Radiotherapy and cytokines: A systems view of immunotherapy and toxicity (Review)

SIYUAN ZHOU[1], YURONG JIANG[2], JIXU FAN[1], MINJIE GUO[1], YI WEN[1] and CHUNHUA DAI[1]

[1]Department of Radiation Oncology, Cancer Institute of Jiangsu University, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu 212001, P.R. China; [2]Department of Nuclear Medicine, The First People's Hospital of Lianyungang, Lianyungang, Jiangsu 222000, P.R. China

Received September 5, 2025; Accepted February 10, 2026

DOI: 10.3892/ijmm.2026.5848

Abstract. Radiotherapy (RT) is increasingly recognized as a system-level immunomodulator capable of reshaping cytokine networks across spatial, temporal and dosimetric dimensions. This review synthesizes existing evidence on RT parameters, key signaling axes, major effector cells, organ-specific contexts and clinical translation. It describes how the cyclic GMP-AMP synthase/stimulator of interferon genes (STING)/IFN-I, NF-κB and TGF-β pathways coordinate immune activation and immune suppression after irradiation. It then summarizes macrophage-centered regulatory circuits and chemokine axes, including C-C motif chemokine ligand (CCL)2/CCR2 and CCL22/CCR4 that govern T-cell trafficking and functional states. A map of organ-specific cytokine programs that link therapeutic benefit and toxicity in the brain, lung, gastrointestinal tract, oral mucosa and liver is then provided, and actionable targets within inflammasome-associated pyroptosis and fibrogenic cascades are highlighted. RT technical parameters, including fractionation, treatment volume, stereotactic body RT, Fast Linear Accelerator-based Scanning Hybrid ultra-high dose-rate delivery and proton therapy can differentially shape cytokine dynamics and modify the therapeutic window. The DNA damage response network with poly (ADP-ribose) polymerase (PARP)1 as a central node represents a second hub that interfaces with antigen presentation and IFN signaling, supporting rational combinations with PARP inhibitors and immune checkpoint blockade. Finally, a translational algorithm with three pillars is proposed. The first pillar uses IFN-related gene signatures and circulating cytokine profiles to stratify tumors by baseline IFN activity. The second pillar aligns RT timing with endogenous STING or IFN pulses and incorporates CCR2, CCR4 or colony stimulating factor 1 receptor blockade to counter myeloid cell-mediated immunosuppression. The third pillar co-manages treatment-related toxicities by targeting the NLR family pyrin domain containing 3/gasdermin D axis or by using fibrosis-modulating interventions. Furthermore, ongoing clinical trials of cytokine-directed agents combined with RT are summarized. This framework positions cytokines as measurable and modifiable variables for individualizing combined RT and immunotherapy.

Correspondence to: Dr Chunhua Dai, Department of Radiation Oncology, Cancer Institute of Jiangsu University, Affiliated Hospital of Jiangsu University, 438 Jiefang Road, Jingkou, Zhenjiang, Jiangsu 212001, P.R. China
E-mail: daichunhua8@163.com

Abbreviations: RT, radiotherapy; TME, tumor microenvironment; TAM, tumor-associated macrophage; DC, dendritic cell; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; CAF, cancer-associated fibroblast; IFN-I, type I interferon; IFNAR, type I IFN receptor; TNF, tumor necrosis factor; IL, interleukin; TGF-β, transforming growth factor β; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; CCR, C-C chemokine receptor; ROS, reactive oxygen species; dsDNA, double-stranded DNA; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; NF-κB, nuclear factor κB; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; DDR, DNA damage response; TLR, Toll-like receptor; RILD, radiation-induced liver disease

Key words: radiotherapy, cytokines, immunotherapy, tumor microenvironment

Contents

1. Introduction

Despite ongoing improvements in approaches to cancer detection and treatment, cancer continues to pose a major

public health burden worldwide. For advanced malignancies, comprehensive treatment strategies commonly include surgical resection, chemotherapy, radiotherapy (RT) and combinations of these modalities. As a cornerstone of oncologic treatment (1), RT has historically been effective for managing advanced tumors (2-4). Approximately 50 to 60% of patients with cancer receive RT for primary or metastatic lesions, either as a standalone modality or in combination with surgery and chemotherapy (5,6).

RT encompasses a broad range of regimens that can be classified by fractionation, including conventional, hypofractionation and hyperfractionation, and by delivery technique, including three-dimensional (3D) conformal radiotherapy, intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT). The use of stereotactic RT has expanded rapidly because it can deliver ablative doses to the target with high precision, while limiting exposure of adjacent normal tissues (7,8). Ionizing radiation directly damages biomolecules such as DNA and indirectly generates reactive oxygen species (ROS) via water radiolysis, thereby triggering oxidative stress (9-11). This process results in DNA lesions, such as double-strand breaks, and induces multiple forms of cell death, including apoptosis, autophagy and necrosis, ultimately eliminating cancer cells (12). The selection of definitive or adjuvant RT depends on factors including tumor radiosensitivity. Indications have broadened with high-precision fractionated techniques such as stereotactic RT. For example, current guidelines recommend stereotactic approaches in selected hepatocellular carcinoma and in oligometastatic disease (8). However, RT efficacy is constrained by multiple factors, among which the tumor microenvironment (TME) is a key determinant.

The TME refers to the complex ecosystem surrounding malignant cells, including immune cells, blood vessels, extracellular matrix components and soluble mediators such as cytokines. These components influence tumor evolution and treatment responsiveness, creating a permissive niche that supports cancer cell survival and proliferation (13,14). Cytokines are key mediators through which immune cells coordinate immune responses, and major classes include interleukins, interferons, members of the TNF superfamily, chemokines and growth factors (15-19). More than 100 cytokines have been identified, and their signaling cascades and biological functions have been characterized in detail (16,20-26). Cytokines act through autocrine, paracrine and endocrine modes and influence diverse cell populations in the TME, thereby shaping clinical outcomes in cancer (27). Accumulating evidence supports the therapeutic value of cytokine administration and of agents that block cytokine signaling. For instance, granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes antitumor immunity via dendritic cell activation and has been used in approaches including GM-CSF gene-transduced tumor cell vaccines (28-31), sipuleucel-T (32) and the oncolytic virotherapy Talimogene laherparepvec (33). In addition, neutralizing antibodies and small molecule inhibitors directed against cytokines or their receptors have demonstrated activity in cancer and in immune-mediated diseases (34). Recent translational studies have increasingly focused on integrating RT with cytokine-directed interventions. For example, the colony stimulating factor 1 receptor (CSF1R) inhibitor PLX3397 combined with RT antagonizes CSF1R signaling and can deplete irradiation-recruited M2-type tumor-associated macrophages (TAMs), thereby mitigating RT-associated immunosuppression (35-37). Conversely, RT combined with G-CSF or GM-CSF can enhance neutrophil-mediated antitumor functions by increasing ROS generation and promoting cytotoxic T-cell activation, which can improve local tumor control and induce abscopal responses (38). In addition, a mitochondria-targeted radionuclide, ^{223}Ra-TPP, has been engineered to trigger mitochondrial DNA damage and engage the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING)/IL-1β axis, thereby amplifying systemic immunity (39). These findings indicate that defining key cytokine networks within the TME is important for the rational design of immunotherapy strategies.

Tumor cells evade immune surveillance by establishing an immunosuppressive microenvironment, a hallmark of cancer. This state is maintained by immunosuppressive cells such as TAMs and regulatory T (Treg) cells together with specific cytokines (40,41). RT exerts complex and frequently bidirectional effects on the TME. On the one hand, RT can stimulate antitumor immunity and can function as an *in situ* vaccination approach. Irradiation triggers immune-activating events, including damage-associated molecular pattern release, pro-inflammatory cytokine production and engagement of the cGAS/STING axis (42). Radiation-induced immunogenic cell death recruits immune cells and promotes dendritic cell antigen presentation through damage-associated molecular patterns and activation of the cGAS-STING pathway and pattern recognition receptors, ultimately activating $CD8^+$ T cells. Higher intratumoral $CD8^+$ T-cell density is associated with favorable outcomes after RT (40,43-48). RT can also reprogram neutrophils toward an antitumor phenotype. These RT-activated neutrophils produce increased ROS, directly kill tumor cells and secrete pro-inflammatory factors such as TNF-α and interferon (IFN)-γ to promote systemic immunity (38). Administration of G-CSF further increases the number of RT-induced antitumor neutrophils and enhances ROS production, accompanied by upregulation of the antitumor N1 marker ICAM-1 (38,49). On the other hand, RT can induce immunosuppression. For example, irradiation-induced increases in ROS and hypoxia-inducible factor (HIF)-1α can promote the release of TGF-β and C-X-C motif chemokine ligand (CXCL)12, driving the expansion of Treg cells, myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs), enhancing M2 polarization and increasing immunosuppressive cytokine production. In parallel, immune checkpoint pathways, including programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte associated protein (CTLA)-4 can be upregulated, further constraining antitumor immune responses (50-53). RT can also promote tumor cell secretion of M-CSF via the NF-κB-p65 pathway, inducing TAM polarization toward an M2 phenotype and increasing secretion of IL-10 and Arginase 1 (54). Furthermore, irradiated tumor cells may release exosomes enriched in microRNA (miR)-21 that are transferred to TAMs via the CCL2 and CCL3 axis, contributing to an immunosuppressive milieu (35). This remodeling may partially explain why, in locally advanced non-small cell lung cancer, adding

programmed cell death ligand (PD-L1) blockade to standard chemoRT improves outcomes, while >50% of patients later develop progressive disease (55).

Traditional RT research has largely focused on direct cytotoxic effects, with less emphasis on how RT regulates the tumor immune microenvironment and systemic immunity. Beyond inducing lethal DNA damage, RT promotes intercellular communication by generating mediators such as ROS. ROS can function as ligand-like cues that activate cell-surface receptors, thereby initiating apoptosis or senescence in a stress-dependent manner (56), promoting proliferation (12,57), and orchestrating immune signaling through the induction of pro-inflammatory cytokines, including IL-1 and TNF (40). Numerous preclinical studies have established that host immune competence is a key determinant of RT efficacy (58-60). These observations support a conceptual shift in which RT is viewed not only as a cytotoxic modality but also as a driver of cytokine network remodeling within the TME. Ionizing radiation can influence therapeutic success by initiating immune signaling cascades, positioning RT as a core component of radioimmunotherapy (61).

Different RT modalities can regulate cytokine programs in distinct ways. For example, ultra-high dose-rate Fast Linear Accelerator-based Scanning Hybrid (FLASH) RT reduces the release of profibrotic factors such as TGF-β and IL-1β, thereby alleviating radiation-induced lung injury, while promoting $CD4^+$ T-helper-cell secretion of tissue-reparative cytokines, including IL-10 and IL-22 (62,63). By contrast, proton therapy leverages the Bragg peak to better spare circulating lymphocytes and, when combined with immunotherapy, increases the frequency of intratumoral IFN-γ-positive T cells, while suppressing TGF-β signaling (64). These advances provide a rationale for RT selection and customization in immunotherapy-compatible treatment designs.

Building on this background, the present study proposes a multi-layered framework integrating five dimensions: RT parameters, key signaling axes, effector cells, organ-specific contexts and clinical translation. First, the dynamic roles of major cytokine families in the post-irradiation tumor immune microenvironment were summarized, including IFN-I/III, chemokines and key mediators, such as IL-1, IL-6, IL-10 and TGF-β. The focus is on antagonistic and cooperative networks that balance immune activation and immunosuppression. Second, focusing on macrophages as a key effector cell population, their hub function in RT responses through CSF1R and CCR2 signaling and downstream metabolic reprogramming were examined, and mechanisms of polarization control and paracrine circuits were summarized. Third, the analysis was extended to organ-specific radiation injury by summarizing tissue-characteristic cytokine signatures and candidate interventional targets. Glial-cell activation mediated by IL-1β, IL-6 and TNF-α in radiation-induced brain injury (RBI) was analyzed. The review then delineated the development of pulmonary radiation fibrosis dominated by TGF-β and IL-13. Mucosal barrier dysfunction linked to IL-33 and TSLP in gastrointestinal injury was then discussed. Subsequently, the roles of IL-1 and TNF in the inflammatory cascade of oral mucositis were summarized. The coupling between IL-6/STAT3 axis-driven regenerative repair and TGF-β-mediated fibrosis in liver injury was also described. Finally, from a translational perspective, key parameters in combined RT and immunotherapy strategies were evaluated, including fractionation selection, immunotherapy sequencing, candidate synergistic dose windows and predictive biomarkers. This synthesis is intended to support individualized evidence-based integration of RT with immunotherapy (Fig. 1).

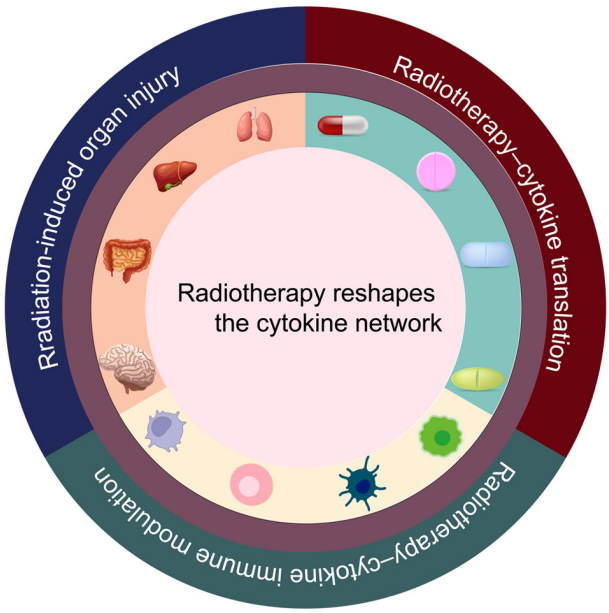

Figure 1. Radiotherapy rewires cytokine networks across antitumor immunity, normal-tissue injury and clinical translation.

2. IFNs

IFN-I represents the largest IFN family and includes IFN-α, IFN-β, IFN-ε and IFN-ω, which signal through the type I IFN receptor (IFNAR) (65). Burnette *et al* (66) showed that RT-mediated tumor control is lost in IFNAR-deficient mice, indicating that host IFN-I signaling is required for RT-induced antitumor immunity. The magnitude and duration of IFN-I signaling can influence RT efficacy (66,67). IFN-I pathways can therefore exert both promotive and inhibitory effects on RT responses through immune mechanisms.

Augmenting local IFN-I signaling in the TME can counteract immunosuppression and promote antitumor immunity. Irradiation can induce tumor-infiltrating myeloid cells to produce IFN-α and IFN-β through autocrine signaling. These IFN-I signals propagate within the hematopoietic compartment and enable tumor-infiltrating dendritic cells to cross-prime $CD8^+$ T cells, supporting adaptive immune attack on the tumor (66). This response is coupled to a cytosolic DNA sensing cascade involving cGAS, STING and IFN regulatory factor 3 (IRF3) (67). In this cascade, cGAS functions as a cytosolic DNA sensor that allows dendritic cells to detect DNA derived from irradiated tumors and represents a key node through which RT initiates antitumor immunity (68). Ionizing radiation also induces DNA strand breaks and micronuclei formation, and micronuclear DNA can activate STING and TANK-binding kinase 1 (TBK1), thereby stimulating IFN production (69,70). The resulting IFN release promotes dendritic cell maturation and major histocompatibility complex class I (MHC-I)

upregulation, enhances tumor antigen cross-presentation and elicits antigen-specific cytotoxic T-lymphocyte responses that mediate antitumor efficacy (66,71,72).

Poly (ADP-ribose) polymerase (PARP) inhibition can lead to cytosolic double stranded DNA accumulation, engage the cGAS/STING/TBK1/IRF3 axis and induce IFN-I production and associated immune programs (67,73). In triple-negative breast cancer models, olaparib activates cGAS-STING signaling and drives mediator release that activates dendritic cells, resulting in increased $CD8^+$ T-cell infiltration and activation (74). These findings suggest that PARP inhibitors can cooperate with RT to engage innate and adaptive immunity through a double-stranded DNA-driven cGAS/STING/IRF3/IFN-I signaling pathway. Activation of the cGAS-STING pathway is often accompanied by PD-L1 upregulation, which has been linked to IFN-I activity (75,76). Accordingly, STING agonists have been proposed as candidate sensitizers to PD-1 or PD-L1 checkpoint blockade (77). Beyond IRF3, STING can also engage IκB kinase and NF-κB-inducing kinase to activate NF-κB, supporting antitumor effects across tumor initiation, progression and metastasis (77-80).

IFN-I signaling is also constrained by negative feedback circuits. Irradiation-induced STING and IFN-I signaling in dendritic cells can activate STAT2 and increase expression of the m6A reader YTH domain-containing family protein 1 (YTHDF1). YTHDF1 promotes translation of cathepsin A and cathepsin B mRNAs, increases lysosomal protease abundance and accelerates lysosomal STING degradation, thereby reducing IFN-I production and limiting dendritic cell antitumor activity (81). In addition, neoadjuvant RT studies in rectal cancer have identified an inflammatory CAF subset characterized by high IRF1 expression. This subset is polarized by IFN-γ signaling and recruits T cells and dendritic cells through secretion of CCL4 and CCL5, thereby augmenting antitumor immunity (82).

