		CAFs-derived exosomes containing miR-93-5p downregulated FOXA1 and upregulating TGFB3	Enhanced radioresistance	[102]
	CRC		miR-590-3p delivery via exosomes derived from CAFs through the positively regulated CLCA4-dependent PI3K/Akt signaling pathway	Enhanced radioresistance	[103]
	NPC		CAF-secreted IL-8 activated the NF-κB signaling pathway	Enhanced radioresistance	[104]
	PC		HNRNPC-RhoA/ROCK2-YAP/TAZ signaling pathway promotes CAF activation	Enhanced radioresistance	[105]

Table 2 (continued)

Effect of CAFs		Fibroblasts source	Underlying mechanisms	Results	Refe-rence
	BC		CAF-secreted IL-6 activated the STAT3 signaling pathway	Enhanced radioresistance	[108]
	NSCLC		CAFs-secreted midkine regulated DNA damage by promoting the glycolysis, up-regulating, and stabilizing c-Myc through activation of the Wnt/β-catenin signaling pathway	Enhanced radioresistance	[106]
	NSCLC		SMAD3 from CAFs activated the ITGA6/PI3K/Akt pathway	Enhanced radioresistance	[109]

Abbreviations: *MM* Melanoma, *HR* Hormone receptor, *NPC* Nasopharyngeal carcinoma, *ROS* Reactive oxygen species

Table 3 The underlying mechanism of irradiated CAFs in regulating tumor development during RT

Effect of CAFs	Fibroblasts source	radiation dose of CAFs	Underlying mechanisms	Results	Refe-rence
Proliferation and growth	CRC	18 Gy	RT-activated CAFs initiated the paracrine IGF1/IGF1R signaling	Promoted cancer progression	[72]
	NSCLC	1*18; 3*6 Gy	Increased release of bFGF and decreased release of the anti-angiogenic factors thrombospondin-1 and −2 (TSP-1/2)	The volume of xenograft tumors in mice was reduced	[99]
Invasion and metastasis	PC	4 Gy	Irradiated CAFs-derived CXCL12 activated the P38 pathway through CXCR4 signaling	Promoted tumor cell EMT and invasion	[110]
	BC	5/16/50 Gy	The secretion of SDF-1, TGF-β1, IL-8 and IL-6 decreased in a radiation-dependent manner	Radiation inhibits paracrine carcinogenesis, EMT promotion, and stem cell effects of BC CAFs	[77]
	ESCC	2/4/6/8 Gy	CAFs enhanced the expression of HGF	Promoted tumor cell invasion and metastasis	[111]
ECM remodeling	NSCLC	18 Gy	MMP-1 、cell surface integrin was upregulated and MMP-3 was upregulated	Inhibited the proliferation, migration, and invasion of lung CAFs	[25]
Angiogenesis	NSCLC	18 Gy	The levels of angiogenesis factors were down-regulated, and inflammatory cytokines such as IL-6, IL-8, and TNF-α were unchanged	No significant change in tumor proliferation and migration	[26]
Resistance to radiotherapy	BC	6 Gy	CAFs-derived HGF activated the c-Met signaling pathway and radiationed-CAFs further enhanced HGF secretion and c-Met expression in BC cells	Enhanced radioresistance	[73]
	NSCLC	10 Gy	Senescence-like CAFs-derived IL-6 activated the JAK/STAT pathway	Enhanced radioresistance	[112]
	PDAC	5 Gy	CAFs activated by radiation increased iNOS/NO signaling in tumor cells through the NF-κB pathway	Enhanced radioresistance	[74]
	NSCLC	18 Gy	Overexpression of MDM2 led to excessive inactivation of p53	Enhanced radioresistance	[69]

Effects of CAFs on tumor development

CAFs in tumorigenesis and proliferation

CAFs can promote the malignant transformation of non-tumorigenic epithelial cells. This function was first discovered in a mouse model of human prostate cancer. And tumorigenesis and progression of

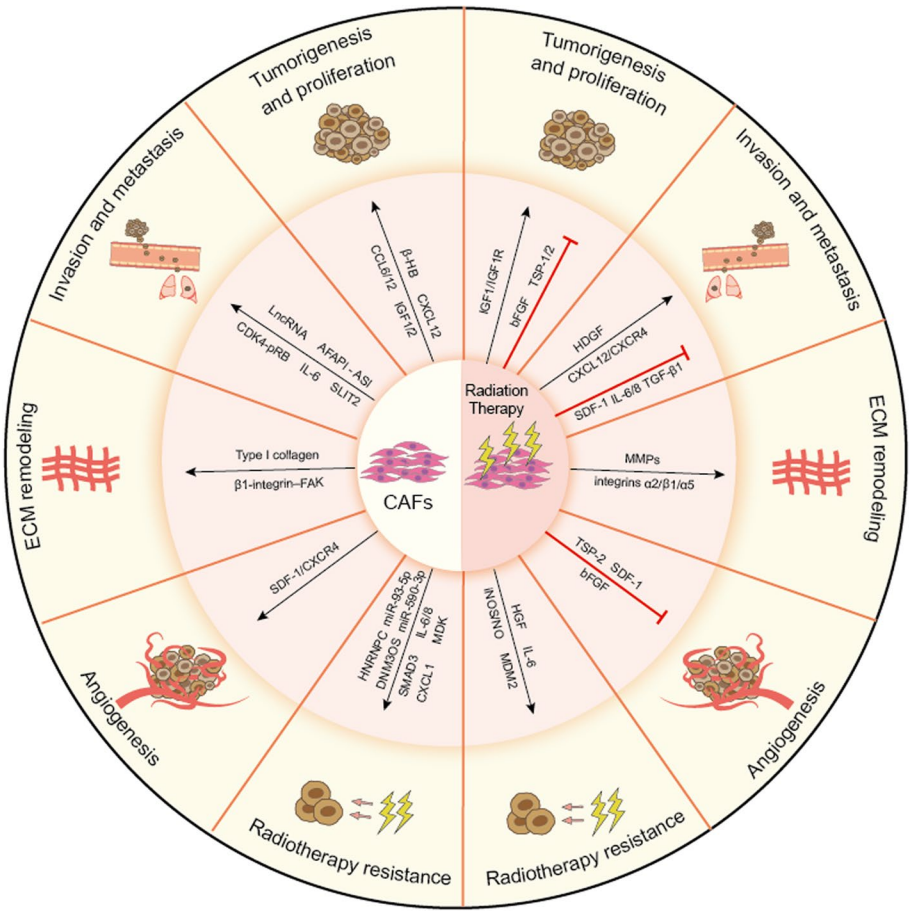

Fig. 1 CAFs or irradiated CAFs are involved in multiple aspects of tumor progression by secreting cytokines or chemokines