By contrast, intratumoral IFN-I activation has been associated with unfavorable outcomes and resistance to several treatment modalities including RT (83-86). In settings combining RT with CTLA-4 or PD-L1 checkpoint blockade, IFN signaling can contribute to treatment resistance (87). Chen *et al* (88) reported that genetic ablation of Ifnar1 enhances $CD8^+$ T cell-dependent antitumor responses after RT, and they identified serine protease inhibitor b9 as a critical factor that is reduced in Ifnar1-deficient tumor cells.

Collectively, IFN-I has a dual role in RT responses (Fig. 2). IFN-I can enhance antitumor immunity by activating dendritic cells and promoting $CD8^+$ T-cell cross-priming through the cGAS/STING/IRF3 pathway. However, sustained or excessive IFN-I activity may increase PD-L1 expression, accelerate YTHDF1-dependent STING turnover and activate additional tolerance programs that ultimately constrain effector T-cell function.

3. Chemokine family

CC chemokines comprise a chemokine subfamily defined by an N-terminal C-C motif (89). CCL2, also known as monocyte chemoattractant protein 1 (MCP-1), can bind multiple receptors, and RT can induce CCL2 expression (90,91). Within radiation-induced immune responses, CCL2 exerts pleiotropic effects. It can act downstream of IL-6 to mediate macrophage infiltration into tumors after irradiation (92). RT can activate STING signaling and increase IFN-I production, which can induce CCL2, CCL7 and CCL12 expression and drive monocyte trafficking into tumors (93). In murine head and neck squamous cell carcinoma, a 7.5-Gy dose increased CCL2 and promoted infiltration of TNFα-producing monocytes and $CCR2^+$ Treg cells. Monocyte-derived TNFα activated Treg cells and could undermine RT responses (94). Tumor-derived CCL2 has also been implicated in adaptive radioresistance in pancreatic ductal adenocarcinoma models, in which CCL2 blockade improved the efficacy of RT (95). Upregulation of CCL2 has been linked to radiation toxicities, including radiation-induced lung injury, radiation-induced liver injury and cognitive impairment after RBI (96-98). CCL3, also known as macrophage inflammatory protein 1α, contributes to RT responses. Through CCR1 engagement, CCL3 promotes type 2 T-helper (Th2)-cell infiltration and exacerbates radiation-associated lung injury and fibrotic remodeling. In hepatocellular carcinoma, combining CCL3 with RT enhanced $CD8^+$ T cell-driven antitumor immunity, and CCL3 has also been evaluated as a candidate predictor of breast cancer RT response (99). CCL5, also known as regulated on activation, normal T cell expressed and secreted, can exert context-dependent effects. RT induces tumor cells and mesenchymal stromal cells to release CCL5, which recruits macrophages and can promote M2 polarization and metastatic progression (100,101). By contrast, CCL5 can also recruit $CD8^+$ T cells and enhance antitumor immunity, indicating that its net effect depends on tumor context and radiation dose (102). CCL8, also known as MCP2, binds multiple receptors, including CCR1, CCR2, CCR3 and CCR5, and mainly recruits monocytes and Treg cells. Thoracic irradiation elevates CCL8, enhances macrophage infiltration and has been associated with increased pulmonary metastasis in a preclinical study (103). CCL11, also known as eotaxin 1, recruits eosinophils through CCR3. Radiation-associated increases in CCL11 have been linked to injury across multiple tissues. In intestinal radiation fibrosis, irradiation drives mucosal myofibroblasts to secrete CCL11, which recruits eosinophils and accelerates fibrotic progression (104). After radiation injury to skin and brain tissue, increased CCL11 can also promote migration of eosinophils and other immune cells to damaged sites, aggravating inflammation and tissue injury (105,106). CCL7 has been implicated in radiation-induced lung fibrosis. In a radiation-sensitive murine model, CCL7 was found to be markedly induced and was able to promote lung fibrosis by recruiting profibrotic immune populations (107). CCL22 is constitutively secreted by specific dendritic cell subsets in secondary lymphoid organs, particularly the $CD103^+$ $CD11b^-$ $CD8^+$ subset. By binding CCR4 on Treg cells, CCL22 promotes direct dendritic cell- and Treg-cell contact that suppresses effector T-cell activation and proliferation. Loss of CCL22 enhances vaccine-induced antigen-specific $CD8^+$ T-cell responses and antitumor immunity (108).

Overall, CC chemokines function as regulators of the RT-conditioned TME by coordinating monocyte influx, macrophage polarization, trafficking of T cells and Treg cells, and eosinophil-associated remodeling. Table I summarizes their reported net effects on antitumor immunity, radioresistance and RT-associated toxicity. Conversely,

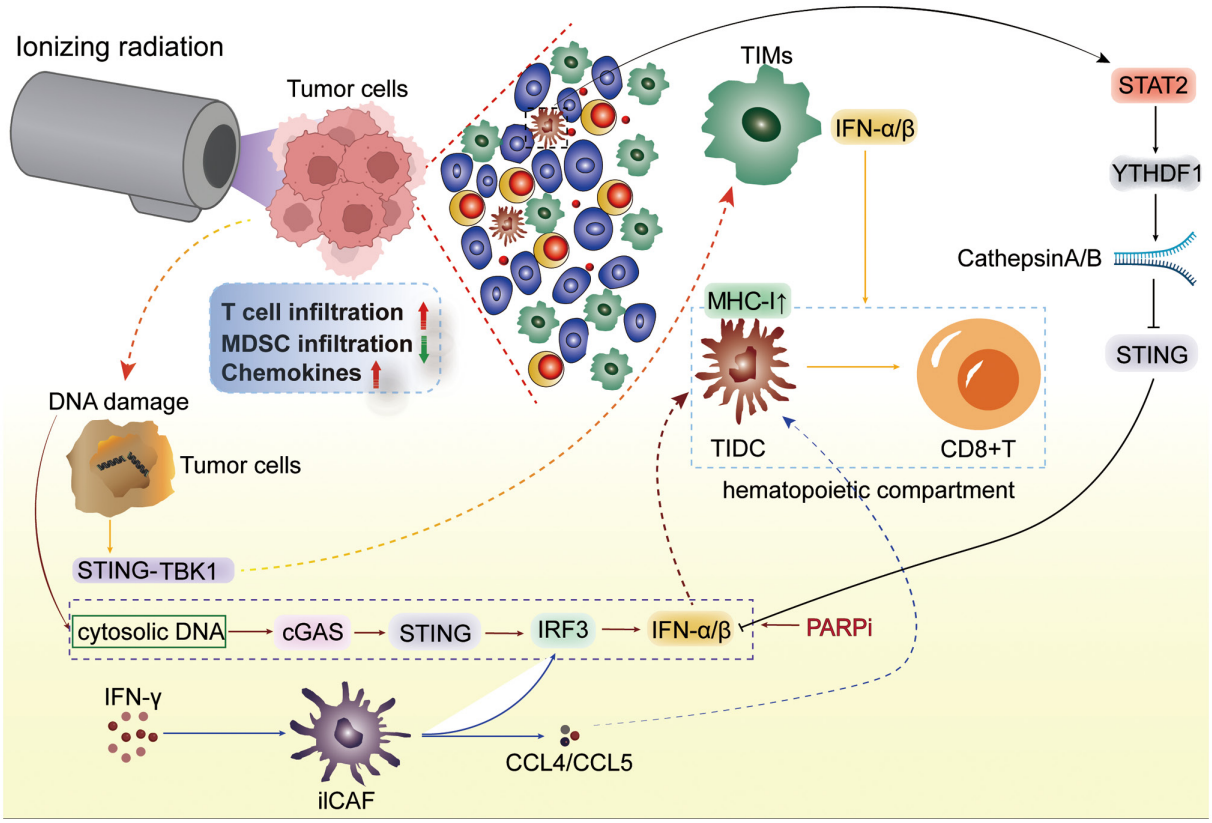

Figure 2. IR-activated cGAS/STING/IFN-I hub links DNA damage to DC cross-priming and CD8⁺ T-cell activation. IR generates cytosolic dsDNA and micronuclei that are sensed by cGAS, triggering the STING/TBK1/IRF3 cascade and induction of IFN-α and IFN-β. IFN-α and IFN-β produced by TIMs act within the hematopoietic compartment to license TIDCs for efficient cross-presentation, increase tumor MHC-I expression and prime CD8⁺ T cells. Chemokine induction, including CCL4 and CCL5, enhances T-cell recruitment and, in responsive contexts, limits MDSC accumulation. PARPi potentiate this axis by increasing cytosolic dsDNA. A DC-intrinsic negative-feedback circuit is also depicted: IR and IFN-I signaling induce STAT2-dependent upregulation of the m6A reader YTHDF1, which enhances translation of cathepsins A and B and accelerates lysosomal degradation of STING, thereby dampening IFN-I output and cross-presentation. In parallel, IFN-γ polarizes an ilCAF subset that secretes CCL4 and CCL5 to further recruit T cells and DCs, reinforcing pro-immune trafficking. Collectively, this hub defines an adjustable post-RT immune set point between activation and tolerance and provides a mechanistic rationale for combination strategies involving PARPi and immune checkpoint blockade. TIMs, tumor-infiltrating myeloid cells; TIDCs, tumor-infiltrating dendritic cells; PARPi, PARP inhibitor; ilCAF, IFN-responsive CAF; IR, ionizing radiation; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; IFN-I, type I interferon; DC, dendritic cell; CD8⁺, cluster of differentiation 8 positive; dsDNA, double-stranded DNA; TBK1, TANK-binding kinase 1; IRF3, IFN regulatory factor 3; IFN-α, interferon α; MHC-I, major histocompatibility complex class I; CCL4, C-C motif chemokine ligand 4; MDSC, myeloid-derived suppressor cell; STAT2, signal transducer and activator of transcription 2; m6A, N6-methyladenosine; YTHDF1, YTH N6-methyladenosine RNA-binding protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; RT, radiotherapy.

pro-immunogenic chemokines such as XCL1 and CXCL16 can recruit cross-presenting dendritic cells and effector CD8⁺ T cells to strengthen antitumor immunity (109,110), whereas axes such as CXCL12/CXCR4 and CXCL8/CXCR1/2 promote vasculogenesis, DNA damage repair and survival signaling that support recurrence and radioresistance (111-113). More broadly, radiation-responsive chemokine programs are emerging as important determinants of immune-cell trafficking and treatment outcome; a recent review summarized the central role of CC chemokines in radiation responses, and experimental evidence in lung cancer further showed that RT can enhance activation of CD8⁺ T cells with high CXCR3 expression by inducing IFN-γ-mediated CXCL10 and ICAM-1 expression (114,115).

4. Pro- and anti-inflammatory cytokines

RT kills tumor cells by inducing DNA double-strand breaks and simultaneously triggers dynamic changes in pro-inflammatory and anti-inflammatory cytokine networks (Fig. 3). These changes can have opposing consequences. Pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β, can activate NF-κB, STAT3 and angiogenesis-related pathways, thereby promoting tumor-cell proliferation and invasion and contributing to radioresistance. For example, TNF-α overexpression in non-small cell lung cancer is associated with reduced radiosensitivity, and increased serum IL-1β, IL-6 and TNF-α in head and neck squamous cell carcinoma is associated with worse outcomes (116,117). RT-induced immune reprogramming can also involve IL-6-dependent regulation. In nasopharyngeal carcinoma, irradiation increases mTOR complex 1 activity and alters p62 phosphorylation, which suppresses p62-dependent selective autophagy and ultimately increases endothelial protein C receptor (PROCR) expression. By promoting IL-6 secretion, PROCR suppresses Th1 differentiation and compromises CD8⁺ T-cell effector function, thereby attenuating antitumor immunity (118). IL-34 suppresses IL-12 in post-irradiation TAMs, limiting recruitment and activation of IFN-γ-producing CD8⁺ T cells and blunting RT-induced antitumor immunity. In IL-34-deficient

Table I. Chemokines shaping RT responses: Immunobiology, net effects and representative evidence.

Chemokine	Principal biological effects under RT	Overall impact	(Refs.)
CCL2	Recruits CCR2$^+$ monocytes and regulatory T cells. Upregulated by RT in head and neck squamous cell carcinoma. CCR2$^+$ monocytes contribute to radiation-induced lung injury and fibrosis.	Immunosuppressive and toxicity-associated	(98-106)
CCL3	Signals via CCR1 and recruits profibrotic leukocytes.	Toxicity-associated	(99)
CCL5	RT activates cGAS-STING-CCL5 signaling in mesenchymal stromal cells, recruits macrophages and may promote metastasis. NK-derived CCL5 can also recruit cDC1.	Context-dependent, may promote metastasis or enhance antitumor immunity	(100-102)
CCL8	Binds CCR1, CCR2, CCR3 and CCR5. Thoracic RT increases CCL8, increases macrophage infiltration and has been associated with lung metastasis.	Pro-metastasis	(103)
CCL11	Recruits eosinophils through CCR3. Eosinophils contribute to fibrosis.	Toxicity-associated	(104-106)
CCL22	Constitutively secreted by specific dendritic cell subsets. Promotes dendritic cell and regulatory T-cell contact that suppresses effector priming.	Immunosuppressive	(108)
XCL1	Derived from NK cells and CD8$^+$ T cells. Recruits XCR1$^+$ cDC1 and supports cross priming.	Pro-immunogenic	(109)
CXCL16	RT upregulates CXCL16 on tumor cells. Attracts CXCR6$^+$ effector CD8$^+$ T cells into irradiated tumors.	Pro-immunogenic	(110)
CXCL12	HIF-1-dependent SDF-1 and CXCR4 axis recruits bone marrow-derived myeloid cells and supports vasculogenesis after radiotherapy.	Recurrence- and resistance-associated	(111-112)
CXCL8	Promotes DNA damage repair programs and glycolytic shift. Attracts neutrophils and MDSCs.	Radioresistance and immune suppression	(113-114)
CXCR2 ligands (CXCL1/2/5)	Recruits CXCR2$^+$ neutrophils and MDSCs. Shapes an immunosuppressive tumor microenvironment.	Tumor-promoting and resistance- associated	(115)
CXCL9/10/11	IFN-I inducible. Recruits CXCR3$^+$ CD8$^+$ T cells. RT through cGAS-STING increases CXCL10 and endothelial ICAM-1.	Pro-immunogenic	(40,42,64)

RT, radiotherapy; CCR1, C-C motif chemokine receptor 1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; NK, natural killer; cDC1, conventional dendritic cell type 1; XCR1, X-C motif chemokine receptor 1; CD8$^+$, cluster of differentiation 8 positive; HIF-1, hypoxia-inducible factor 1; SDF-1, stromal cell-derived factor 1; MDSCs, myeloid-derived suppressor cells; CXCR2, C-X-C motif chemokine receptor 2; IFN-I, type I interferon; ICAM-1, intercellular adhesion molecule 1.

tumors, RT promotes pro-inflammatory macrophage differentiation and IL-12 induction, strengthening immune-mediated tumor eradication (119). Cytokines are also key mediators of immunogenic cell death. Under immunogenic conditions, they can drive dendritic cell maturation and antigen cross-presentation and enhance CD8$^+$ T-cell responses through NF-κB and IFN-I pathways, contributing to abscopal effects. In breast cancer models, combining irradiation with valproic acid reprograms the irradiated field TME, increases CD8$^+$ T-cell infiltration and M1-like polarization and suppresses growth of distant lesions (120,121). Anti-inflammatory mediators such as IL-10 can mitigate normal tissue toxicity. For example, low-level laser therapy can ameliorate oral mucositis in part by reducing IL-6 (122). However, excessive anti-inflammatory signaling can suppress immune surveillance and is associated with reduced survival. For example, in glioblastoma, dexamethasone-induced anti-inflammatory cascades correlate with shorter survival (123). In specific contexts, such as combination with γ irradiation, IL-10 upregulation has also been reported to promote tumor-cell apoptosis, as observed with ebselen combination therapy in breast cancer models (124). Radiation dose is a determinant of the immune microenvironment. Low- and intermediate-dose RT tends to favor M2-macrophage polarization and an immunosuppressive microenvironment (125), whereas high-dose RT combined with PD-L1 blockade can activate the cGAS-STING pathway, amplify pro-inflammatory cytokine release and enhance CD8$^+$ T-cell responses, thereby increasing abscopal effects (126). When pro- and anti-inflammatory signals are imbalanced, TGF-β-driven pathways may promote radiation fibrosis or radioresistance (127), and excessive anti-inflammatory signaling may weaken immune clearance