prostate epithelial cells were observed when immortalized human prostate epithelial cells were implanted in mice with CAFs instead of NFs [86]. Similarly, inoculation of fibroblasts or human pancreatic stellate cells (HPSCs) overexpressing TGF-β or HGF was associated with oncogenic growth of human mammary epithelia and increased pancreatic tumorigenesis in mouse models [87, 88]. CAFs are not only pro-tumorigenesis but also promote the proliferation and growth of tumors through their paracrine function. Chu et al. observed that co-injecting of Hela cells with CAFs into non-obese diabetic-severe combined immunodeficiency (NOD-SCID) mice resulted in larger tumors than injecting Hela cells alone. And similarly, greater proliferation was also observed in irradiated Hela cells cultured with CAFs-conditional medium (CM). The study also identified that CAFs-secreted IGF-2, insulin-like growth factors binding proteins (IGFBPS), fibroblast growth factor-4 (FGF-4), and epidermal growth factor (EGF) may be associated with increased survival of cancer cells after radiation [89]. Another study showed that CAFs-derived IGF1/2, CXCL12, or the intermediate metabolite β-hydroxybutyrate (β-HB) promoted cancer cell recovery and tumor regrowth afterradiation by inducing cancer cell autophagy. They also conducted a retrospective analysis of lung cancer and hepatocellular carcinoma (HCC). It was found that local/remote recurrence and survival of patients treated with traditional external beam radiotherapy (EBRT) were superior to those treated with image-guided RT. This result supported the hypothesis that the failure of stereotactic body radiation therapy (SBRT) to destroy peripheral CAFs promoteed cancer cell recovery and tumor recurrence after RT [90]. In addition, Demircioglu et al. elucidated the potential mechanism through which CAFs with low focal adhesion kinase (FAK) expression regulate the metabolic process of malignant cells via paracrine signaling. Specifically, FAK-depleted CAFs upregulated the expression of cytokines CCL6 and CCL12, which activated CCR1/CCR2 activity and protein kinase A (PKA) in cancer cells. This activation enhanced glycolysis and

promoted tumor growth of malignant cells in human breast and pancreatic cancer (PC) [91].

CAFs in tumor invasion and metastasis

CAFs are important mediators in shaping the metastasis-promoting TME. It can promote tumor metastasis in situ and metastasis site tumor growth and invasion phenotype by secreting cytokines or chemokines [84]. Studies have shown that CAFs could up-regulate IL-6 in esophageal squamous cell carcinoma (ESCC) to induce an EMT phenotype or promote its invasive phenotype through exosomal transfer of lncRNA actin filament-associated protein 1-antisense RNA 1 (AFAP1-AS1) [92, 93]. A multi-omics study attempted to explore the crosstalk between cancer cells and fibroblasts from different regions (including normal, adjacent, and tumor core) found that TAF from the margins of LUAD was able to induce EMT in cancer cells more robustly than TCF when they were in direct contact with cancer cells [52]. The DII1 + BC subtype, which is associated with cancer cell dissemination and metastasis, showed increased cancer stem cell (CSC) populations and a stem cell phenotype after radiation. And there was a strong positive correlation with the increased number of mCAFs (α-SMA and FAP high expression). The experimental results further demonstrated that DII1 + tumor cells activated and recruited CAFs in TME through the IL6/JAK-STAT3 pathway after RT. In turn the recruited CAFs enhanced the stemness of DII1 + tumor cells by activating Wnt signaling [94]. Another study showed that slit homolog 2 (SLIT2) produced by CAFs promotes gastric cancer metastasis through its binding to roundabout homolog 1 (ROBO1) [95].

CAFs in ECM remodling

ECM components act as scaffolds to facilitate cancer cell motility. Alterations in ECM components such as collagen, MMPs and density during RT promote tumor growth and progression. Meanwhile, CAFs play a critical role in reguating ECM stiffness or degradation [96]. To investigate the functional interactions between PC cells and pancreatic stellate cells (PSCs) in the formation of the connective tissue proliferative response to PC, Armstrong et al. co-cultured PSCs with cancer cell CM. They found that cancer cells not only promote PSCs proliferation, but may also increase PSCs collagen secretion (mainly type I collagen) through TGF-β1. In turn, PSCs promote PC ECM accumulation through secretiing higher levels of MMPs and tissue inhibitors of matrix metalloproteinases (TIMPS). Then PC cells can support cancer cell proliferation and resistance to apoptosis through type I collagen and gain growth and survival advantage [97]. Another study directly co-cultured PC cells and PSCs, revealing that blocking FAK, a downstream enzyme of β1-integrin, blocked PSCs-mediated radio-protection. This suggested that integrins transmit signals from ECM adhesion and solubility factors to cancer cells, thereby modulating the degree to which tumors respond to treatment [98].