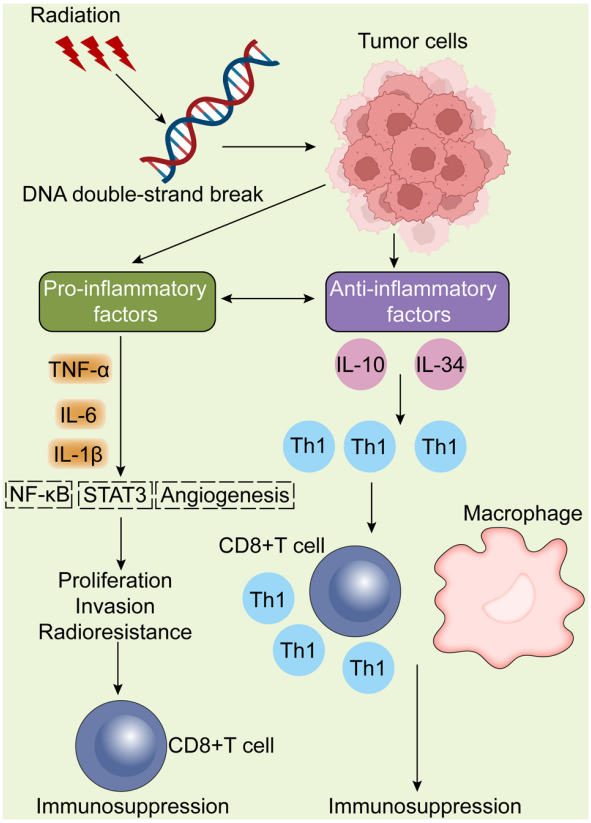

Figure 3. RT-induced pro- vs. anti-inflammatory cytokine competition resets immune tone and radiosensitivity. RT elicits concurrent induction of pro-inflammatory and anti-inflammatory cytokine programs that collectively reshape the tumor immune microenvironment and influence radiosensitivity. Pro-inflammatory mediators, exemplified by TNF-α, IL-6 and IL-1β, can activate NF-κB and STAT3 signaling and are associated with tumor proliferation, invasion and radioresistance in defined contexts. Counter-regulatory programs, represented by IL-10 and IL-34, can mitigate normal-tissue injury, yet may also suppress immune surveillance and facilitate immune escape when sustained. RT-associated pathway nodes that bias this balance are highlighted, including mTORC1/p62/PROCR/IL-6 signaling and IL-34-dependent suppression of TAM-derived IL-12, which limits IFN-γ output and $CD8^+$ T-cell recruitment or activation. Conversely, pro-inflammatory signaling together with RT promotes immunogenic cell death, supporting DC maturation, antigen cross-presentation and $CD8^+$ T-cell infiltration. Dose dependence is emphasized: Low-to-intermediate RT tends to favor M2 polarization and an immunosuppressive milieu, whereas high-dose RT combined with PD-L1 blockade can activate cGAS/STING signaling, increase pro-inflammatory cytokine release, strengthen $CD8^+$ T-cell responses and enhance abscopal effects. Representative intervention nodes include URB937, siltuximab and CTLA-4 blockade. RT, radiotherapy; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor β; mTORC1, mammalian target of rapamycin complex 1; PROCR, protein C receptor; TAM, tumor-associated macrophage; IFN-γ, interferon γ; $CD8^+$, cluster of differentiation 8 positive; DC, dendritic cell; PD-L1, programmed death-ligand 1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

and increase the risk of recurrence (121). Clinically, modulation of cytokine networks has been explored to remodel the TME. For example, URB937-mediated suppression of IL-1β, IL-6 and TNF-α mitigates radiation-induced lung injury (128), siltuximab improves RT responses in multiple myeloma (129) and CTLA-4 blockade can potentiate RT-induced abscopal effects (130). To maximize antitumor efficacy while minimizing adverse effects, real-time monitoring and rational modulation of this network remain important (131).

5. The critical role of macrophages

Macrophages are key immune components of the TME and contribute to tumor initiation, immune evasion and antitumor immunity (Fig. 4) (132). RT can reshape the TME by altering the polarization of TAMs (133). Different radiation doses can promote transitions toward a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype through NF-κB and downstream cytokine signaling, resulting in dose-dependent immunomodulation (125,134-137). Low-dose RT (<2 Gy) can inhibit NF-κB p65 activity, reduce expression of pro-inflammatory factors such as TNF-α and IL-1β, and increase TGF-β release, thereby promoting an immunosuppressive M2 phenotype (125,134). Moderate-dose RT from 2 to 10 Gy can activate NF-κB p65 p50 heterodimers, increase the secretion of TNF-α, IL-6 and IL-12, upregulate M1 markers including CD80, CD86 and MHC-II, and suppress M2 markers such as CD163 and IL-10, thereby enhancing antitumor immune responses (135,136,138). By contrast, high-dose RT >10 Gy can increase the expression of chemokines such as CCL2, CCL5 and CXCL12 through hypoxia-induced HIF-1α signaling, driving monocyte differentiation toward M2-like TAMs. High-dose RT can also favor NF-κB p50 homodimer activity, upregulate immunosuppressive factors including IL-10 and TGF-β, and contribute to tumor immune escape (111,139,140).

TAMs modulate tumor radiosensitivity by secreting cytokines and chemokines. CCL2 and CXCL6 secreted by M2-like TAMs can recruit MDSCs or activate EMT programs, thereby promoting radioresistance (93,141-143). After irradiation, tumor-derived exosomes can transfer miR-193b-3p and hsa_circ_0001610 to TAMs and reduce radiosensitivity through MAPK kinase kinase 3 repression or PD-L1 upregulation (144,145). High-dose RT can also induce CAFs to secrete CCL2, which cooperates with TAM-derived VEGF and heparin-binding EGF-like growth factor to promote angiogenesis and DNA damage repair, thereby enhancing radioresistance (146-148). Conversely, M1-like TAMs secrete TNF-α and IL-12, promote cytotoxic T-lymphocyte recruitment and enhance antigen presentation, which can counteract immunosuppression and improve radiosensitivity (149,150). In addition, RT-derived microparticles can activate the JAK/STAT pathway, promote polarization toward M1 macrophages and induce the release of danger signals such as ATP and high mobility group box 1 (HMGB1), thereby enhancing immunogenic cell death (151,152).

Given the role of TAMs in radiosensitivity, targeting macrophage-associated cytokines has become an important strategy to improve RT efficacy. Inhibition of CCL2/CCR2 or CCL5/CCR5 signaling can limit macrophage infiltration and M2 polarization (153). Anti-CSF1R antibodies can block monocyte to macrophage differentiation, and combining these agents with RT can delay tumor recurrence (37,154). VEGF-neutralizing antibodies can counteract macrophage-driven angiogenesis (147,155). Nanotechnology-based delivery approaches, such as nanogels carrying Toll-like receptor (TLR)7 or TLR8 agonists, can reprogram macrophages toward an M1 phenotype (156-159). Iron oxide nanoparticles can act as radiosensitizers by increasing ROS and promoting the secretion of pro-inflammatory cytokines

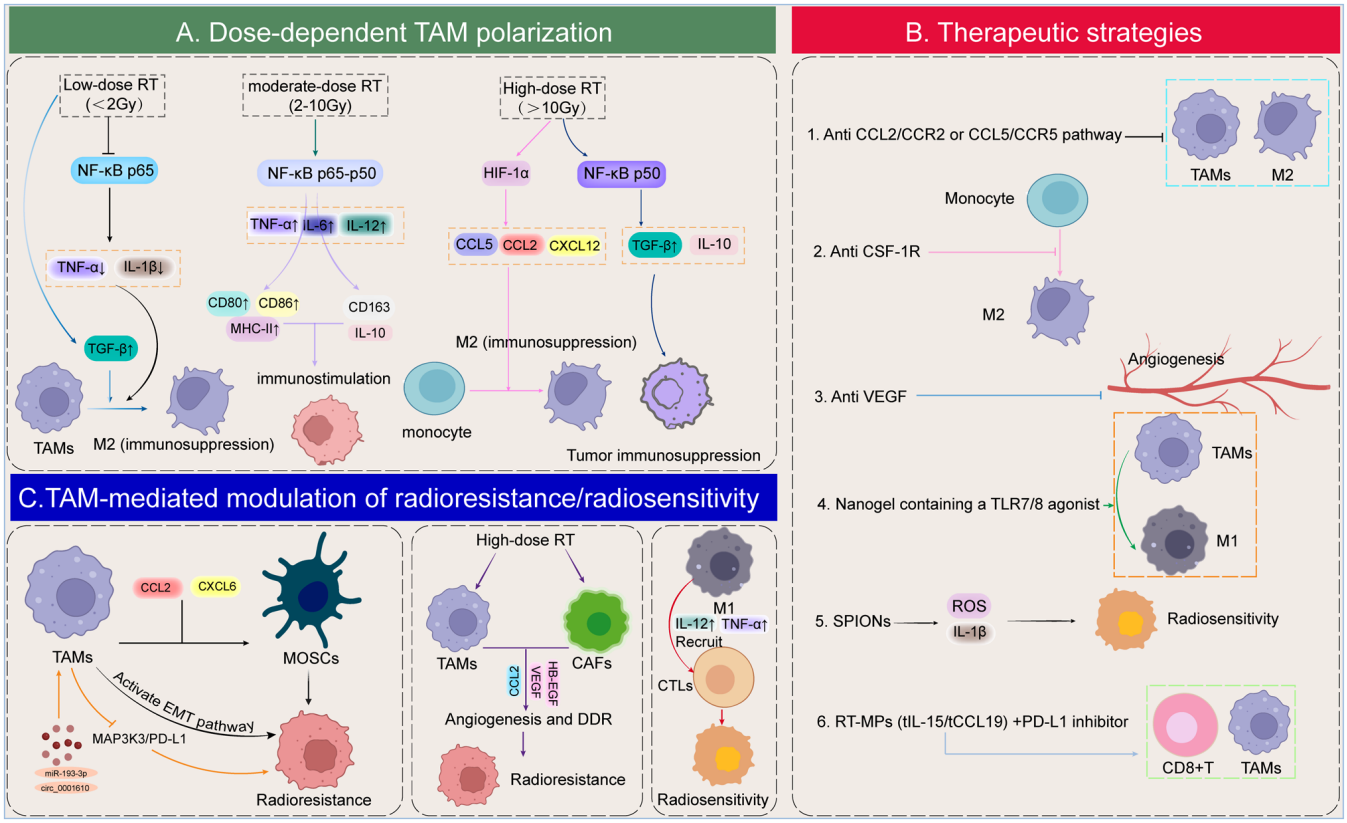

Figure 4. Dose-shaped TAM polarization in RT: Resistance circuits and actionable interventions. (A) Dose-dependent polarization. Low-dose RT (<2 Gy) suppresses NF-κB p65 activity and increases TGF-β, favoring M2-like polarization and immunosuppression. Intermediate-dose RT (2-10 Gy) activates NF-κB p65-p50 heterodimers, increases TNF-α, IL-6 and IL-12, and upregulates M1-associated markers, including CD80, CD86 and MHC-II, supporting an immunostimulatory milieu. High-dose RT (>10 Gy) increases hypoxia and HIF-1α signaling and, together with NF-κB p50 homodimer activity, induces CCL2, CCL5 and CXCL12, as well as IL-10 and TGF-β, promoting M2-like polarization and immune suppression. (B) Actionable strategies. Representative approaches include blockade of CCL2-CCR2 or CCL5-CCR5, CSF-1R inhibition, VEGF neutralization, TLR7 or TLR8 agonist nanogels to reprogram TAMs toward an M1-like state, SPIONs to increase ROS and IL-1β, and RT-derived microparticles carrying tIL-15 and tCCL19 combined with PD-1 or PD-L1 blockade to co-activate $CD8^+$ T cells and macrophage programs. (C) TAM-mediated radioresponse. M2-associated mediators, including CCL2 and CXCL6, together with tumor exosomal transfer of miR-193b-3p and circ_0001610 that modulates MAP3K3 or PD-L1 and promotes EMT, contribute to radioresistance. High-dose RT can also induce CAF-derived CCL2 and cooperate with TAM-derived VEGF and HB-EGF to promote angiogenesis and DDR, further supporting resistance. By contrast, M1-associated TNF-α and IL-12 support CTL recruitment and enhance radiosensitivity. TAM, tumor-associated macrophage; RT, radiotherapy; NF-κB, nuclear factor κB; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; MHC-II, major histocompatibility complex class II; HIF-1α, hypoxia-inducible factor 1α; IL-10, interleukin 10; CXCL6, C-X-C motif chemokine ligand 6; miR-193b-3p, microRNA 193b-3p; circ_0001610, circular RNA 0001610; MAP3K3, MAPK kinase kinase 3; PD-L1, programmed death-ligand 1; EMT, epithelial-mesenchymal transition; CAF, cancer-associated fibroblast; VEGF, vascular endothelial growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; DDR, DNA damage response; CTL, cytotoxic T lymphocyte; CCR2, C-C motif chemokine receptor 2; CSF-1R, colony-stimulating factor 1 receptor; TLR7, Toll-like receptor 7; SPIONs, superparamagnetic iron oxide nanoparticles; ROS, reactive oxygen species; tIL-15, tethered IL-15; tCCL19, tethered C-C motif chemokine ligand 19; PD-1, programmed cell death protein 1.

such as IL-1β (151,160). In addition, RT-derived microparticles co-expressing tethered (t)IL-15 and tCCL19 combined with PD-1 inhibitors can activate $CD8^+$ T-cells and cooperate with macrophages to enhance antitumor activity (161).

In summary, RT regulates TAM polarization through cytokine networks, particularly NF-κB, CCL/CCR and CSF1R signaling, which represent central determinants of tumor radiosensitivity. Although cytokine-targeted approaches and nanotechnology-based delivery strategies have shown efficacy in preclinical studies, heterogeneity in dose effects, potential normal tissue toxicity and immune feedback resistance mechanisms such as compensatory PD-L1 upregulation remain key challenges for clinical translation (162). Future studies using single-cell analyses and related technologies are needed to define functional heterogeneity among macrophage subsets and to support individualized strategies for combining RT with immunotherapy.

6. Mechanisms of RBI

RBI is a common adverse effect of tumor RT and effective treatments remain limited (163,164). Cellular senescence is considered a major risk factor for RBI initiation and progression (165-167). RT can induce pericyte senescence and promote the secretion of senescence-associated secretory phenotype factors, including IL-6, TNF-α, IL-1β and CCL2, which can disrupt blood-brain barrier (BBB) integrity and impair endothelial tight junctions *in vitro* (168). These factors can further impair endothelial, vascular, glial and hippocampal neuronal function through paracrine signaling (169-172). Radiation injury can also cause autophagy defects and lysosomal dysfunction in perivascular cells, leading to the accumulation of toxic proteins, accelerated senescence and demyelination of microglia, neurons and oligodendrocyte progenitor cells, thereby worsening cognitive dysfunction (173). Based on

these mechanisms, activation of autophagy or elimination of senescent cells has been explored as a strategy to mitigate RBI. For example, rapamycin enhances lysosome-mediated protein clearance, suppresses perivascular cell senescence and partially restores proliferative capacity (174,175). Dasatinib plus quercetin and all-trans retinoic acid can selectively eliminate senescent pericytes and reduce senescence-associated secretory phenotype secretion, thereby improving BBB integrity and cognitive function (176-178). In models driven by microglial inflammation and neuronal loss, pregabalin has shown neuroprotective effects by blocking HMGB1-mediated TLR2, TLR4 and RAGE/NF-κB signaling and by reducing the production of IL-6, IL-1β and TNF-α (179).

In RT for high-grade brain tumors and metastases, neuron-derived ectodysplasin A2 receptor (EDA2R) has been proposed as a predictor of early responses, such as neurocognitive impairment after cranial irradiation, although the mechanism remains elusive (180). In cachexia-associated muscle atrophy, oncostatin M upregulates EDA2R expression through activation of the noncanonical NF-κB pathway (181). Another report suggested that after hypoxic injury, EDA2R can modulate inflammatory mediators, including TNF-α and IL-1β (182). Based on these observations, a plausible mechanism is that RT acutely activates multiple immune-cell types, including microglia (183,184), and increases the secretion of inflammatory mediators after the peak dose. Under these conditions, oncostatin M may promote EDA2R upregulation through NF-κB signaling and thereby modulate the local inflammatory microenvironment (Fig. 5) (169,170,185,186). In addition, upregulation of CCL8 in the hippocampus can mediate macrophage accumulation and exacerbate neuroinflammation, contributing to cognitive impairment after cranial irradiation (112).

7. Radiation-induced lung injury

Radiation-induced lung injury arises from direct irradiation-mediated cytotoxicity in normal lung tissue and the subsequent inflammatory and fibrotic responses (Fig. 6) (187). Sustained post-irradiation increases in cytokines such as IL-6 can damage type I alveolar epithelial cells (AECI) and stimulate proliferation of AECII (188). Subsequently, at ~6 to 8 weeks after irradiation, a second wave of cytokines including TNF-α can contribute to acute pneumonitis (189). Ionizing radiation damages alveolar epithelial cells and vascular endothelial cells, releasing damage-associated molecular patterns (DAMPs) and cytokines including TNF-α, IL-1β, IL-6, IL-8 and TGF-β1. These mediators activate the NF-κB and MAPK pathways, promote the recruitment of macrophages, neutrophils and dendritic cells, and amplify local inflammation (190-192). In parallel, injured AECII show reduced surfactant production, impaired tissue homeostasis and activation of EMT via TGF-β1 and β-catenin signaling, promoting fibrotic progression (193). Radiation can also polarize lung resident macrophages toward an M1 phenotype, leading to the production of ROS and chemokines such as CCL2, CXCL9 and CXCL10. This process promotes continued $CD8^+$ T-cell infiltration and exacerbates tissue injury (133,194). In the late phase, radiation-activated cGAS/STING signaling can promote macrophage polarization toward an M2 phenotype through the regulation of CCL2 and can increase the secretion of profibrotic factors such as TGF-β and platelet-derived growth factor (PDGF). These changes induce fibroblast to myofibroblast differentiation, increase extracellular matrix deposition and contribute to radiation-induced pulmonary fibrosis (195-197). Macrophage-derived CCL22 is selectively upregulated in rat models of radiation pneumonitis (198). Targeting mediators such as TGF-β, alone or in combination, and strategies that target CCL22 through the TNF-related apoptosis-inducing ligand pathway have been proposed for severe radiation lung toxicity (199). A previous study also indicated that irradiation-activated bronchial club cells can modulate the local immune microenvironment by secreting club cell secretory protein, suppressing MDSCs and enhancing T-cell function, suggesting that distinct pulmonary cell types contribute to immunoregulation in lung injury and fibrosis (200). In addition, chemokines including CCL5, CCL8 and CCL3 have been linked to the progression of radiation-induced lung injury.