CAFs in tumor angiogenesis

CAFs also induce aberrant blood vessel formation in tumors to provide nutrients for tumor growth. Orimo et al. demonstrated that SDF-1 secreted by CAFs from human breast recruited endothelial progenitor cells into cancer, significantly increasing tumor angiogenesis and growth [22]. Grinde et al. co-injected CAFs and lung cancer cells into mice and then characterized the angiogenesis, inflammation, and other biological of transplanted tumors collected at late growth stages by histology and immunohistochemistry. It was found that although co-injection of tumor cells and CAFs had stronger tumor growth dynamics compared to tumor cell injection alone, no variability in the degree of angiogenesis was observed. When the experiment was repeated with the collection of barely invisible early transplanted tumors, the higher level of new angiogenesis was found in tumors collected at an early stage than later stage. It is therefore thought that human CAFs implanted in mice may play a role in the early stage of tumor angiogenesis [99].

CAFs enhanced radioresistance

RT is widely utilized as an effective local therapy in tumor treatment, not only directly killing tumor cells but also significantly impacting various cells within the TME, particularly CAFs. There were many descriptions of CAFs mediating tumor radioresistance during RT, among which the effects on DNA damage repair, cell cycle redistribution, and apoptosis of cancer cells are the central effects.

The long-stranded non-coding RNA DNM3OS highly expressed in cancer cells, can confer significant radioresistance to ESCC by modulating double-stranded DNA damage (DDR). Then CAFs promote DNM3OS expression in a PDGβ /PDGFRβ/FOXO1 signaling pathway-dependent manner [100]. CAFs-derived exosomes promote stemness, EMT, and metastasis of CRC cells [101] and enhance the RT resistance of CRC by reducing apoptosis and enhancing DNA damage repair ability after radiation [102, 103]. In addition, paracrine cytokines secreted by CAFs are also capable of influencing the radiosensitization of cancer cells. Huang et al. reported that CAFs secreted IL-8 to activate the NF-κB pathway in irradiated nasopharyngeal carcinoma (NPC) cells to reduce DNA damage [104].

Besides, alterations in the metabolic environment are also associated with cancer cell radioresistance. Xia et al. reported that elevated levels of heterogeneous nuclear ribonucleoprotein C (HNRNPC) and the small GTPase RhoA in cancer cells promote the formation of a metabolic environment that supports proliferation and confers resistance to RT [105]. In contrast, another study described in more detail the effect of CAFs on DNA damage repair in NSCLC cells and the specific mechanism. After 72 h of incubation with CAF-CM, it was observed that damage repair proteins were significantly upregulated in irradiated NSCLC cells and most cancer cells were blocked in the radiation-resistant S phase. Further studies showed that midkine, an intermediate factor secreted by CAFs, activated the Wnt/β-catenin signaling pathway to up-regulate and stabilize c-Myc and promote the glycolysis in A549 and PC-9 cells [106].

Effect of irradiated CAFs on tumor development

In clinical practice, ionizing radiation is focused only on a finely outlined tumor target volume. However, the cellular and non-cellular components present in TME also affect the efficiency of RT. The series of responses triggered by irradiated CAFs are critical for tumor progression and response to therapy [8]. The effect of RT on CAFs and the tumor-promoting effect of CAFs in the RT environment have been described in detail previously. Irradiated CAFs can also induce ECM remodeling and regulate the metabolic environment through paracrine function to further promote or inhibit tumor invasion or RT resistance.

Irradiated CAFs in tumorigenesis and proliferation

Tommelein et al. discovered that a cumulative dose of 18 Gy RT activated CAFs to secrete IGF1, which subsequently triggered the IGF1R in CRC cells and created a metabolic environment favorable for glutamine metabolism. Moreover, RT-activated CAFs initiated a deleterious paracrine loop via the IGF1/IGF1R/Akt/mTOR pathway, leading to a decrease in the sensitivity of cancer cells to radiation [72]. More remarkably, some of the findings found that RT-activated CAFs may also weaken or disappear its inherent tumor-promoting ability. In an animal model, although increased release of bHGF and decreased secretion of TSP-1/2 were observed in CAFs exposed to fractionated doses (3×6 Gy) of ionizing radiation, and enhanced microvascular density was noted after co-injection with A549 cells, the volume of xenograft tumors ultimately decreased. The authors speculated that this might be related to the inefficient vascular formation and functional development of the vasculature caused by the mixed injection of irradiated CAFs [99].

Irradiated CAFs in tumor invasion and metastasis

Ionizing radiation can also activate CAFs, enhancing or reversing their ability to promote tumor invasion and metastasis. CAFs exposed to 4 Gy of ionizing radiation secreted high levels of CXCL12. Subsequently, the CXCL12-CXCR4 signaling pathway promoted EMT and invasion in PC cells by activating the P38 pathway [110]. Similarly, CAFs exposed to ionizing radiation have also been shown to promote ESCC EMT by upregulating the expression of HGF, which led to increased β-catenin expression and reduced E-cadherin levels in ESCCs [111]. In contrast, Aboussekhra et al. observed that the paracrine cancer-promoting functions of CAFs were suppressed after exposure to different doses (5 Gy, 16 Gy, and 50 Gy) of radiation [77]. Unlike other studies that examined CAFs 12–24 h post-irradiation, this research collected serum-free CM from CAFs cultured for 3 weeks after radiation to treat tumor cells. This difference in timing may be the primary reason for the divergent conclusions, highlighting the critical importance of selecting the appropriate time point for studying the interaction between irradiated CAFs and tumor cells.

Irradiated CAFs in ECM remodeling and tumor angiogenesis

Hellevik et al. discovered that NSCLC CAFs exposed to a single 18 Gy dose of radiation exhibited reduced invasive and migratory capabilities due to ECM remodeling caused by the overexpression of cell surface integrins [25]. Unfortunately, the study did not further explore the ultimate impact of irradiated CAFs on tumor cell development through ECM remodeling. Later, the researchers also investigated the effect of irradiated CAFs on tumor angiogenesis. The results demonstrated that irradiated CAFs exhibited significantly reduced secretion of angiogenic factors and SDF-1 while this did not affect the tumor's angiogenic capacity [26].

Irradiated CAFs enhanced radioresistance

Irradiated CAFs have been validated in multiple tumor types, such as BC, NSCLC, and PDAC, to further enhance the radioresistance of tumor cells [73, 74, 107, 112]. The cytokines secreted by RT-activated CAFs and the key signaling pathways involved are summarized in Table 3.

Interaction between CAFs and immune cells

TME conducive to tumor growth and immunosuppressive properties can be created among tumor cells, immune cells, and CAFs by releasing intercellular plasmids. Previous studies have shown that CAFs can promote the immune escape of tumor cells through interactions with different immune cells such as macrophages, Natural killer cells (NKs), and T cells [113–115]. RT is

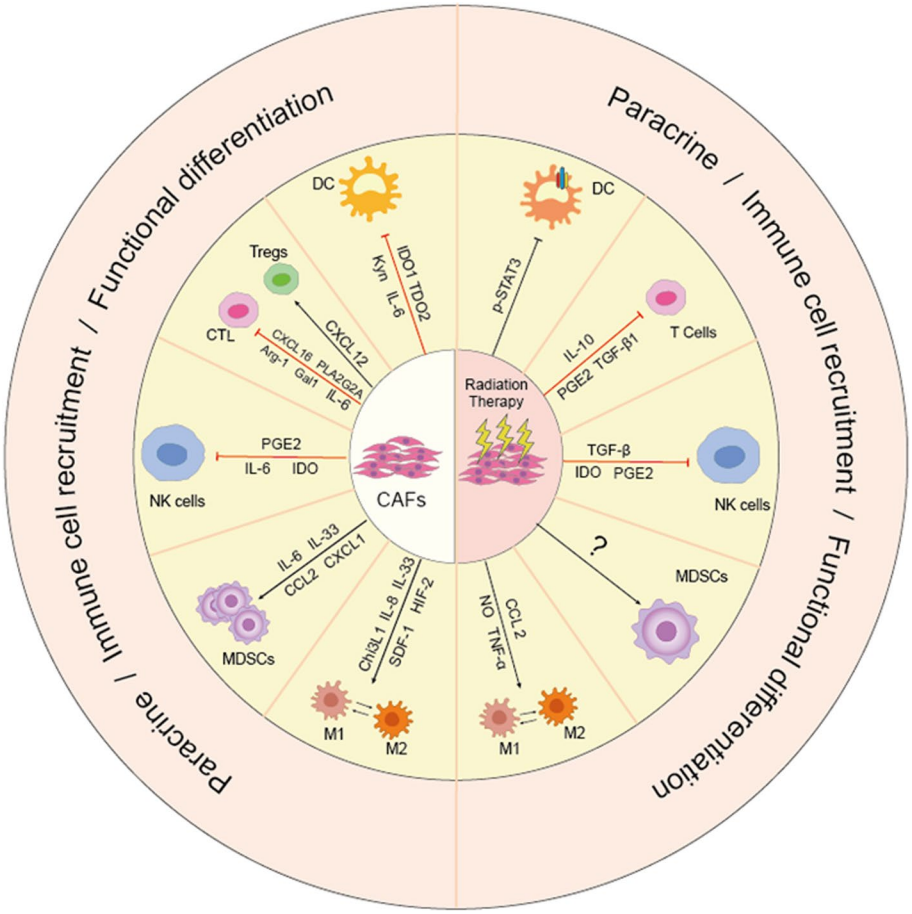

Fig. 2 CAFs or irradiated CAFs regulate the tumor-associated immune microenvironment by secreting cytokines or chemokines

an inherently inflammatory injury. And it is particularly important to understand the effect of crosstalk between CAFs /irradiated CAFs and immune cells on tumor cells in the context of RT (Fig. 2). This will not only provide a better understanding of how tumors are resistant to different treatment modalities but also provide directions for therapeutic strategies that target intercellular communication [116]. We detailed the process of crosstalk between CAFs or irradiated CAFs and immune cells in Table 4 and Table 5, respectively (Fig. 2).

Tumor-associated macrophages (TAMs) recruitment and M2 polarization

Tumor-infiltrating macrophages known as TAMs are classified into two distinct subpopulations: anti-tumorigenic (M1) and tumor-promoting (M2) [117]. The combination of CAFs and M2 macrophage markers jointly predicted disease-free survival (DFS) and overall survival (OS) in patients with CRC, suggesting a tight interaction between the two cell types [118]. Studies have shown that cytokines such as IL-8, IL-33, HIF-2, and SDF-1 secreted by CAFs promote M2 polarization of macrophages and induce their pro-tumorigenic phenotype, which plays an essential role in tumor progression and shaping the tumor immunosuppressive microenvironment [119–123]. Expressions of CD14, CD80, and CD86 in macrophages were upregulated after CAFs-CM culture or co-culture [124]. Until now, some studies have evaluated the effects of RT on macrophages. The results showed that macrophages with low to moderate (≤2 Gy) dose radiation have a reduced migration capacity and exhibit a more anti-inflammatory and M1 phenotype [125–127]. After high-dose radiation (1×25 Gy/4×15 Gy), macrophages expressed higher levels of iNOS, Arg-1, and COX-2 and promoted early tumor growth in vivo [128]. Furthermore, the immunosuppressive effects of irradiated CAFs on macrophages have been also widely concerned. CAFs suppressed the proinflammatory features of M1 macrophages by reducing the production of NO, pro-inflammatory cytokines, expression of migration, and M1 surface markers. However, RT with a single high dose or fractionated regimen (1×18 Gy/3×6 Gy)