To reduce the risk of radiation-induced lung injury, clinical management should integrate advanced planning and delivery techniques such as IMRT and SBRT with evidence-based supportive measures, including anti-inflammatory agents, immunomodulatory strategies, and, in selected contexts, mesenchymal stromal cell-based interventions, to control radiation-induced inflammation and limit fibrotic progression. In parallel, the development of therapeutics that target key cytokine pathways implicated in pneumonitis and fibrosis remains an important research direction for the prevention and treatment of radiation-induced lung injury.

8. Radiation-induced gastrointestinal injury

Radiation-induced gastrointestinal injury is a common complication of cancer RT. Radiation esophagitis is a major dose-limiting toxicity in RT for lung cancer and head and neck squamous cell carcinoma (Fig. 7). Among patients with non-small cell lung cancer receiving concurrent chemoRT, the incidence can reach 95 and 33% experience grade 3 or higher events. Similar rates have been reported for 3D conformal RT, IMRT and proton beam therapy (201-203). Evidence suggests that IFN-α acts as a pro-inflammatory mediator in radiation esophagitis (204). Plasmacytoid dendritic cells (pDCs) in the esophageal mucosa can recognize endogenous RNA and DNA released as damage-associated molecular patterns released after tissue injury via TLR7 and TLR9, producing large amounts of IFN-α and serving as a major source of IFN-I in radiation esophagitis (205-207). Depletion of pDCs using anti-CD317 antibodies or inhibition of pDCs function with bortezomib can suppress IFN-α upregulation and alleviate mucosal inflammation and tissue injury. These findings support a pro-inflammatory plasmacytoid dendritic cell IFN-α pathway and provide a rationale for targeted intervention. Beyond IFN-α, upregulation of IL-16, CCL3 and CCL7 is associated with increased esophagitis severity. By contrast, upregulation of CCL5, CXCL12, CCL22 and IGF-1 is consistent with trends toward injury repair (108).

Radiation-induced rectal injury refers to rectal damage caused by RT for pelvic malignancies and is commonly categorized as acute or chronic, with 3 months used as a practical cutoff (208). Preclinical studies indicate that PDGF-C, through engagement of PDGFR and activation

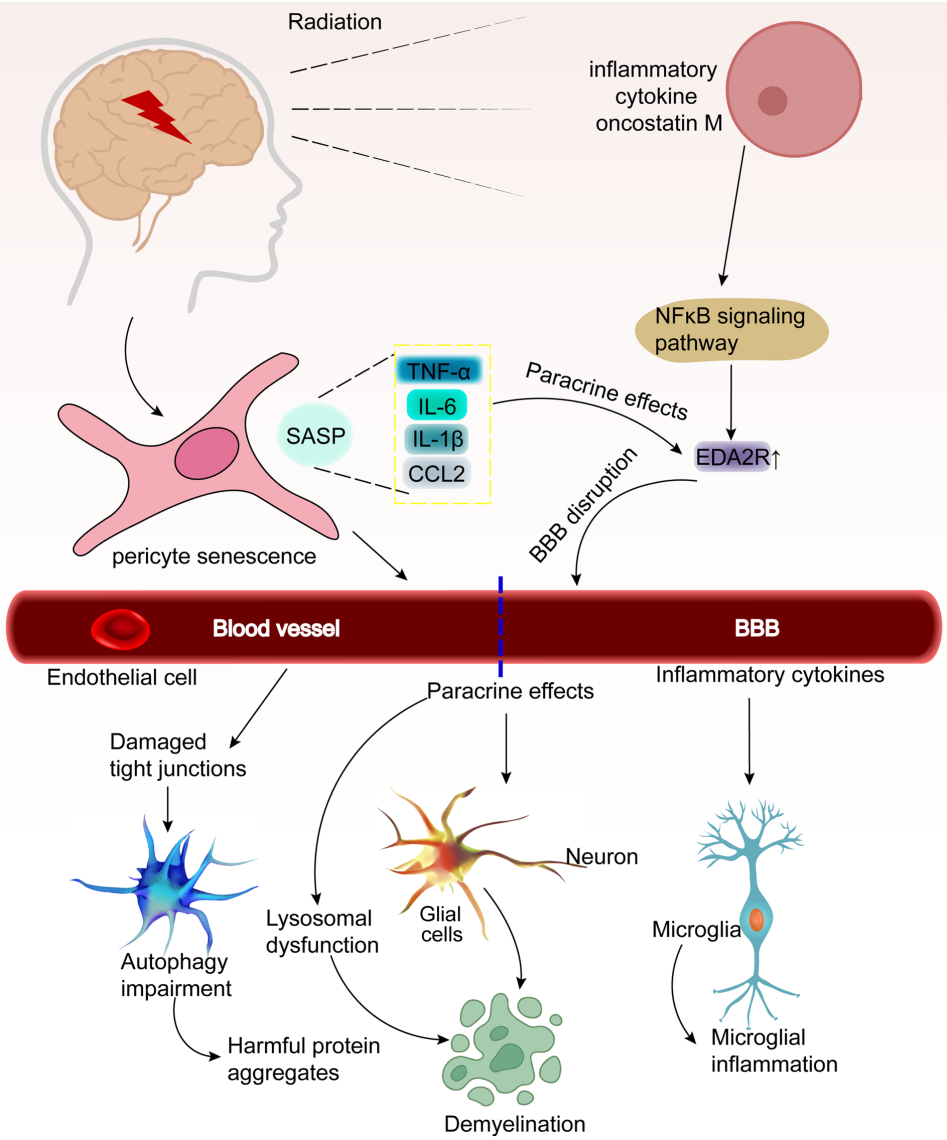

Figure 5. RT-induced pericyte senescence/SASP/BBB axis links microvascular injury to neuroinflammation and demyelination. Ionizing radiation induces pericyte senescence and an SASP enriched in TNF-α, IL-6, IL-1β and CCL2. These mediators act in a paracrine manner on endothelial, glial and neuronal compartments, impair tight-junction integrity and BBB function, and are associated with autophagy-lysosome dysfunction. Consequent accumulation of neurotoxic protein aggregates contributes to demyelination and cognitive impairment. SASP-associated cytokines also promote microglial activation. In parallel, oncostatin M-driven NF-κB signaling is depicted as a candidate upstream input for neuronal EDA2R upregulation, representing a putative feedback node that may modulate excessive TNF-α and IL-1β signaling after irradiation. BBB, blood-brain barrier; RT, radiotherapy; SASP, senescence-associated secretory phenotype; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; CCL2, C-C motif chemokine ligand 2; NF-κB, nuclear factor κB; EDA2R, ectodysplasin A2 receptor.

of a downstream ETS translocation variant 1-mediated CXCR4 signaling axis, promotes colorectal inflammation and fibrosis. Accordingly, the PDGFR antagonist crenolanib has been proposed as a candidate agent for the prevention and treatment of radiation-induced rectal lesions (209). During pelvic RT, depletion of *Akkermansia* reduces concentrations of its metabolite 3-hydroxybutyrate in the gut and circulation, limiting activation of the intestinal cell surface receptor G-protein-coupled receptor 43. This change relieves the suppression of IL-6, thereby driving intestinal inflammation and tissue injury (210). In addition, irradiation induces intestinal mucosal myofibroblasts to release CCL11, which recruits eosinophils via CCR3 and exacerbates fibrosis (104). Hypoxia can also activate VEGF and TGF-β pathways, promoting inflammation and fibrosis and accelerating late-stage rectal injury (211,212). Several cytokines also represent potential therapeutic targets. For example, CCL2 has been proposed as a biomarker of late rectal toxicity after RT in prostate cancer, and early assessment and intervention may reduce risk (213). LR-IFN-β released by the probiotic *Lactobacillus reuteri* can alleviate gastrointestinal acute radiation syndrome after total abdominal irradiation (214). In addition, the microbial metabolite indole-3-carboxaldehyde can protect the intestine from radiation injury by activating Aryl hydrocarbon receptor/IL-10/wingless-related integration site 3 signaling and by increasing the abundance of probiotic bacteria (215).

9. Radiation-induced oral mucositis

Radiation-induced oral mucositis is a common toxicity of RT for head and neck tumors, with an incidence ranging from 26.4 to 100% (216,217). Clinically, oral mucositis presents

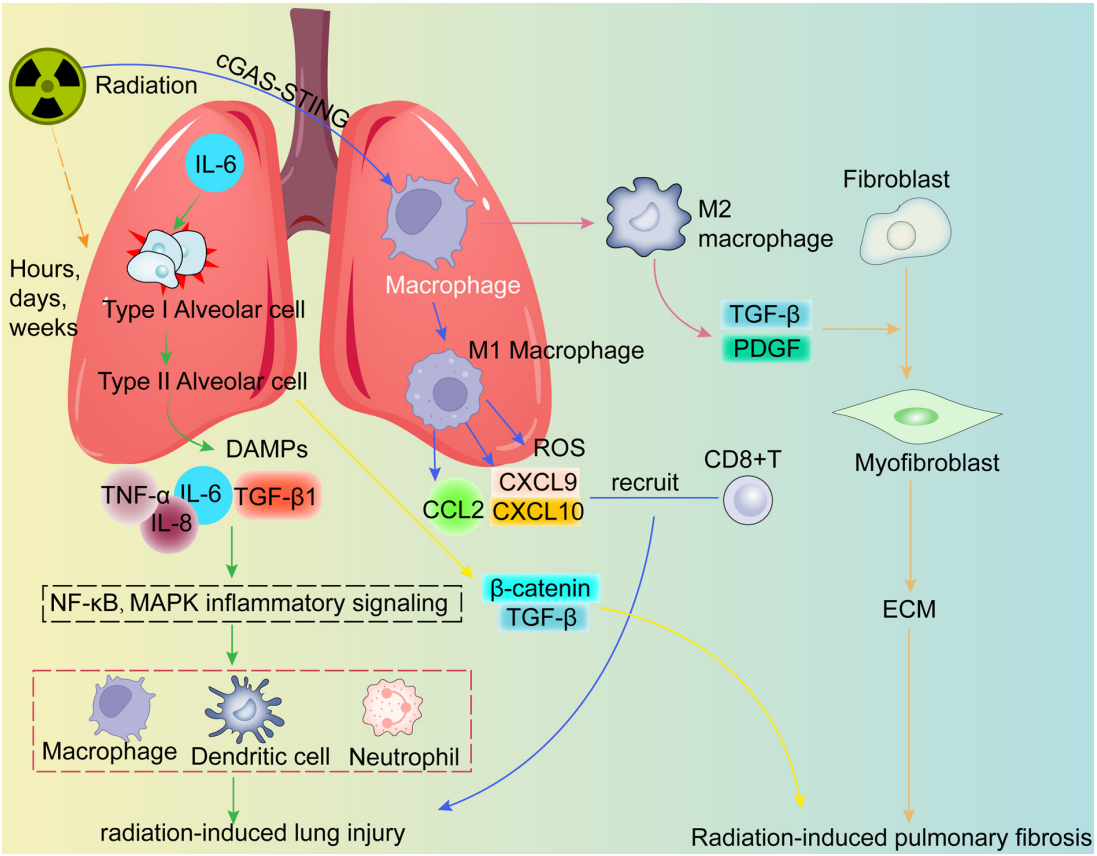

Figure 6. Cytokine trajectories in RT-induced lung injury from acute inflammation to fibrosis. Ionizing radiation injures alveolar epithelium and vascular endothelium, induces DAMP release and increases TNF-α, IL-1β, IL-6, IL-8 and TGF-β1. NF-κB and MAPK pathways are activated, promoting recruitment of macrophages, neutrophils and DCs and amplifying inflammation. AECII dysfunction includes reduced surfactant production and disrupted tissue homeostasis, while TGF-β1 and β-catenin signaling promote EMT. Early after irradiation, resident macrophages preferentially polarize toward an M1-like state, generate ROS and secrete chemokines, including CCL2, CXCL9 and CXCL10, sustaining $CD8^+$ T cell infiltration and tissue injury. At later stages, cGAS/STING activation increases CCL2, shifts macrophage polarization toward an M2 phenotype and elevates pro-fibrotic mediators, including TGF-β and PDGF, to promote fibroblast-to-myofibroblast transition and excessive ECM deposition, culminating in fibrosis. CCL22 upregulation is associated with pneumonitis and is shown as an intervention node, alone or in combination with TGF-β blockade or TRAIL-based strategies. Club cell-derived CCSP is depicted as a modulator that restrains MDSCs and supports T-cell function. RT, radiotherapy; DAMPs, damage-associated molecular patterns; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; TGF-β1, transforming growth factor β1; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; DCs, dendritic cells; AECII, type II alveolar epithelial cells; EMT, epithelial-mesenchymal transition; M1, classically activated macrophage; ROS, reactive oxygen species; CCL2, C-C motif chemokine ligand 2; CXCL9, C-X-C motif chemokine ligand 9; $CD8^+$, cluster of differentiation 8 positive; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; M2, alternatively activated macrophage; PDGF, platelet-derived growth factor; ECM, extracellular matrix; TRAIL, TNF-related apoptosis-inducing ligand; CCSP, club cell secretory protein; MDSCs, myeloid-derived suppressor cells.

with erythema and ulceration in the acute stage and can evolve into persistent chronic injury, substantially compromising quality of life (218,219). Oral mucositis development is closely linked to cytokine network dynamics (Fig. 8). RT damages mucosal cell DNA and generates ROS, triggering the release of DAMPs (220). These signals activate TLR, NF-κB and MAPK pathways, drive the secretion of pro-inflammatory cytokines including TNF-α, IL-1β and IL-6, and increase apoptosis and inflammation (218,220,221). Oral dysbiosis can further enhance DAMPs signaling, sustaining epithelial NF-κB activation and cytokine production (222,223). During progression, M1 macrophages accumulate in the submucosa and secrete TNF-α and IL-1β, amplifying inflammation (224). $CD4^+$ T-cells influence the disease course through modulation of the balance among Th1, Th17 and Treg-cell subsets (225,226). In the recovery phase, M2 macrophages predominate and support tissue repair (227). Based on these mechanisms, multiple interventions have been evaluated. Melatonin reduces pro-inflammatory cytokine expression by scavenging ROS and inhibiting NF-κB signaling. Mouthwash and gel formulations have reduced the incidence of severe mucositis by a ~34% in clinical studies (228). Chlorhexidine mucosal patches reduce pro-inflammatory cytokine levels through activation of macrophage α2 receptors, and a phase II trial reported a reduced incidence of severe mucositis (229,230). Pentoxifylline inhibits TNF-α production and, when combined with vitamin E, can shorten mucositis duration (231,232). Recombinant human IL-11 (rhIL-11) has been evaluated to reduce ulcer severity and accelerate healing by promoting mucosal repair (233,234). Curcumin has also been reported to reduce pain and clinical severity through inhibition of TNF-α (233-237). Photobiomodulation can accelerate mucosal repair by modulating cytokine activity and promoting angiogenesis (238,239) and has been recommended for prevention by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology guidelines with level I to II evidence (240,241). Future work should evaluate cost-effectiveness in larger clinical trials and

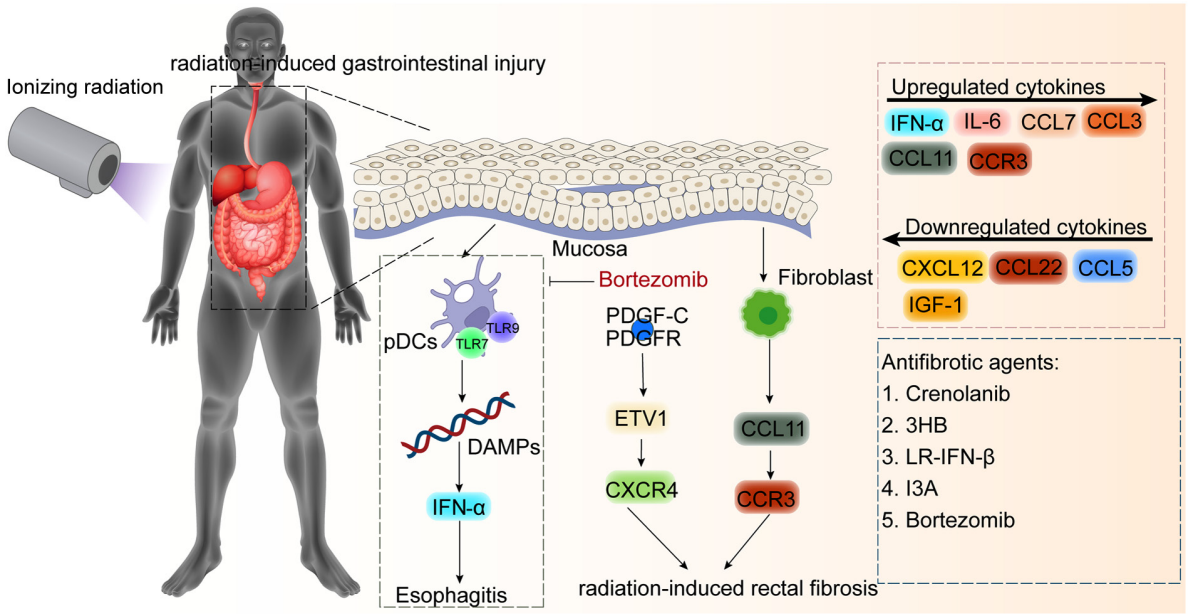

Figure 7. Cytokine circuits and anti-fibrotic intervention nodes in RT-induced gastrointestinal injury. Ionizing radiation injures gastrointestinal mucosa and induces the release of damage signals. pDCs sense these cues via TLR7 and TLR9 and produce TNF-α, contributing to esophagitis. Bortezomib is shown as an inhibitor of pDC activity that reduces TNF-α induction. In rectal fibrosis, PDGF-C signaling through PDGFR activates the ETV1/CXCR4 axis, promoting fibroblast activation and matrix deposition, which can be antagonized by crenolanib. Cytokine and chemokine programs exhibit temporal dynamics, with representative increases in TNF-α, IL-6, CCL7, CCL3, CCL11 and CCR3, and representative decreases in CXCL12, CCL22, CCL5 and IGF-1. Candidate anti-fibrotic strategies include crenolanib, the *Akkermansia muciniphila*-derived metabolite 3HB, I3A and bortezomib. These interventions target inflammatory sensing and pro-fibrotic signaling and may mitigate tissue injury and fibrosis. RT, radiotherapy; pDCs, plasmacytoid dendritic cells; TLR7, Toll-like receptor 7; TNF-α, tumor necrosis factor α; PDGF-C, platelet-derived growth factor C; PDGFR, PDGF receptor; ETV1, ETS variant 1; CXCR4, C-X-C motif chemokine receptor 4; IL-6, interleukin 6; CCL3, C-C motif chemokine ligand 3; CCR3, C-C motif chemokine receptor 3; CXCL12, C-X-C motif chemokine ligand 12; IGF-1, insulin-like growth factor 1; 3HB, 3-hydroxybutyrate; I3A, indole-3-carboxaldehyde.