Table 4 Regulation of tumor-associated immune microenvironment by CAFs

Immune cell	Fibroblasts source	Underlying mechanisms	Results	Refer-ence
TAMs	OSCC	up-regulated the expression of CD68, CD163, CD200R, and CD206	promoted an immunosuppressive TME	[124]
	PCA	SDF-1 produced by CAF and IL-6 produced by cancer cells promote the differentiation of monocytes into M2-type macrophages	Promote tumor angiogenesis and invasion	[119]
	CRC	CAF-induced M2 polarization through the IL-8/CXCR2 pathway	Promoted the migration of cancer cells	[120]
	LUAC	CAF recruited TAMs and induced M2 polarization by upregulating collagen levels	promoted an immunosuppressive TME	[121]
	PC	Enhanced TAMs recruitment and M2 phenotype activation by IL-33-ST2-NF-κB-MMP9 axis	Promoted cancer metastasis	[122]
	PDAC	CAFs drove macrophage M2 repolarization in a HIF2-dependent paracrine fashion	Weakened the Response of PDAC to Immunotherapy	[123]
	BC and LC	Chi3L1 activated the MAPK and PI3K signaling pathways in tumor cells	promoted an immunosuppressive and growth-promoting TME	[155]
NK	CRC	CAF-induced TAMs inhibited NK cell function	impaired NK cells killing CRC cells	[120]
	MM	Down-regulated NK cell receptors by secreting PGE2	impaired NK cells killing cells	[32]
	HCC	Increased the levels of PGE2 and IDO	impaired NK cells killing cells	[135]
	PDAC	IL-6-induced activation of STAT3	Inhibited NK cell activity and led to PDAC metastasis	[136]
	PDAC	IL-6-induced activation of STAT3	Elimination of cytotoxic effects of NK cells	[134]
MDSC	CRC	Increased the expression of CCL2	promoting resistance to immune checkpoint blockade	[156]
	LSCC	CAF-derived CCL2-induced monocytes to immunoinhibitory MDSCs	promoted an immunosuppressive TME	[157]
	HCC	attracted MDSCs to tumor sites in a CCR2-dependent way	promoted tumor growth and immunosuppressive TME	[139]
	HCC	IL-6 and IL-33 expressed by CAFs mediated hyperactivated 5-LO metabolism in MDSCs	enhanced cancer stemness	[158]
	ESCC	IL-6 secreted by CAFs promoted the generation of M-MDSCs via activating STAT3	promoted MDSC production and cancer drug resistance	[141]
	LC	CAF secretion of CXCL1 and recruitment of neutrophils were inhibited by CSF-1 secreted by cancer cells	Promoted MDSC migration and tumor proliferation	[140]
DCs	HCC	CAF activated DCs through IL-6-mediated STAT3	Impaired T cell proliferation	[144]
	LC	Expression of IDO1 and TDO2 and production of Kyn	Impaired ability to induce naive CD4 + T cell proliferation	[145]
T	HGSOC	CAF attracted T cells by activating the CXCL12/CXCR4 axis	promoted an immunosuppressive TME	[148]
	MM	CAF increased the expression levels of Arg-1, VISTA, and HVEM	Inhibited the killing ability of CD8 + T cells	[149]
	reRCC	CAF up-regulated the expression of Gal1	induced apoptosis of CD8 T cells	[150]
	VFL	Activation of IL-6/JAK2/STAT3 pathway	induced CD8 + T cell apoptosis, and Treg recruitment	[151]
	PDAC	CAF-derived PLA2G2A activated MAPK/Erk and NF-κB signaling pathways	blunted the antitumor activity of CD8 + T cells	[152]
	STS	glyCAF expressed CXCL16 in a GLUT1-dependent manner	impeded cytotoxic T-cell infiltration into the tumor	[153]

Abbreviations: *PCA* Prostate carcinoma, *LSCC* Lung squamous cell carcinoma, *reRCC* Recurrent renal cell carcinoma

did not alter the immunomodulatory characteristics exerted by CAFs on macrophages in vitro [129]. Sheng et al. co-cultured CAF radiated with 8 Gy with M0 macrophages, which showed upregulated expressions of CD206 in M0 macrophages and M2 markers arginase-1 (Arg-1), CCL22 and fibronectin-1 (FN1). Further studies showed that CCL2 secreted by CAFs after high-dose radiation promoted the M2 phenotypic transformation in

Table 5 Regulation of tumor-associated immune microenvironment by irradiated CAFs

Immune cell	Radiation dose of CAF	Fibroblasts source	Underlying mechanisms	Results	Refer-ence
TAMs	8 Gy	CC	CAFs promoted macrophage M2 polarization through the CCL2	Induced Radiosensitivity in CC	[130]
	1*18 Gy/3*6 Gy	NSCLC	reduced the secretion of TNF-α and IL-12 in M1 macrophages	inhibit the pro-inflammatory features of M1-macrophages	[129]
NK	1*18 Gy/3*6 Gy	NSCLC	Immunosuppressive molecules (such as TGF-β、PGE2 和 IDO) secreted by CAF remained unchanged after radiation	Reduced NK cell toxicity	[137]
DCs	1*18 Gy/3*6 Gy	NSCLC	Increased p-STAT3 expression level in DCs	IR curtailed immunosuppressive effects from CAF on DCs	[146]
T	1*18 Gy	NSCLC	Immunosuppressive molecules (such as PGE2, IL-6, IL-10 and TGF-β) secreted by CAF remained unchanged after radiation	Promoted an immunosuppressive TME	[154]

macrophages, thereby inducing radioresistance of cervical cancer (CC) [130].

Inhibition of cytotoxic effects of NKs

NKs are innate lymphocytes with cytotoxic functions that impede tumor growth through immune surveillance without prior immune memory and play a vital role in innate immunity [131]. However, it has been found that low-dose radiation can induce NKs apoptosis and attenuate the cell-killing effect of NKs in a RT environment [132]. Surprisingly, low-dose radiation enhanced the natural cytotoxicity of NKs against tumor cells, implying that there appears to be an optimal dose threshold for radiation-mediated increases in NK cytotoxicity [133]. Previously, it has been demonstrated that CAFs can secrete prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), IL-6, and other cytokines to down-regulate the surface receptors of NKs and inhibit the acquisition of cytolytic granules to inhibit the activity and killing ability of NKs [32, 134–136]. In the co-culture model of CRC, CAFs can also promote the M2 polarization of macrophages through secreting IL-8, synergistically inhibiting the function of NKs [120]. In addition, while irradiated CAFs upregulated the NK-suppressing receptors NKG2A and TIGIT/CD96 and their ligand surface HLA-E and PVR/CD155, this neither ameliorated nor attenuated CAFs-mediated general immunosuppression of NK cell function [137].

MDSCs recruitment and production

MDSCs are mainly categorized as granulocytes/polymorphonuclear cells -MDSCs (PMN-MDSCs) or monocytes -MDSCs (M-MDSCs), with PMN-MDSCs phenotypically and morphologically similar to neutrophils and M-MDSCs similar to monocytes. Immunosuppression is one of the main characteristics of MDSCs, and their main target is T cells [138]. CAFs are involved in the differentiation and recruitment of MDSCs to tumor sites through different signaling pathways. For example, HCC-derived CAFs attracted MDSCs to the tumor site in a CCR2-dependent manner [139]. In human lung cancer, CAFs-derived CM recruited neutrophils and monocytes via CXCL1 and CCL2, respectively, while CAFs polarized monocytes into an MDSCs phenotype that strongly inhibited CD8 + T cell proliferation and IFNγ production [140]. In ESCC, CAFs-derived IL-6 and miR21-rich exosomes synergistically induced monocyte differentiation into M-MDSCs through activating STAT3 [141]. Moreover, Liang et al. reported that the extrinsic mechanism of tumor radioresistance was regulated by host CCR2-M-MDSCs. The use of CCR2 knockout mice or CCR2-depleted antibodies prevented MDSCs from recruitment into the tumor after RT thereby reversing radioresistance [142].

Inhibited proliferation and immunomodulatory function of dendritic cells (DCs)

As specialized antigen-presenting cells, DCs bridge innate and adaptive immunity and regulate the balance between immunity activation and tolerance, playing a pivotal role in tumor immunity. DCs continuously capture dead cells through endocytosis and process proteins for further presentation to naive T cells in peripheral lymphoid organs, where antigen presentation and T cell activation occur [143]. DCs co-cultured with CAFs were induced to differentiate into regulatory DCs and tended to express more immunosuppressive cytokines such as IL-10, TGF-β, and HGF, etc. The mechanism behind this phenomenon was that CAFs induced impaired T cell proliferation by activating DCs secretion of IDO through

IL-6-mediated STAT3 [144]. DCs cultured in lung cancer CAFs-CM showed impaired ability to induce proliferation of naive CD4 + T cells and increased production of immunosuppressive factor IL-10. The expression of IDO1 and TDO2 and the production of Kyn were responsible for CAFs-mediated immunosuppression [145]. Berzaghi et al. investigated the CAFs-mediated immunomodulatory effects on monocyte-derived DCs in different RT settings. They observed that CAFs significantly hindered the differentiation of monocytes into DCs and induced a tolerance phenotype in mature DCs. Fractional moderate-dose radiation (3 × 6 Gy) reversed the CAFs-mediated suppression of DCs function by upregulating p-STAT3 expression in DCs. However, this effect was not observed with single high-dose radiation, indicating that only specific RT regimens can effectively modulate the intrinsic immunosuppressive influence of CAFs on DCs [146].

Regulation of T cells function and infiltration

CAFs regulate the function and infiltration of T cells by secreting a variety of cytokines, changing the ECM, and directly contacting immune cells, thus affecting the immune escape of tumors [147]. Givel et al. identified four subpopulations of CAFs in high-grade serous ovarian cancer (HGSOC) and successfully isolated CXCl12β-accumulated CAF-S1 progenitor cells. Then the results demonstrated that CAF-S1, enriched in tumors, exerted immunosuppressive functions by recruiting regulatory T cells and enhancing their survival, differentiation, and inhibitory activity [148]. MM-derived CAFs-secreted soluble factors, including Arg-1, "V-domain immunoglobulin suppressor of T cell activation (VISTA), and herpesvirus entry mediator (HVEM), significantly downregulated CD69 expression on the surface of activated CD8 + T cells and reduced the production and release of granzyme B. The latter effect may contribute to the suppression of CD8 + T cells cytotoxicity in vitro [149]. Similarly, CAFs also induced apoptosis and inhibited the anti-tumor immune function of CD8 + T cells through different signaling pathways in recurrent RCC, precancerous vocal fold leukoplakia (VFL), and PDAC models [150–152]. Not only that, in immune-rejecting tumors with low response rates to T cell-based therapy, Broz et al. identified a subset of glycolytic-associated CAF (GlyCAF) in a soft-tissue sarcomas (STS) mouse model. GlyCAF relied on GLUT1-dependent expression of CXCL16 to prevent cytotoxic T cells from infiltration into tumor parenchyma, and targeting glycolysis reduced the restricted GlyCAF accumulation at the tumor margins T cells, thereby enhancing T cell infiltration [153]. Notably, human NSCLC CAFs showed potent immunosuppression of T cells, affecting their function and migration rate. And single high-dose radiation (1 × 18 Gy) did not affect the immunosuppressive function of CAFs [154]. This suggested that we need to pay further attention to RT doses when using RT as an immunoadjuvant.

Therapeutics strategies targeting CAFs

Given that CAFs are key players in TME, the field of targeting CAFs as a tumor therapeutic target has been explored with the promise of introducing new therapeutic avenues for tumor patients. The field is centered around the following four main aspects: CAF depletion, "normalization" of activated CAF phenotype, inhibition of CAF-secreted cytokines, and transitions between CAF subtypes [159, 160].