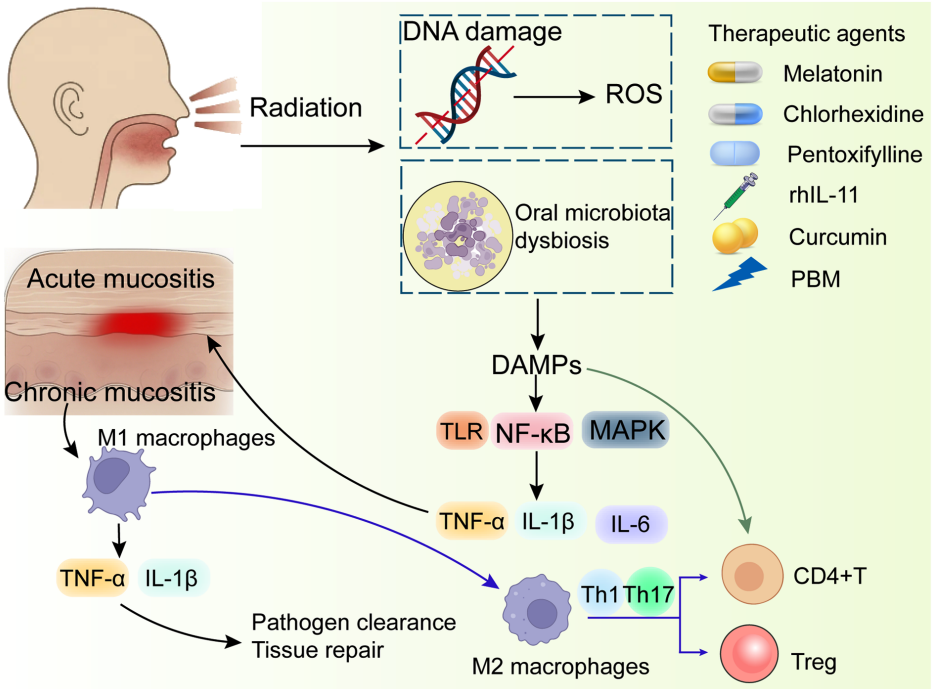

Figure 8. Cytokine and immune circuits in RT-induced oral mucositis. Ionizing radiation induces DNA damage in the oral epithelium and increases ROS, while dysbiosis amplifies danger signals. DAMPs activate TLR, NF-κB and MAPK signaling, increasing TNF-α, IL-1β and IL-6, which drive acute mucositis and may progress to chronic injury. During the amplification phase, M1 macrophages accumulate and intensify inflammation. During resolution, M2 macrophages support pathogen clearance and tissue repair. The balance among $CD4^+$ T cell subsets, including Th1, Th17 and Treg, modulates the disease trajectory. Representative interventions include melatonin to reduce ROS and suppress NF-κB-responsive cytokines, chlorhexidine-based formulations to reduce mucosal inflammatory burden, pentoxifylline to inhibit TNF-α production, rhIL-11 to promote epithelial regeneration, curcumin to reduce TNF-α-associated inflammatory pain and PBM to modulate cytokine activity and angiogenesis and accelerate healing. RT, radiotherapy; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; TLR, Toll-like receptor; NF-κB, nuclear factor κB; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; Th1, type 1 T helper cell; Treg, regulatory T cell; rhIL-11, recombinant human IL-11; PBM, photobiomodulation.

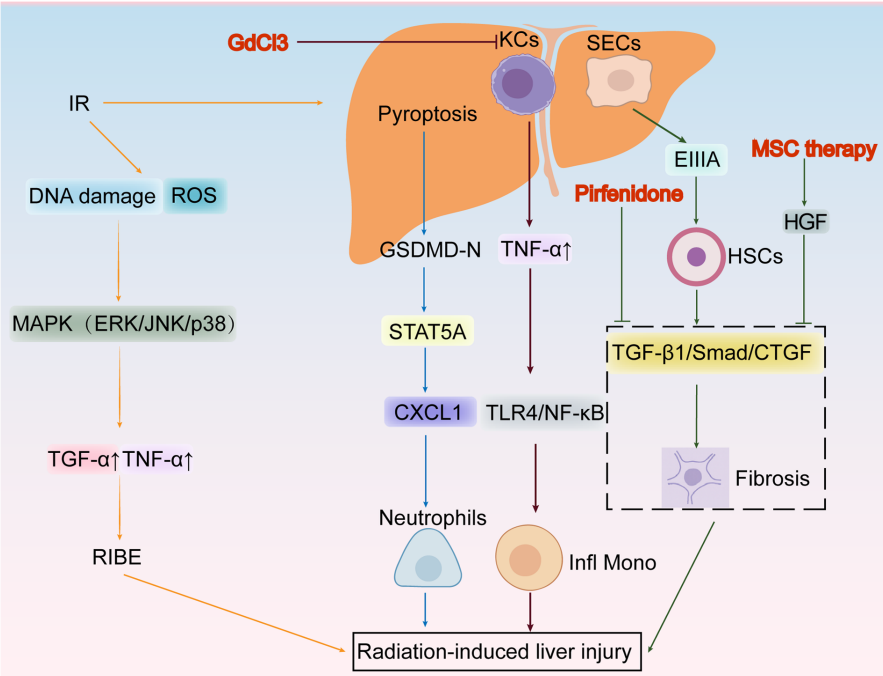

Figure 9. Immune and cytokine pathways in RT-induced liver injury: Pyroptosis links inflammation and fibrosis. Ionizing radiation induces DNA damage and ROS bursts and activates MAPK/ERK/JNK/p38 signaling, increasing TGF-α and TNF-α and amplifying RIBE. In the liver, Kupffer cells undergo pyroptosis characterized by GSDMD-N pore formation and STAT5A-dependent upregulation and release of CXCL1, which recruits neutrophils. KC-derived TNF-α signals via TLR4/NF-κB to promote inflammatory monocyte recruitment. Sinusoidal endothelial-cell injury and loss of fenestrae increase fibronectin EIIIA, contributing to activation of HSCs. Activated HSCs engage the TGF-β1/Smad/CTGF axis, increasing ECM production and driving fibrotic remodeling that culminates in RT-induced liver injury. Candidate interventions include GdCl3 to suppress KC activity and TNF-α-associated signaling, pirfenidone to attenuate TGF-β1/Smad/CTGF signaling and MSC-based therapy to limit HSC activation and support tissue repair. RIBE, RT-induced bystander effects; RT, radiotherapy; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; TGF-α, transforming growth factor α; TNF-α, tumor necrosis factor α; GSDMD-N, gasdermin D N-terminal fragment; STAT5A, signal transducer and activator of transcription 5A; CXCL1, C-X-C motif chemokine ligand 1; KC, Kupffer cell; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; HSC, hepatic stellate cell; TGF-β1, transforming growth factor β1; CTGF, connective tissue growth factor; ECM, extracellular matrix; GdCl3, gadolinium chloride; MSC, mesenchymal stem cell.

integrate virtual screening to develop specific cytokine inhibitors for prevention and treatment (242,243).

10. Radiation-induced liver injury

Radiation-induced liver disease (RILD) is a serious complication of RT for upper abdominal and thoracic tumors and can limit the broader use of RT (244,245). RT can increase inflammatory cytokine levels and promote the infiltration of immune cells, leading to tissue fibrosis and hepatic dysfunction (Fig. 9) (246). However, immunoregulatory mechanisms in RILD remain incompletely defined. Pyroptosis is an inflammatory form of programmed cell death mediated by gasdermin D (GSDMD) that can reshape the immune microenvironment through the release of intracellular contents and cytokines (247-250). In a murine RILD model, RT increases hepatocellular expression of full-length GSDMD (GSDMD-FL) and its N-terminal fragment (GSDMD-N). This process promotes CXCL1 transcription through activation of STAT5A, while GSDMD-N pore formation facilitates CXCL1 release. The resulting CXCL1 signaling recruits neutrophils and exacerbates liver injury. Genetic deletion or pharmacologic inhibition of GSDMD and neutralization of CXCL1 can alleviate radiation-induced liver injury (251). Accordingly, pharmacologic approaches such as disulfiram that suppress both GSDMD-FL and GSDMD-N have been proposed as targeted strategies to prevent RILD (252-255).

RILD pathogenesis also involves complex cytokine network regulation. Ionizing radiation activates the DNA damage response through direct DNA damage and ROS bursts, initiating ATM and ATR signaling and MAPK cascades, including ERK/JNK/p38. These events promote autocrine growth factor release, including TGF-α and TNF-α, radiation-induced bystander effects and inflammatory responses (256-259). Hepatic non-parenchymal cells act as key effector populations. After irradiation, Kupffer cells secrete TNF-α, which drives inflammatory monocyte infiltration through TLR4/NF-κB signaling, inducing hepatocyte apoptosis and secondary injury (260-264). In parallel, sinusoidal endothelial cells undergo apoptosis and lose fenestrae, causing microcirculatory disturbance and promoting the secretion of fibronectin EIIIA, which activates hepatic stellate cells (265,266). Activated hepatic stellate cells respond to TGF-β1 signaling by increasing collagen synthesis through the TGF-β1/Smad/connective tissue growth factor axis and by suppressing extracellular matrix degradation, resulting in radiation-induced liver fibrosis (267-271). Radiation-induced senescent cells can also secrete pro-inflammatory factors such as IL-6 through the SASP, further worsening the microenvironment (272,273). Translational studies have focused on targeting cytokine pathways implicated in these processes. In animal studies, inhibiting Kupffer-cell function reduces TNF-α release and alleviates sinusoidal endothelial cell apoptosis and acute liver injury (260,274). Approaches targeting TGF-β1,

including antisense oligonucleotides and small-molecule inhibitors such as pirfenidone, can suppress fibrotic signaling and improve radiation-induced liver fibrosis (271,275). Natural antioxidants, including curcumin and resveratrol, can modulate pathways such as nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 and miR-34a-sirtuin 1 to suppress ROS/TNF-α/NF-κB-driven inflammatory axes, thereby reducing oxidative stress and fibrotic progression (276-279). Mesenchymal stem cell therapy can inhibit TGF-β/Smad signaling and promote tissue repair through the secretion of anti-inflammatory mediators such as hepatocyte growth factor (266,280). However, targeted therapeutics remain limited. Future work should integrate precision RT approaches such as stereotactic RT and explore combinations with immune checkpoint inhibitors to balance efficacy and hepatotoxicity (281).

11. Translational and clinical implications

Given the role of IFN-I in RT-induced innate and adaptive immunity, IFN-I has been explored as a therapeutic lever in cancer (282). Early studies showed that IFN-$\gamma^{+}CD8^{+}$ T-cells can increase radiosensitivity in hypoxic tumors (283). RT-induced IFN-β can remodel the antitumor immune microenvironment and has been associated with improved disease-free survival in lung cancer (284). Preclinical murine tumor studies indicated that loss of IFN signaling in the host or tumor after RT, with or without immune checkpoint blockade, weakens local and systemic immune responses (66,67,285). By contrast, a study in a murine tumor model suggested that persistent IFN signaling can contribute to resistance to immune checkpoint therapy (87). Tumor cells with high Argonaute 2 (AGO2) expression may suppress responsiveness to IFN-γ through a negative feedback loop involving AGO2/protein tyrosine phosphatase non-receptor type 6/STAT1, thereby promoting immune evasion. Targeting this pathway has been proposed for tumors with high AGO2 expression (286). These findings support a practical clinical strategy based on patient stratification. Baseline and early post-RT IFN-related gene signatures and circulating cytokine profiles can be used to classify tumors by their IFN-I signaling state (83,91,213,287). In tumors with low baseline IFN-I signaling, STING agonists or IFN-I agonists may be considered to enhance priming (66,67,77,131,282). In tumors with chronically high IFN-I signaling, the risk of tolerance and resistance should be evaluated, and shortened exposure or intermittent dosing may be more appropriate (83,85-88). This approach treats IFN-I as a modifiable system variable rather than a single-direction target (131).

Mechanistically, the cGAS-STING pathway lies upstream of RT-induced IFN-β production and links dendritic cell cross-presentation with $CD8^{+}$ T-cell priming, forming a central axis from innate sensing to adaptive immunity. STING signaling is required for effective adaptive responses in multiple models. Loss or inhibition of YTHDF1 reduces cathepsin A- and cathepsin B-mediated STING degradation, restores STING stability, increases irradiation-induced IFN-β secretion and dendritic cell antigen cross-presentation, and promotes $CD8^{+}$ T-cell cytotoxicity, thereby strengthening RT efficacy. Based on this mechanism, a dendritic cell vaccine generated by YTHDF1 knockout or treatment with the small-molecule inhibitor salvianolic acid C enhanced the efficacy of RT alone and RT combined with PD-L1 blockade in a preclinical model (81). In addition, combining RT with the STING agonist cGAMP can reduce radioresistance and enhance host antitumor immunity (67).

As described above, the CCL22/CCR4 axis contributes to immune regulation. Targeting this axis may disrupt interactions between Treg cells and DCs, enhance tumor antigen-specific T-cell responses and potentially synergize with PD-1 or CTLA-4 inhibitors (108). In a murine pancreatic cancer model, stereotactic body RT combined with locally delivered IL-12 fusion protein remodeled the TME, increased infiltration and activity of antitumor macrophages and $CD8^{+}$ T cells and resulted in durable tumor regression (288).

The DNA damage response network is another hub linking immunity and RT. When DNA repair is efficient, immunogenic cell death and cGAS-STING activation may be reduced, whereas impaired repair can increase cytosolic DNA signaling. Esophageal squamous cell carcinoma often exhibits radioresistance and poor prognosis (289). Overcoming radioresistance remains a priority, and the DNA damage response machinery that detects and repairs radiation-induced lesions represents a mechanistic contributor (290,291). PARP1 functions as a central sensor protein in this network (292). PARP inhibitors can activate cGAS/STING signaling and promote innate immune activation (74), consistent with RT-driven cytokine-mediated adaptive immunity (42,293). Although direct links between PARPis and specific cytokines require further definition, mechanistic intersections are plausible and clinically relevant. In esophageal cancer, astrocyte elevated gene-1 recruits the deubiquitinase biquitin-specific peptidase 10 to remove K48-linked polyubiquitination at Lys425 of PARP1, reducing PARP1 degradation and increasing recruitment to double-strand break sites. This mechanism enhances homologous recombination-mediated repair and reduces radiation lethality in esophageal squamous carcinoma cells (294). Vav guanine nucleotide exchange factor 2 (VAV2) is another candidate target. Increased VAV2 promotes the formation and activity of the Ku70-Ku80 complex involved in nonhomologous end joining repair and reduces radiation-induced DSBs. Under irradiation, VAV2 can also activate STAT1 signaling and promote radioresistance, and the STAT1 inhibitor fludarabine can reverse this phenotype in a preclinical model (295).