CAF depletion, which involves reducing the population of CAFs in the tumor, represents the most direct therapeutic strategy. However, the application of this method is limited by the absence of specific target markers for CAFs. Murakami et al. demonstrated that over 85% of docetaxel-coupled nanoparticles were successfully delivered to α-SMA + stroma in situ breast tumor models of 4T1 and MDA-MB-231. Approximately 50% of the tumor stroma was depleted within 16 h post-injection, and α-SMA + stromal clusters became nearly undetectable within one week [161]. FAP lay more emphasis on preclinical therapy and research. The FAPα-activated prodrug Z-GP-DAVLBH was shown to promote the apoptosis of FAPα hepatic stellate cells, inhibiting angiogenesis, and overcome bevacizumab resistance [162]. In recent years, FAP-targeted near-infrared photoimmunotherapeutic strategies have provided a promising strategy for selectively targeting FAP + CAF tumors, which can inhibit tumor growth and improve tumor immunosuppression by significantly reducing CAFs in TME [163–165]. Another promising therapeutic strategy involves the "normalization" of the CAFs phenotype, which aims to reprogram CAFs. For instance, inhibition of TGF-β signaling, a key pathway responsible for CAF activation, represents a potential approach to achieve this goal. In a TME 3D cell culture model of PDAC, inhibition of TGFβ/ROCK2 signaling in PSC cells normalized ECM tissue and improved its permeability to various macromolecules [166]. Perez-Penco et al. also developed a TGF-β-based immunomodulatory vaccine that not only reduced the percentage of CAFs and TAMs in tumors but also turned CAFs away from myofibroblast-like phenotypes. However, the mechanism of action was still unclear [167]. Targeting cytokines secreted by CAFs and their downstream signaling is also a means of interfering with the crosstalk between CAFs and cancer cells or immune cells. For example, Imatinib or liptinib (tyrosine kinase inhibitors) blocked the PDGF receptor α and β signaling in CAFs to inhibit the growth of CAFs and FGFR-expressing cancer cells. But the potential benefits

of targeting PDGFR need to be weighed against adverse effects in normal tissues [168, 169]. The PD-L1&CXCR4 bi-specific nanoantibodies developed by Li et al. reduced angiogenesis and EMT processes in a PDAC mouse model and altered the immune landscape by promoting CD8 + T cell infiltration [170]. As research in the field of CAFs heterogeneity intensifies, the transformation between CAFs subpopulations has also emerged as a promising therapeutic strategy. Giulia Biffi et al. found that IL1 induced LIF expression and downstream JAK/STAT activation to generate iCAFs. This effect demonstrated that TGF-β antagonizes this process by down-regulating IL1R1 expression and promoting differentiation into mCAF. Thus, the targeting of iCAF populations can be achieved by neutralizing leukemia inhibitory factor (LIF) or IL1R antagonists in vivo [43]. However, the breadth of CAF isoforms and functions presents a challenge to the field. And functional and nomenclatural harmonization of CAF isoforms in different tumor species is necessary.

Perspectives and conclusion

In this review, we have provided a detailed overview of the current understanding of CAFs origin and heterogeneity, as well as the latest advancements in the biological behavior of CAFs influenced by RT. Additionally, we have summarized the profound impact of CAFs on the cellular and function of the TME in the context of RT, emphasizing their critical role in multiple hallmarks of cancer. However, given the complex interplay among CAFs, tumor cells, and immune cells, and the incomplete understanding of the underlying mechanisms, developing effective therapeutic strategies remains a significant challenge.

Firstly, therapeutic strategies targeting CAFs require reliable markers to distinguish different subtypes and their association with treatment responses. With the advancement of single-cell sequencing technologies, it has been recognized that CAF populations are multifunctional. Different spatial locations, tumor ligands, and complex cellular origins endow various CAF subtypes with distinct markers and functions (Table 1). However, the intricate heterogeneity of CAFs has not diminished the enthusiasm for targeting them. Researchers have begun to explore how to target specific CAF subtypes in treatment-resistant tissues and the dynamic biological processes between different CAF subtypes [45, 47, 63]. In addition, the molecular mechanisms that drive the formation of different subtypes of CAFs also represent a highly promising areas of research.

Secondly, RT can influence the phenotype and function of CAFs. And this is related to different doses and radiation regimens. Most studies have shown that radiation has negative effects on CAFs, such as growth arrest and decreased invasive ability while it can further stimulate its SASP phenotype and promote tumor growth. However, some studies suggested that RT could normalize the activation characteristics of CAFs and make them anti-tumor growth [77]. This phenomenon appears to be related to variations in radiation dose and frequency. Notably, the majority of studies collected CM from CAFs 12–24 h post-irradiation to treat tumor cells, which may not adequately capture the potential long-term effects of RT on CAFs. Additionally, whether RT-activated CAFs can unify different subtypes and their impact on subsequent treatment cycles warrants further investigation.

Thirdly, there were currently few studies on the role of irradiated CAFs in regulating tumor growth and antitumor therapy in vivo. Meng et al. found that targeting radiation-induced senescent-like CAFs and inducing their apoptosis can also enhance the radiosensitivity of NSCLC and alleviate radiation-induced pulmonary fibrosis in vivo [112]. However, there have also been reported that human CAFs became untraceable two weeks after implantation at the transplant site. And a reduction in the number of implanted CAFs was observed in early-stage tumors collected from the co-injection group with irradiated CAFs [99]. This suggested that the attenuation of the tumorigenic effect of irradiated CAFs may be attributed to the reduction in the number of CAFs promoting tumorigenesis due to the high-dose radiation or the radiation-induced phenotypic changes. In this case, exploring the tumor regulatory role and therapeutic effect of irradiated CAFs in vivo will be more challenging. Moreover, it should be noted that the clinical relevance of the existing preclinical study designs was not very strong because clinical RT protocols never radiated the stroma alone but both the stroma and the tumor simultaneously within a safety margin [171]. Therefore, future preclinical studies can adopt a more clinical setting, such as co-injection of CAFs and tumor cells after simultaneous irradiation. When implementing the therapeutic strategy targeting irradiated CAFs, attention should be paid to the treatment efficacy and corresponding side effects of RT dose and frequency.