Cytokine mechanisms of radiation injury are discussed above. Translational studies also suggest that irradiation can activate the constitutively expressed NLR family pyrin domain containing 3 (NLRP3) inflammasome in bone marrow-derived macrophages, inducing pyroptosis and IL-1β production, and contributing to tissue injury and immune-cell loss (296). A plausible mechanism is that irradiation activates TLRs, leading to priming and increased NLRP3 expression, which promotes caspase-1 activation, IL-1β processing and pyroptosis (297-299). Caspase-1-dependent pyroptosis is not restricted to NLRP3. Other inflammasomes, including NLRP1, NLRC4 and the DNA-sensing absent in melanoma 2 (AIM2) inflammasome, may also contribute to radiation-associated caspase-1 activation (298-300). Irradiation can also induce the release of M1-type pro-inflammatory cytokines and MCP-1 (301,302), and may amplify inflammatory cascades through DAMPs and

additional inflammasome pathways, including AIM2 (300,303). These data support targeting NLRP3-driven pyroptosis as a strategy to reduce radiation-associated immune-cell loss, pro-inflammatory cytokine cascades and tissue injury.

This section also summarizes cytokine-related clinical studies, including therapeutic targets, drug classes and combination paradigms involving RT with or without immunotherapy, to support the development and clinical application of cytokine-directed agents in the RT setting (Table II) (8,304). Table III provides a concise cross-cytokine overview of representative clinical trials grouped by cytokine axis, cancer type, RT-containing regimen and study focus, thereby highlighting recurring translational patterns across IFN-, IL-2-, GM-CSF- and TGF-β-directed strategies. Several themes emerge from these trials. TGF-β inhibition has been explored across multiple tumor types: Fresolimumab is being evaluated in combination with RT in metastatic breast cancer (NCT01401062) and with stereotactic ablative body radiotherapy in early-stage non-small-cell lung cancer (NCT02581787), while bintrafusp α, a bifunctional TGF-β/PD-L1 inhibitor, is under investigation with RT in esophageal squamous cell carcinoma (NCT04595149) and in combination with SBRT and IL-12 agonist M9241 in advanced pancreatic cancer (NCT04327986). IL-2-based strategies represent another active area, with trials combining SBRT and high-dose IL-2 in melanoma (NCT01416831), intralesional IL-2 with RT in refractory metastatic NSCLC (NCT03224871) and bempegaldesleukin (NKTR-214) plus nivolumab with RT in sarcoma (NCT03282344). GM-CSF has been combined with SBRT in stage IV NSCLC after second-line chemotherapy failure (NCT02623595) and with RT and PD-1 inhibition in advanced recurrent or metastatic head and neck tumors (NCT05760196). IFN-based approaches include adjuvant IFN-α2b with postoperative RT for metastatic melanoma (NCT00003444) and IFN-β combined with avelumab with or without RT for Merkel cell carcinoma (NCT02584829). Collectively, these trials reflect a broad effort to target cytokine axes across diverse tumor histologies and RT delivery platforms.

12. Discussion

The efficacy of combining RT with immune checkpoint inhibitors depends on remodeling the immune state of the TME. Identification and modulation of key immunoregulatory factors are therefore important for optimizing combination strategies. IFN-I signaling induced by irradiation is required to initiate systemic antitumor immunity. For instance, in IFN-I receptor knockout models, RT shows minimal efficacy, suggesting that IFN-I signaling may have predictive value for response to RT combined with immunotherapy (66,67). Clinically, IFN-related gene signatures may help estimate radiosensitivity and the likelihood of benefit from immunotherapy (83). This pathway also offers actionable targets. STING agonists and PARPis can amplify RT-induced innate immune signaling and may enhance responses to PD-1 or PD-L1 blockade (77). In parallel, TAMs and macrophage-mediated immunosuppression contribute to radioresistance. After RT, tumors can exhibit increased macrophage infiltration and M2 polarization, and chemokines such as CCL2 produced in this setting can recruit MDSCs and weaken antitumor immunity (92,94). High macrophage density and hyperactivation of the CCL2/CCR2 axis have been associated with poor outcomes in RT-immunotherapy combinations and may serve as candidate biomarkers of response. Interventions targeting this mechanism have shown benefit in preclinical models. CSF1R inhibitors can deplete intratumoral macrophages, improve local control and delay recurrence when combined with RT (35-37,154). Blockade of CCL2/CCR2 signaling can reduce macrophage chemotaxis, remodel the TME and increase radiosensitivity (95,153). These findings support an approach in which IFN signaling and macrophage-related cytokine profiles are assessed to guide the selection of adjunctive immunomodulatory interventions.

Mechanism-based prevention and management of RT-related toxicity is a key translational priority while pursuing antitumor efficacy. Radiation-induced lung injury is linked to dysregulated immune responses. RT can trigger an acute inflammatory cascade in the lung with early increases in mediators such as IL-1, TNF-α and IL-6, whereas persistent inflammatory signaling contributes to chronic fibrotic remodeling (188,190-192). Excessive STING activation can have context-dependent effects. In normal lung tissue, STING signaling can exacerbate fibrosis by promoting CCR2-dependent monocyte recruitment and M2 macrophage polarization (195). A preclinical study indicated that CCR2 deficiency or pharmacologic blockade reduces inflammatory cell infiltration and capillary damage and can reduce lung injury after irradiation (96). These findings support monitoring of inflammatory biomarkers such as IL-6 and TGF-β during RT to identify patients at increased risk and to consider the timely use of anti-inflammatory or anti-fibrotic interventions to limit progression from acute inflammation to chronic injury (189,191). Radiation-induced liver injury can also involve an innate immunity-driven inflammatory loop. Ionizing radiation can activate the NLRP3 inflammasome in Kupffer cells and induce pyroptosis, leading to the release of IL-1β and other inflammatory mediators and exacerbating parenchymal injury (250,251). Targeting inflammasome-associated pyroptosis has therefore been proposed as an interventional strategy. In preclinical models, disulfiram inhibits GSDMD-mediated pyroptosis and reduces irradiation-induced hepatocyte injury and neutrophil infiltration (252,254). In clinical practice, liver function and relevant inflammatory biomarkers should be monitored during RT, and hepatoprotective and anti-inflammatory measures should be implemented when abnormalities are detected to prevent irreversible decompensation (244,245).

Oral mucositis, a frequent consequence of head and neck RT, reflects a cascade of immune responses initiated by epithelial injury. After disruption of the oral mucosal barrier, exposed basal cells and microbial products can activate pathways such as NF-κB, induce the release of pro-inflammatory mediators including TNF and IL-6, and promote neutrophil and macrophage infiltration, leading to ulceration and pain (220,221). Consistent with this mechanism, peripheral blood inflammatory markers correlate with mucositis severity, and routine monitoring of TNF and IL-6 may provide an adjunctive tool for assessing mucosal damage during treatment (221). Multiple randomized controlled trials have evaluated targeted interventions, including topical recombinant human IL-11 mouthwash to promote mucosal regeneration, anti-inflammatory mouth rinses and photobiomodulation to

Table II. Cytokine-guided RT combinations: Clinical translation and trials overview.

Related cytokine	Cancer type	Drug name	Description	Trial no. (Refs.)
TGF-β	Breast cancer	LY2157299	RT+LY2157299 in metastatic breast cancer	NCT02538471
IL-2	Melanoma	SBRT + high-dose IL-2	Comparison of best overall tumor response between high-dose IL-2 alone and SBRT + high-dose IL-2	NCT01416831 (304)
GM-CSF	Pancreatic cancer	GV1001 + GM-CSF	RT+GM-CSF with the telomerase vaccine GV1001 in pancreatic cancer	NCT01342224
IL-2	Sarcoma	Bempegaldesleukin (NKTR-214)	Bempegaldesleukin + nivolumab in metastatic or locally advanced sarcoma	NCT03282344, NCT02983045
IL-2; TLR7/8	Colon carcinoma, mammary carcinoma, fibrosarcoma	Bempegaldesleukin + NKTR-262	Bempegaldesleukin + NKTR-262 is being evaluated clinically, and preclinical data suggest increased $CD8^+$ T-cell cytotoxicity compared with bempegaldesleukin + RT	NCT03435640 (8)
TGF-β	Breast cancer, NSCLC	Fresolimumab	Fresolimumab combined with RT to reduce immunosuppression	NCT02581787
TGF-β; IL-12	Pancreatic cancer	M7824, M9241, SBRT	Bintrafusp α (M7824) and NHS-IL12 (M9241) in combination with SBRT in advanced pancreatic cancer	NCT04327986
IL-12	Advanced solid tumors	MEDI1191 + durvalumab	Phase I study evaluating intratumoral IL-12 mRNA therapy MEDI1191 in sequential and concurrent combination with durvalumab. Preclinical work suggests that IL-12 delivery may synergize with SBRT	NCT03946800
IL-2	B cell NHL	Rituximab, DI-Leu16-IL2	Phase I study of De-immunized DI-Leu16-IL-2 immunocytokine in patients with B-cell NHL	NCT00720135
TGF-β	Early-stage NSCLC	SABR + fresolimumab	SABR-ATAC trial evaluating TGF-β inhibition with fresolimumab + SABR in early-stage NSCLC	NCT02581787
TGF-β	Metastatic breast cancer	RT + fresolimumab	Study testing safety of combining fresolimumab with local RT and evaluating tumor regression	NCT01401062
GM-CS	NSCLC	SBRT + rh GM-CSF	Study assessing safety and efficacy of SBRT combined with rh GM-CSF in stage IV NSCLC after failure of second-line chemotherapy	NCT02623595
IL-2	Oral cancer	RT + proleukin	Surgery and RT with or without IL-2 for recurrent squamous cell carcinoma of the head and neck	NCT00002702
IL-2	NHL	RT + IL-2	Study comparing post-transplant IL-2 maintenance with observation in refractory or relapsed NHL	NCT00002649
IL-2	NSCLC	RT + intralesional IL-2	Phase I trial evaluating RT at 8 Gy in three fractions + intralesional IL-2 in refractory metastatic NSCLC receiving ongoing PD-1 or PD-L1 therapy, with safety and tolerability as the primary endpoint	NCT03224871
IL-2	Metastatic melanoma	RT + IL-2 + ipilimumab	RT with combination immunotherapy for relapsed or refractory metastatic melanoma	NCT03297463

Table II. Continued.

Related cytokine	Cancer type	Drug name	Description	Trial no. (Refs.)
GM-CSF	Advanced recurrent or metastatic head and neck tumors	RT + GM-CSF	RT combined with PD-1 inhibitor and GM-CSF for advanced recurrent or metastatic head and neck tumors	NCT05760196
IL-2; GM-CSF	Advanced refractory solid tumors	RT + IL-2 + GM-CSF	Hypofractionated RT combined with PD-1 inhibitor followed by sequential GM-CSF and IL-2 for advanced refractory solid tumors	NCT04892498
TGF-β	Invasive breast cancer	RT	Randomized study evaluating the relationship between plasma TGF-β1 and fractionation in RT for breast cancer	NCT00301041
TGF-β	Breast cancer	RT + LY2157299	LY2157299 monohydrate + RT in metastatic breast cancer	NCT02538471
TGF-β	Esophageal squamous cell carcinoma	RT + bintrafusp alfa	TGF-β and PD-L1 inhibition with bintrafusp alfa in esophageal squamous cell carcinoma combined with chemoradiation therapy	NCT04595149
IFN-α2b	Metastatic melanoma	RT + IFN-α2b	Phase III randomized trial evaluating postoperative RT + adjuvant IFN-α2b for cervical, axillary or inguinal lymph node metastases from cutaneous melanoma	NCT00003444
IFN-β	Merkel cell carcinoma	RT or IFN-β + avelumab	Localized RT or recombinant IFN-β and avelumab with or without cellular therapy for Merkel cell carcinoma	NCT02584829
IFN-α	Pancreatic cancer	RT + IFN-α	Adjuvant chemoradiotherapy and IFN-α in resected pancreatic cancer	NCT00059826
IFN-α2b	Malignant pleural mesothelioma	RT + IFN-α2b	Cisplatin, IFN-α, surgery and RT for malignant pleural mesothelioma	NCT00003263
IFN-α	Esophageal cancer	RT + IFN-α	PFL-alpha chemotherapy followed by surgery or FHX for early-stage esophageal cancer as a pilot study	NCT00004897

RT, radiotherapy; TGF-β, transforming growth factor β; IL-2, interleukin 2; SBRT, stereotactic body radiation therapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; NSCLC, non-small cell lung cancer; NHS-IL12, NHS interleukin 12; NHL, non-Hodgkin lymphoma; SABR, stereotactic ablative radiotherapy; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; IFN-α2b, interferon α-2b; IFN-α, interferon α; rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; NCT, ClinicalTrials.gov identifier.

accelerate ulcer healing (232,236,237). Photobiomodulation, supported by its anti-inflammatory and pro-healing effects, has been recommended by clinical guidelines as a first-line measure for preventing and managing radiation-induced oral mucositis (239,240). Thus, mechanism-guided monitoring and intervention may reduce the incidence and severity of RT-related toxicities.

The selection of the RT modality and parameters can alter immune trajectories and toxicity profiles through effects on cytokine networks, providing an additional dimension for clinical optimization. Hypofractionated regimens such as SBRT generate systemic immune and inflammatory environments that can differ from conventional fractionation because of high conformality and steep dose gradients (305). High-dose irradiation-induced cellular damage leads to the release of ROS, inflammatory mediators and adhesion molecules that can function as danger signals and enhance immune responses (306). In a clinical study evaluating SBRT combined with IL-2 in metastatic melanoma or renal cell carcinoma, the combination increased the frequency of proliferating $CD4^+$ T cells and early activated effector memory phenotype cells, with an objective response rate exceeding historical benchmarks (307). Preclinical work has also evaluated SBRT combined with cytokine modulation in pancreatic cancer models. In that setting, IL-12-related effects depend on IFN-γ signaling and have been linked to the reversal of T-cell exhaustion (308). A comparative

Table III. Cytokine-guided RT combinations: Clinical translation and trials overview.

Related cytokine	Cancer type	Drug name	Description	Trial no. (Refs.)
IFN-α-2b	Metastatic melanoma	RT+ IFN-α-2b	Phase III RCT: Post-op RT + adjuvant IFN-α2b for cervical/axillary/inguinal LN metastases from cutaneous melanoma	NCT00003444
IFN-α	Pancreatic cancer	RT+IFN-α	Adjuvant chemoradiotherapy and IFN-α in treating patients with resected pancreatic cancer	NCT00059826
IFN-α2b	Malignant pleural mesothelioma	RT+IFN-α2b	Cisplatin, IFN-α, surgery and RT in treating patients with malignant pleural mesothelioma	NCT00003263
IFN-α	Esophageal cancer	RT+ IFN-α	PFL-alpha chemotherapy followed by surgery or FHX for early stage esophageal cancer - a pilot project	NCT00004897
IFN-β	Merkel cell carcinoma	RT/IFN-β+ avelumab	Localized RT or recombinant IFN-β and avelumab with or without cellular therapy for Merkel cell carcinoma	NCT02584829
IL-2	Melanoma	SBRT+high-dose IL-2	Best overall tumor response of high dose IL-2 vs. SBRT+high dose IL-2	NCT01416831 (304)
IL-2	Sarcoma	NKTR-214	NKTR-214 + nivolumab in metastatic and/or locally advanced sarcoma	NCT03282344; NCT0298304.
GM-CSF	Colon carcinoma; mammary carcinoma; fibrosarcoma	Bempegaldesleukin + NKTR-262	Combining bempegaldesleukin + NKTR-262 improves CD8+ T cell cytotoxicity over BEMPEG+RT	NCT03435640 (8)
IL-2	B-cell non-Hodgkin lymphoma	Rituximab, DI-Leu16-IL-2	A phase I study of de-immunized DI-Leu16-IL-2 immunocytokine in patients with B-cell non-Hodgkin lymphoma	NCT00720135
IL-2	Oral cancer	RT+Proleukin	Surgery and RT with or without IL-2 in treating patients with recurrent squamous cell cancer of the head and neck	NCT00002702
IL-2	Non-Hodgkin's lymphoma	RT+IL-2	Compares post-transplant IL-2 maintenance with observation to evaluate effectiveness in refractory/relapsed non-Hodgkin's lymphoma	NCT00002649
IL-2	NSCLC	RT+IL-2	Phase I: RT (8 Gy x 3) + intralesional IL-2 with ongoing PD-1/PD-L1 therapy in refractory metastatic NSCLC; primary endpoint: Safety/ tolerability	NCT03224871
IL-2	Metastatic melanoma	RT+IL-2+Ipilimumab	RT with combination immunotherapy for relapsed/refractory metastatic melanoma	NCT03297463
IL-2, GM-CSF	Advanced refractory solid tumors	RT+IL-2+GM-CSF	Hypofractionated radiotherapy combined with PD-1 inhibitor sequential GM-CSF and IL-2 for the treatment of advanced refractory solid tumors	NCT04892498
IL-12	Pancreatic cancer	SBRT+IL-12	Integrating IL-12 mRNA nanotechnology with SBRT eliminates T cell exhaustion in preclinical models of pancreatic cancer	NCT03946800
GM-CSF	Pancreatic cancer	GV1001+GM-CSF	RT + GM-CSF with telomerase vaccine in pancreatic cancer	NCT01342224
GM-CSF	NSCLC	SBRT+rhGM-CSF	Assessment of the safety and efficacy of stereotactic body radiotherapy combined with recombinant human GM-CSF in patients with stage IV NSCLC who failed second-line chemotherapy	NCT02623595

Table III. Continued.

Related cytokine	Cancer type	Drug name	Description	Trial no. (Refs.)
GM-CSF	Advanced Recurrent Metastatic head and neck tumors	RT+GM-CSF	RT combined with PD-1 inhibitor and GM-CSF for advanced recurrent metastatic head and neck tumors	NCT05760196
TGF-β	Breast cancer	LY2157299	RT + LY2157299 in metastatic breast cancer	NCT02538471
TGF-β	Breast cancer; non-small cell lung cancer	Fresolimumab	Fresolimumab with radiotherapy to reduce immunosuppression	NCT02581787
TGF-β, IL-12	Pancreatic cancer	M7824, M9241+SBRT	M7824 and the M9241 in combination with SBRT in adults with advanced pancreatic cancer	NCT04327986
TGF-β	Early stage non-small cell lung cancer	SABR+Fresolimumab	SABR-ATAC: A trial of TGF-β inhibition and stereotactic ablative RT for early stage non-small cell lung cancer	NCT02581787
TGF-β	Metastatic breast cancer	RT+fresolimumab	Assessment of the safety of combining fresolimumab and local radiotherapy and whether the combination can achieve tumor regression	NCT01401062
TGF-β	Invasive breast cancer	RT	The relationship between plasma transforming TGF-β and fractionation in RT for breast cancer: A randomized study	NCT00301041
TGF-β	Breast cancer	RT+LY2157299	LY2157299 monohydrate (LY2157299) and radiotherapy in metastatic breast cancer	NCT02538471
TGF-β	Esophageal squamous cell carcinoma	RT+ bintrafusp α	TGF-β and PD-L1 inhibition in esophageal squamous cell carcinoma combined with chemoradiation therapy	NCT04595149

IFN-α-2b, interferon α-2b; RT, radiotherapy; RCT, randomized controlled trial; Post-op, post-operative; LN, lymph node; PFL-Alpha, cisplatin, 5-fluorouracil, leucovorin-alpha interferon; FHX, 5-fluorouracil, hydroxyurea, radiation; SBRT, stereotactic body radiation therapy; IL-2, interleukin-2; NKTR-214, bempegaldesleukin-2; Sarcom., sarcoma; TLR7/8, Toll-like receptor 7/8; BEMPEG, bempegaldesleukin; DI-Leu16-IL2, de-immunized DI-Leu16-interleukin-2; NSCLC, non-small cell lung cancer; Gy, Gray; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; mRNA, messenger RNA; GV1001, telomerase peptide vaccine GV; rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; TGF-β, transforming growth factor β; LY2157299, galunisertib; Fresolimumab, anti-TGF-β monoclonal antibody; M7824, bintrafusp alfa; M9241, NHS-IL-12; SABR, stereotactic ablative radiotherapy; ATAC, anti-TGF-β and checkpoint; PD-L1, programmed death-ligand 1.

study of RT techniques from a cytokine perspective reported that hypofractionated stereotactic RT reduced IL-10 and IL-17 with limited effects on IL-1α, IL-6, macrophage inflammatory protein 1α and TNF-α. These patterns were interpreted as consistent with lower pulmonary toxicity and limited systemic immune perturbation. By contrast, IMRT altered multiple cytokine pathways associated with both antitumor and protumor effects, and outcomes may depend on individual and protocol-specific factors (287).

FLASH RT delivered at ultra-high dose rates has been reported to reduce normal tissue injury while maintaining antitumor activity in preclinical models. In animal studies, FLASH RT reduces free radical accumulation and endothelial injury in normal tissues and suppresses the production of multiple pro-inflammatory and profibrotic cytokines. Compared with conventional RT, FLASH reduces mediators such as TGF-β and IL-1β in lung tissue, alleviates lung injury and promotes $CD4^+$ T-cell secretion of reparative cytokines, including IL-10 and IL-22, which may support tissue regeneration (62,63). Proton therapy improves dose distribution and can reduce normal tissue exposure. When combined with immunotherapy, proton therapy has been associated with increased intratumoral IFN-γ^+ T cells and reduced TGF-β signaling, potentially enhancing systemic antitumor immunity (64). These observations suggest that dose, fractionation, dose rate and irradiation field should be considered controllable variables that influence the balance between immune activation and immunosuppression, and between antitumor efficacy and normal tissue toxicity.

In summary, integrating mechanistic understanding of RT-induced immune signaling with clinical decision-making can support measurable and adjustable therapeutic strategies. Candidate approaches include profiling cytokines and immune-cell composition, selecting RT regimens based on

patient-specific immune features and incorporating targeted agents to modulate detrimental inflammatory or immunosuppressive pathways. These steps may enhance RT-driven antitumor immunity while limiting normal tissue injury (192). With improved mechanistic resolution and clinically implementable monitoring and intervention strategies, RT can be developed as a component of systemic immunomodulatory treatment, supporting individualized radioimmunotherapy.

Acknowledgements

Not applicable.

Funding

This study received funding from the following sources: The Key Research Project of Jiangsu Provincial Health Commission (grant no. ZDB2020022) and the Guidance Science and Technology Plan Project for Social Development of Zhenjiang City (grant no. FZ2023049).

Availability of data and materials

Not applicable.

Authors' contributions

SZ, YJ, JF, MG, YW and CD collected the relevant literature and drafted the manuscript. CD designed the review framework and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rodriguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC and Demaria S: Immunological mechanisms responsible for radiation-induced abscopal effect. Trends Immunol 39: 644-655, 2018.
2. Han B, Li C, Meng H, Gomes Romeiro F, Mancuso A, Zhou Z, Levi Sandri GB, Xu Y, Han T, Han L, *et al*: Efficacy and safety of external-beam radiation therapy for hepatocellular carcinoma: An overview of current evidence according to the different target population. Biosci Trends 13: 10-22, 2019.
3. Kagawa Y, Smith JJ, Fokas E, Watanabe J, Cercek A, Greten FR, Bando H, Shi Q, Garcia-Aguilar J, Romesser PB, *et al*: Future direction of total neoadjuvant therapy for locally advanced rectal cancer. Nat Rev Gastroenterol Hepatol 21: 444-455, 2024.
4. McPhail S, Barclay ME, Swann R, Johnson SA, Alvi R, Barisic A, Bucher O, Creighton N, Denny CA, Dewar RA, *et al*: Use of radiotherapy in patients with oesophageal, stomach, colon, rectal, liver, pancreatic, lung, and ovarian cancer: an International Cancer Benchmarking Partnership (ICBP) population-based study. Lancet Oncol 25: 352-365, 2024.
5. Liauw SL, Connell PP and Weichselbaum RR: New paradigms and future challenges in radiation oncology: an update of biological targets and technology. Sci Transl Med 5: 173sr2, 2013.
6. Begg AC, Stewart FA and Vens C: Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 11: 239-253, 2011.
7. Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, Al-Hallaq HA, Arina A, Khodarev NN, Janisch L, *et al*: Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. J Clin Oncol 36: 1611-1618, 2018.
8. Pollom EL, Chin AL, Diehn M, Loo BW and Chang DT: Normal tissue constraints for abdominal and thoracic stereotactic body radiotherapy. Semin Radiat Oncol 27: 197-208, 2017.
9. Vignard J, Mirey G and Salles B: Ionizing-radiation induced DNA double-strand breaks: A direct and indirect lighting up. Radiother Oncol 108: 362-369, 2013.
10. Zou Z, Chang H, Li H and Wang S: Induction of reactive oxygen species: An emerging approach for cancer therapy. Apoptosis 22: 1321-1335, 2017.
11. Wang H, Mu X, He H and Zhang XD: Cancer radiosensitizers. Trends Pharmacol Sci 39: 24-48, 2018.
12. Maier P, Hartmann L, Wenz F and Herskind C: Cellular pathways in response to ionizing radiation and their targetability for tumor radiosensitization. Int J Mol Sci 17: 102, 2016.
13. Vitale I, Manic G, Coussens LM, Kroemer G and Galluzzi L: Macrophages and metabolism in the tumor microenvironment. Cell Metab 30: 36-50, 2019.
14. Wang H, Wang T, Yan S, Tang J, Zhang Y, Wang L, Xu H and Tu C: Crosstalk of pyroptosis and cytokine in the tumor microenvironment: from mechanisms to clinical implication. Mol Cancer 23: 268, 2024.
15. Aggarwal BB, Gupta SC and Kim JH: Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood 119: 651-665, 2012.
16. Lazear HM, Schoggins JW and Diamond MS: Shared and distinct functions of type I and III Interferons. Immunity 50: 907-923, 2019.
17. Rose-John S: Interleukin-6 family cytokines. Cold Spring Harb Perspect Biol 10: a028415, 2018.
18. Zhang Y, Alexander PB and Wang XF: TGF-beta family signaling in the control of cell proliferation and survival. Cold Spring Harb Perspect Biol 9: a022145, 2017.
19. Briukhovetska D, Dorr J, Endres S, Libby P, Dinarello CA and Kobold S: Interleukins in cancer: from biology to therapy. Nat Rev Cancer 21: 481-499, 2021.
20. Dougan M, Dranoff G and Dougan SK: GM-CSF, IL-3, and IL-5 family of cytokines: Regulators of inflammation. Immunity 50: 796-811, 2019.
21. Batlle E and Massague J: Transforming growth factor-β signaling in immunity and cancer. Immunity 50: 924-940, 2019.
22. Kang S, Tanaka T, Narazaki M and Kishimoto T: Targeting interleukin-6 signaling in clinic. Immunity 50: 1007-1023, 2019.
23. Leonard WJ, Lin JX and O'Shea JJ: The γ(c) family of cytokines: Basic biology to therapeutic ramifications. Immunity 50: 832-850, 2019.
24. Mantovani A, Dinarello CA, Molgora M and Garlanda C: Interleukin-1 and related cytokines in the regulation of inflammation and immunity. Immunity 50: 778-795, 2019.
25. McGeachy MJ, Cua DJ and Gaffen SL: The IL-17 family of cytokines in health and disease. Immunity 50: 892-906, 2019.
26. Ouyang W and O'Garra A: IL-10 family cytokines IL-10 and IL-22: From basic science to clinical translation. Immunity 50: 871-891, 2019.
27. Dranoff G: Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer 4: 11-22, 2004.
28. Dranoff G, Jaffee E, Lazenby A, Golumbek P, Levitsky H, Brose K, Jackson V, Hamada H, Pardoll D and Mulligan RC: Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci USA 90: 3539-3543, 1993.
29. Berns AJ, Clift S, Cohen LK, Donehower RC, Dranoff G, Hauda KM, Jaffee EM, Lazenby AJ, Levitsky HI, Marshall FF, *et al*: Phase I study of non-replicating autologous tumor cell injections using cells prepared with or without GM-CSF gene transduction in patients with metastatic renal cell carcinoma. Hum Gene Ther 6: 347-368, 1995.

30. Hodi FS, Butler M, Oble DA, Seiden MV, Haluska FG, Kruse A, Macrae S, Nelson M, Canning C, Lowy I, *et al*: Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. Proc Natl Acad Sci USA 105: 3005-3010, 2008.
31. Hodi FS, Mihm MC, Soiffer RJ, Haluska FG, Butler M, Seiden MV, Davis T, Henry-Spires R, MacRae S, Willman A, *et al*: Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci USA 100: 4712-4717, 2003.
32. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, *et al*: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363: 411-422, 2010.
33. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, Delman KA, Spitler LE, Puzanov I, Agarwala SS, *et al*: Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 33: 2780-2788, 2015.
34. Anderton H, Wicks IP and Silke J: Cell death in chronic inflammation: Breaking the cycle to treat rheumatic disease. Nat Rev Rheumatol 16: 496-513, 2020.
35. Xu J, Mo J, Jiang Y, Yang T, Lu Z, Han L, Ding J, Shi F and Liu R: Tumor-associated macrophages inradiotherapy: Mechanisms of polarization, immune regulation and therapeutic strategies. Int Immunopharmacol 161: 115009, 2025.
36. Yan D, Kowal J, Akkari L, Schuhmacher AJ, Huse JT, West BL and Joyce JA: Inhibition of colony stimulating factor-1 receptor abrogates microenvironment-mediated therapeutic resistance in gliomas. Oncogene 36: 6049-6058, 2017.
37. Stafford JH, Hirai T, Deng L, Chernikova SB, Urata K, West BL and Brown JM: Colony stimulating factor 1 receptor inhibition delays recurrence of glioblastoma after radiation by altering myeloid cell recruitment and polarization. Neuro Oncol 18: 797-806, 2016.
38. Takeshima T, Pop LM, Laine A, Iyengar P, Vitetta ES and Hannan R: Key role for neutrophils in radiation-induced antitumor immune responses: Potentiation with G-CSF. Proc Natl Acad Sci USA 113: 11300-11305, 2016.
39. Li X, Wang C, Wu Y, Zhang J, Zhang H, Qin S, Tang L and Yu F: Self-Powered α radionuclide nanomedicine: Mitochondria-targeted multimodal energy recycling for amplified radioimmunotherapy. Adv Mater 37: e2504612, 2025.
40. Barker HE, Paget JT, Khan AA and Harrington KJ: The tumour microenvironment after radiotherapy: Mechanisms of resistance and recurrence. Nat Rev Cancer 15: 409-425, 2015.
41. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
42. Zhang C, Liang Z, Ma S and Liu X: Radiotherapy and cytokine storm: Risk and mechanism. Front Oncol 11: 670464, 2021.
43. Honeychurch J and Illidge TM: The influence of radiation in the context of developing combination immunotherapies in cancer. Ther Adv Vaccines Immunother 5: 115-122, 2017.
44. Weichselbaum RR, Liang H, Deng L and Fu YX: Radiotherapy and immunotherapy: A beneficial liaison? Nat Rev Clin Oncol 14: 365-379, 2017.
45. Colton M, Cheadle EJ, Honeychurch J and Illidge TM: Reprogramming the tumour microenvironment by radiotherapy: Implications for radiotherapy and immunotherapy combinations. Radiat Oncol 15: 254, 2020.
46. De Martino M, Daviaud C and Vanpouille-Box C: Radiotherapy: An immune response modifier for immuno-oncology. Semin Immunol 52: 101474, 2021.
47. Krombach J, Hennel R, Brix N, Orth M, Schoetz U, Ernst A, Schuster J, Zuchtriegel G, Reichel CA, Bierschenk S, *et al*: Priming anti-tumor immunity by radiotherapy: Dying tumor cell-derived DAMPs trigger endothelial cell activation and recruitment of myeloid cells. Oncoimmunology 8: e1523097, 2018.
48. Fridman WH, Pages F, Sautes-Fridman C and Galon J: The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer 12: 298-306, 2012.
49. Liu Q, Hao Y, Du R, Hu D, Xie J, Zhang J, Deng G, Liang N, Tian T, Kasmann L, *et al*: Radiotherapy programs neutrophils to an antitumor phenotype by inducing mesenchymal-epithelial transition. Transl Lung Cancer Res 10: 1424-1443, 2021.
50. Kachikwu EL, Iwamoto KS, Liao YP, DeMarco JJ, Agazaryan N, Economou JS, McBride WH and Schaue D: Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys 81: 1128-1135, 2011.
51. Arina A, Beckett M, Fernandez C, Zheng W, Pitroda S, Chmura SJ, Luke JJ, Forde M, Hou Y, Burnette B, *et al*: Tumor-reprogrammed resident T cells resist radiation to control tumors. Nat Commun 10: 3959, 2019.
52. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, Barcellos-Hoff MH and Demaria S: TGFβ is a master regulator of radiation therapy-induced antitumor immunity. Cancer Res 75: 2232-2242, 2015.
53. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, Stratford IJ, Poon E, Morrow M, Stewart R, *et al*: Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 74: 5458-5468, 2014.
54. Liao Z, Wang Y, Yang Y, Liu X, Yang X, Tian Y, Deng S, Hu Y, Meng J, Li J, *et al*: Targeting the cascade amplification of macrophage colony-stimulating factor to alleviate the immunosuppressive effects following radiotherapy. Research (Wash D C) 7: 0450, 2024.
55. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, *et al*: Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 379: 2342-2350, 2018.
56. Redza-Dutordoir M and Averill-Bates DA: Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta 1863: 2977-2992, 2016.
57. Ouellette MM, Zhou S and Yan Y: Cell signaling pathways that promote radioresistance of cancer cells. Diagnostics (Basel) 12: 656, 2022.
58. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P, *et al*: Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 13: 1050-1059, 2007.
59. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, Beckett M, Sharma R, Chin R, Tu T, *et al*: Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: Changing strategies for cancer treatment. Blood 114: 589-595, 2009.
60. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S and Formenti SC: Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 18: 313-322, 2018.
61. Price JM, Prabhakaran A and West CML: Predicting tumour radiosensitivity to deliver precision radiotherapy. Nat Rev Clin Oncol 20: 83-98, 2023.
62. Yan O, Wang S, Wang Q and Wang X: FLASH radiotherapy: Mechanisms of biological effects and the therapeutic potential in cancer. Biomolecules 14: 754, 2024.
63. Lu H, Li M, Quan C, Li C, Li D, Li Z, Xu J, Zhang L, Liu Q, Dong G and Wang C: FLASH irradiation modulates immune responses and accelerates lung recovery: A single-cell perspective. Adv Sci (Weinh) 12: e01797, 2025.
64. Hu Y, Paris S, Sahoo N, Wang Q, Wang Q, Barsoumian HB, Huang A, Da Silva J, Bienassis C, Leyton CSK, *et al*: Superior antitumor immune response achieved with proton over photon immunoradiotherapy is amplified by the nanoradioenhancer NBTXR3. J Nanobiotechnology 22: 597, 2024.
65. Schneider WM, Chevillotte MD and Rice CM: Interferon-stimulated genes: A complex web of host defenses. Annu Rev Immunol 32, 513-545, 2014.
66. Burnette BC, Liang H, Lee Y, Chlewicki L, Khodarev NN, Weichselbaum RR, Fu YX and Auh SL: The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. Cancer Res 71: 2488-2496, 2011.
67. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T, *et al*: STING-Dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity 41: 843-852, 2014.
68. Ishikawa H, Ma Z and Barber GN: STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature 461: 788-792, 2009.
69. Harding SM, Benci JL, Irianto J, Discher DE, Minn AJ and Greenberg RA: Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature 548: 466-470, 2017.
70. Mackenzie KJ, Carroll P, Martin CA, Murina O, Fluteau A, Simpson DJ, Olova N, Sutcliffe H, Rainger JK, Leitch A, *et al*: cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 548: 461-465, 2017.
71. Lim JY, Gerber SA, Murphy SP and Lord EM: Type I interferons induced by radiation therapy mediate recruitment and effector function of CD8(+) T cells. Cancer Immunol Immunother 63: 259-271, 2014.