Furthermore, the crosstalk between CAFs and other stromal cells in the context of radiation remains largely unknown. The immunomodulatory characteristics of CAFs on tumors were also influenced by the fractionated and cumulative doses of RT, suggesting that different RT regimens need to be carefully considered when combining RT with immunotherapy. The impact of RT-activated CAFs on tumor radiosensitivity through the modulation of the immune microenvironment requires further investigation.

Collectively, CAFs have been shown to be involved in important decisions in tumorigenesis and progression, metastasis, and response to therapy. CAFs can still support tumor growth and influence the tumor immune microenvironment in the context of tumor RT. The mutual crosstalk between CAFs and tumor /immune cells after radiation has gradually received more attention. Preclinical studies aimed at targeting CAFs to inhibit tumor growth and reverse the immunosuppressive microenvironment hold significant promise for offering new therapeutic avenues for cancer patients. Finally, it should be noted that there are some limitations to our study. The heterogeneity in experimental designs and methodologies across the included studies may limit the generalizability of the conclusions drawn in this review. Conclusions on the effects of irradiated CAFs on tumor progression and response to treatment based on limited evidence, requiring further validation. These effects primarily rely on preclinical studies, and the applicability of these findings to human clinical settings remains to be validated. Some key questions such as the complex biological processes involved in different subgroups of CAFs and the different mechanisms of action of RT-activated CAFs in TME remain unanswered. Future research should focus on precisely targeting specific CAF subpopulations and their biological processes to improve radiotherapy efficacy without triggering adverse immune responses.

Abbreviations

Abbreviations

TME	Tumor microenvironment
CAFs	Cancer-associated fibroblasts
ECM	Extracellular matrix
CTL	Cytotoxic T lymphocytes
MDSCs	Myeloid-derived suppressor cells
EMT	Epithelial mesenchymal transformation
EndMT	Endothelial mesenchymal transformation
α-SMA	α-Smooth muscle actin
FSP1	Fibroblast-specific protein 1
FAP	Fibroblast activation protein
PDGFRα/β	Platelet-derived growth factor receptor-α/β
BC	Breast cancer
PDAC	Pancreatic ductal adenocarcinoma
EC	Endometrial cancer
ICC	Intrahepatic cholangiocarcinoma
OSCC	Oral squamous cell carcinoma
iCAFs	Inflammatory CAFs
mCAFs	Stromal CAFs
vCAFs	Vascular CAFs
apCAFs	Antigenic presenting CAFs
NFs	Normal fibroblasts
MMP	Matrix metalloproteinase
POSTN	Podoplanin
DCN	Decorin
SLPI	Secretory leukocyte protease inhibitor
IGF-1	Insulin-like growth factors-1
CRC	Colorectal cancer
LUAD	Lung adenocarcinoma
NSCLC	Non-Small Cell Lung Cancer
BLCA	Bladder cancer
OC	Ovarian cancer
GC	Gastric carcinoma
BMC	Brain metastatic carcinoma
LC	Lung carcinoma
ADCC	Antibody-dependent cell-mediated cytotoxicity
ERS	Endoplasmic reticulum stress
TAF	Tumor-adjacent-fibroblasts
TCF	Tumor core fibroblasts
PCR	Polymerase chain reaction
SDF-1	Stromal cell-derived factor-1
TSP-2	Thrombospondin-2
HGF	Hepatocyte growth factor
VEGF	Vascular endothelial growth factor
HPSCs	Human pancreatic stellate cells
NOD-SCID	Non-obese diabetic-severe combined immunodeficiency
CM	Conditional medium
IGFBPS	Insulin-like growth factors binding proteins
FGF-4	Fibroblast growth factor-4
EGF	Epidermal growth factor
β-HB	β-Hydroxybutyrate
EBRT	External beam radiotherapy
SBRT	Stereotactic body radiation therapy
FAK	Focal adhesion kinase
PKA	Protein kinase A
ESCC	Esophageal squamous cell carcinoma
AFAP1-AS1	Actin filament-associated protein 1-antisense RNA 1
CSC	Cancer stem cell
SLIT2	Slit homolog 2
ROBO1	Roundabout homolog 1
PSCs	Pancreatic stellate cells
TIMPS	Tissue inhibitors of matrix metalloproteinases
RT	Radiation therapy
DDR	Double-stranded DNA damage
NPC	Nasopharyngeal carcinoma
MM	Melanoma
HR	Hormone receptor
PC	Pancreatic cancer
ROS	Reactive oxygen species
SASP	Senescence associated secretory phenotype
NKs	Natural killer cells
TAMs	Tumor-associated macrophage
DFS	Disease-free survival
OS	Overall survival
Arg-1	Arginase-1
FN1	Fibronectin-1
PGE2	Prostaglandin E2
IDO	Indoleamine 2,3-dioxygenase
PMN-MDSCs	Polymorphonuclear cells -MDSCs
M-MDSCs	Monocytes -MDSCs
DCs	Dendritic cells
GSOC	High-grade serous ovarian cancer
VISTA	V-domain immunoglobulin suppressor of T cell activation
HVEM	Herpesvirus entry mediator
VFL	Vocal fold leukoplakia
GlyCAF	Glycolytic-associated CAF
STS	Soft-tissue sarcomas
PCA	Prostate carcinoma
LSCC	Lung squamous cell carcinoma
HCC	Hepatocellular carcinoma
reRCC	Recurrent renal cell carcinoma
CC	Cervical cancer
LIF	Leukemia inhibitory factor

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Authors' contributions
H.Y., C.W. and L.Z. made substantial contributions to conception and determined the final version, D.L. and H.W. collected literatures, W.C. and Y.K.

drawn the pictures, C.Y. and R.Z. drawn the tables, L.Z. and W.C. drafted the manuscript, Y.K. and X.H. revised it critically for important intellectual content. All authors reviewed the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication
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