72. Yamazaki T, Kirchmair A, Sato A, Buque A, Rybstein M, Petroni G, Bloy N, Finotello F, Stafford L, Navarro Manzano E, *et al*: Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy. Nat Immunol 21: 1160-1171, 2020.
73. Shen J, Zhao W, Ju Z, Wang L, Peng Y, Labrie M, Yap TA, Mills GB and Peng G: PARPi triggers the STING-Dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. Cancer Res 79: 311-319, 2019.
74. Pantelidou C, Sonzogni O, De Oliveria Taveira M, Mehta AK, Kothari A, Wang D, Visal T, Li MK, Pinto J, Castrillon JA, *et al*: PARP inhibitor efficacy depends on CD8(+) T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of triple-negative breast cancer. Cancer Discov 9: 722-737, 2019.
75. Ahn J, Konno H and Barber GN: Diverse roles of STING-dependent signaling on the development of cancer. Oncogene 34: 5302-5308, 2015.
76. Garcia-Diaz A, Shin DS, Moreno BH, Saco J, Escuin-Ordinas H, Rodriguez GA, Zaretsky JM, Sun L, Hugo W, Wang X, *et al*: Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. Cell Rep 19: 1189-1201, 2017.
77. Li A, Yi M, Qin S, Song Y, Chu Q and Wu K: Activating cGAS-STING pathway for the optimal effect of cancer immunotherapy. J Hematol Oncol 12: 35, 2019.
78. Stilmann M, Hinz M, Arslan SC, Zimmer A, Schreiber V and Scheidereit C: A nuclear poly(ADP-ribose)-dependent signalosome confers DNA damage-induced IkappaB kinase activation. Mol Cell 36: 365-378, 2009.
79. Demaria O, De Gassart A, Coso S, Gestermann N, Di Domizio J, Flatz L, Gaide O, Michielin O, Hwu P, Petrova TV, *et al*: STING activation of tumor endothelial cells initiates spontaneous and therapeutic antitumor immunity. Proc Natl Acad Sci USA 112: 15408-15413, 2015.
80. Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, Jacob L, Patwa R, Shah H, Xu K, *et al*: Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature 533: 493-498, 2016.
81. Wen C, Wang L, Piffko A, Chen D, Yu X, Zawieracz K, Bugno J, Yang K, Naccasha EZ, Ji F, *et al*: YTHDF1 loss in dendritic cells potentiates radiation-induced antitumor immunity via STING-dependent type I IFN production. J Clin Invest 134: e181612, 2024.
82. Huang L, Lu W, Wu R, Li Y, Ou Z, Chen J, Liu Y, Yang W, Xue W, Mu P, *et al*: Interferon-driven CAF reprogramming augments immunogenic response to neoadjuvant radiotherapy in colorectal cancer. Cell Rep Med 6: 102251, 2025.
83. Weichselbaum RR, Ishwaran H, Yoon T, Nuyten DS, Baker SW, Khodarev N, Su AW, Shaikh AY, Roach P, Kreike B, *et al*: An interferon-related gene signature for DNA damage resistance is a predictive marker for chemotherapy and radiation for breast cancer. Proc Natl Acad Sci USA 105: 18490-18495, 2008.
84. Boelens MC, Wu TJ, Nabet BY, Xu B, Qiu Y, Yoon T, Azzam DJ, Twyman-Saint Victor C, Wiemann BZ, Ishwaran H, *et al*: Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. Cell 159: 499-513, 2014.
85. Erdal E, Haider S, Rehwinkel J, Harris AL and McHugh PJ: A prosurvival DNA damage-induced cytoplasmic interferon response is mediated by end resection factors and is limited by Trex1. Genes Dev 31: 353-369, 2017.
86. Post AEM, Smid M, Nagelkerke A, Martens JWM, Bussink J, Sweep FCGJ and Span PN: Interferon-stimulated genes are involved in cross-resistance to radiotherapy in tamoxifen-resistant breast cancer. Clin Cancer Res 24: 3397-3408, 2018.
87. Benci JL, Xu B, Qiu Y, Wu TJ, Dada H, Twyman-Saint Victor C, Cucolo L, Lee DSM, Pauken KE, Huang AC, *et al*: Tumor interferon signaling regulates a multigenic resistance program to immune checkpoint blockade. Cell 167: 1540-1554 e12, 2016.
88. Chen J, Cao Y, Markelc B, Kaeppler J, Vermeer JA and Muschel RJ: Type I IFN protects cancer cells from CD8+ T cell-mediated cytotoxicity after radiation. J Clin Invest 129: 4224-4238, 2019.
89. Hughes CE and Nibbs RJB: A guide to chemokines and their receptors. FEBS J 285: 2944-2971, 2018.
90. Bravata V, Minafra L, Forte GI, Cammarata FP, Russo G, Di Maggio FM, Augello G, Lio D and Gilardi MC: Cytokine profile of breast cell lines after different radiation doses. Int J Radiat Biol 93: 1217-1226, 2017.
91. Wang P, Guo F, Han L, Wang X, Li J, Guo Y and Lu Y: X-ray-induced changes in the expression of inflammation-related genes in human peripheral blood. Int J Mol Sci 15: 19516-19534, 2014.
92. Wang X, Yang X, Tsai Y, Yang L, Chuang KH, Keng PC, Lee SO and Chen Y: IL-6 mediates macrophage infiltration after irradiation via Up-regulation of CCL2/CCL5 in Non-small cell lung cancer. Radiat Res 187: 50-59, 2017.
93. Liang H, Deng L, Hou Y, Meng X, Huang X, Rao E, Zheng W, Mauceri H, Mack M, Xu M, *et al*: Host STING-dependent MDSC mobilization drives extrinsic radiation resistance. Nat Commun 8: 1736, 2017.
94. Mondini M, Loyher PL, Hamon P, Gerbe de Thore M, Laviron M, Berthelot K, Clemenson C, Salomon BL, Combadiere C, Deutsch E and Boissonnas A: CCR2-dependent recruitment of tregs and monocytes following radiotherapy is associated with TNFα-mediated resistance. Cancer Immunol Res 7: 376-387, 2019.
95. Kalbasi A, Komar C, Tooker GM, Liu M, Lee JW, Gladney WL, Ben-Josef E and Beatty GL: Tumor-derived CCL2 mediates resistance to radiotherapy in pancreatic ductal adenocarcinoma. Clin Cancer Res 23: 137-148, 2017.
96. Wiesemann A, Ketteler J, Slama A, Wirsdorfer F, Hager T, Rock K, Engel DR, Fischer JW, Aigner C, Jendrossek V and Klein D: Inhibition of radiation-induced Ccl2 signaling protects lungs from vascular dysfunction and endothelial cell loss. Antioxid Redox Signal 30: 213-231, 2019.
97. Lee SW, Haditsch U, Cord BJ, Guzman R, Kim SJ, Boettcher C, Priller J, Ormerod BK and Palmer TD: Absence of CCL2 is sufficient to restore hippocampal neurogenesis following cranial irradiation. Brain Behav Immun 30: 33-44, 2013.
98. Malik IA, Moriconi F, Sheikh N, Naz N, Khan S, Dudas J, Mansuroglu T, Hess CF, Rave-Frank M, Christiansen H and Ramadori G: Single-dose gamma-irradiation induces up-regulation of chemokine gene expression and recruitment of granulocytes into the portal area but not into other regions of rat hepatic tissue. Am J Pathol 176: 1801-1815, 2010.
99. Nimalasena S, Gothard L, Anbalagan S, Allen S, Sinnett V, Mohammed K, Kothari G, Musallam A, Lucy C, Yu S, *et al*: Intratumoral hydrogen peroxide with radiation therapy in locally advanced breast cancer: Results from a phase 1 clinical trial. Int J Radiat Oncol Biol Phys 108: 1019-1029, 2020.
100. Mi S, Qu Y, Chen X, Wen Z, Chen P and Cheng Y: Radiotherapy increases 12-LOX and CCL5 levels in esophageal cancer cells and promotes cancer metastasis via THP-1-Derived macrophages. Onco Targets Ther 13: 7719-7733, 2020.
101. Zheng Z, Jia S, Shao C and Shi Y: Irradiation induces cancer lung metastasis through activation of the cGAS-STING-CCL5 pathway in mesenchymal stromal cells. Cell Death Dis 11: 326, 2020.
102. Chen HY, Xu L, Li LF, Liu XX, Gao JX and Bai YR: Inhibiting the CD8(+) T cell infiltration in the tumor microenvironment after radiotherapy is an important mechanism of radioresistance. Sci Rep 8: 11934, 2018.
103. Yan C, Luo L, Urata Y, Goto S and Li TS: Nicaraven reduces cancer metastasis to irradiated lungs by decreasing CCL8 and macrophage recruitment. Cancer Lett 418: 204-210, 2018.
104. Takemura N, Kurashima Y, Mori Y, Okada K, Ogino T, Osawa H, Matsuno H, Aayam L, Kaneto S, Park EJ, *et al*: Eosinophil depletion suppresses radiation-induced small intestinal fibrosis. Sci Transl Med 10: eaan0333, 2018.
105. Lee EJ, Kim JW, Yoo H, Kwak W, Choi WH, Cho S, Choi YJ, Lee YJ and Cho J: Single high-dose irradiation aggravates eosinophil-mediated fibrosis through IL-33 secreted from impaired vessels in the skin compared to fractionated irradiation. Biochem Biophys Res Commun 464: 20-26, 2015.
106. Bostrom M, Kalm M, Eriksson Y, Bull C, Stahlberg A, Bjork-Eriksson T, Hellstrom Erkenstam N and Blomgren K: A role for endothelial cells in radiation-induced inflammation. Int J Radiat Biol 94: 259-271, 2018.
107. Johnston CJ, Williams JP, Okunieff P and Finkelstein JN: Radiation-induced pulmonary fibrosis: Examination of chemokine and chemokine receptor families. Radiat Res 157: 256-265, 2002.
108. Rapp M, Wintergerst MWM, Kunz WG, Vetter VK, Knott MML, Lisowski D, Haubner S, Moder S, Thaler R, Eiber S, *et al*: CCL22 controls immunity by promoting regulatory T cell communication with dendritic cells in lymph nodes. J Exp Med 216: 1170-1181, 2019.
109. Bottcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, Rogers NC, Sahai E, Zelenay S and Reis e Sousa C: NK Cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control. Cell 172: 1022-1037 e14, 2018.

110. Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, Babb JS, Schneider RJ, Formenti SC, Dustin ML and Demaria S: Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. J Immunol 181: 3099-3107, 2008.
111. Kioi M, Vogel H, Schultz G, Hoffman RM, Harsh GR and Brown JM: Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. J Clin Invest 120: 694-705, 2010.
112. Belarbi K, Jopson T, Arellano C, Fike JR and Rosi S: CCR2 deficiency prevents neuronal dysfunction and cognitive impairments induced by cranial irradiation. Cancer Res 73: 1201-1210, 2013.
113. Lumniczky K, Szatmari T and Safrany G: Ionizing radiation-induced immune and inflammatory reactions in the brain. Front Immunol 8: 517, 2017.
114. Wang L, Jiang J, Chen Y, Jia Q and Chu Q: The roles of CC chemokines in response to radiation. Radiat Oncol 17: 63, 2022.
115. Wang CL, Ho AS, Chang CC, Sie ZL, Peng CL, Chang J and Cheng CC: Radiotherapy enhances CXCR3(high)CD8(+) T cell activation through inducing IFNgamma-mediated CXCL10 and ICAM-1 expression in lung cancer cells. Cancer Immunol Immunother 72: 1865-1880, 2023.
116. Zhu R, Xue X, Shen M, Tsai Y, Keng PC, Chen Y, Lee SO and Chen Y: NFκB and TNFα as individual key molecules associated with the cisplatin-resistance and radioresistance of lung cancer. Exp Cell Res 374: 181-188, 2019.
117. Alrehaili AA, Gharib AF, Bakhuraysah MM, Alharthi A, Alsalmi O, Alsaeedi FA, Alhakami RA, Alasmari KA, Mohammed N and Elsawy WH: Serum pro-inflammatory cytokines and leptin as potential biomarkers for treatment response and toxicity in locally advanced squamous cell carcinoma of the head and neck. Diseases 12: 55, 2024.
118. Chen W, Zhang C, Li Z, Xu Z, Ding C, Wu J, Wei H, Deng Z, He T, Long L, *et al*: PROCR diminishes the efficacy of radiation by impairing T-cell-mediated antitumour immunity. Nat Commun 16: 7145, 2025.
119. Han N, Wada H, Kobayashi T, Otsuka R and Seino KI: A mechanism of IL-34-induced resistance against cytotoxic anti-cancer therapies such as radiation by X-ray and chemotherapy by Oxaliplatin. Oncoimmunology 12: 2238499, 2023.
120. Spiotto M, Fu YX and Weichselbaum RR: The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. Sci Immunol 1: EAAG1266, 2016.
121. Kaur R, Lang DK, Singh H, Arora A, Garg N and Saini B: Repurposing of various current medicines as radioprotective agents. Anticancer Agents Med Chem 23: 1104-1121, 2023.
122. Oton-Leite AF, Silva GB, Morais MO, Silva TA, Leles CR, Valadares MC, Pinezi JC, Batista AC and Mendonca EF: Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med 47: 296-305, 2015.
123. Shields LB, Shelton BJ, Shearer AJ, Chen L, Sun DA, Parsons S, Bourne TD, LaRocca R and Spalding AC: Dexamethasone administration during definitive radiation and temozolomide renders a poor prognosis in a retrospective analysis of newly diagnosed glioblastoma patients. Radiat Oncol 10: 222, 2015.
124. Thabet NM and Moustafa EM: Synergistic effect of Ebselen and gamma radiation on breast cancer cells. Int J Radiat Biol 93: 784-792, 2017.
125. Wunderlich R, Ernst A, Rodel F, Fietkau R, Ott O, Lauber K, Frey B, Gaipl US: Low and moderate doses of ionizing radiation up to 2 Gy modulate transmigration and chemotaxis of activated macrophages, provoke an anti-inflammatory cytokine milieu, but do not impact upon viability and phagocytic function. Clin Exp Immunol 179: 50-61, 2015.
126. Zhao X, Hu S, Zeng L, Liu X, Song Y, Zhang Y, Chen Q, Bai Y, Zhang J, Zhang H, *et al*: Irradiation combined with PD-L1(-/-) and autophagy inhibition enhances the antitumor effect of lung cancer via cGAS-STING-mediated T cell activation. iScience 25: 104690, 2022.
127. Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y and Thomas SM: Radiation-induced fibrosis: Mechanisms and implications for therapy. J Cancer Res Clin Oncol 141: 1985-1994, 2015.
128. Li R, Chen G, Zhou L, Xu H, Tang F, Lan J, Tong R, Deng L, Xue J and Lu Y: The fatty acid amide hydrolase inhibitor URB937 ameliorates radiation-induced lung injury in a mouse model. Inflammation 40: 1254-1263, 2017.
129. Suzuki K, Ogura M, Abe Y, Suzuki T, Tobinai K, Ando K, Taniwaki M, Maruyama D, Kojima M, Kuroda J, *et al*: Phase 1 study in Japan of siltuximab, an anti-IL-6 monoclonal antibody, in relapsed/refractory multiple myeloma. Int J Hematol 101: 286-294, 2015.
130. Vanpouille-Box C, Pilones KA, Wennerberg E, Formenti SC and Demaria S: In situ vaccination by radiotherapy to improve responses to anti-CTLA-4 treatment. Vaccine 33: 7415-7422, 2015.
131. Palata O, Hradilova Podzimkova N, Nedvedova E, Umprecht A, Sadilkova L, Palova Jelinkova L, Spisek R and Adkins I: Radiotherapy in combination with cytokine treatment. Front Oncol 9: 367, 2019.
132. Lemke G: How macrophages deal with death. Nat Rev Immunol 19: 539-549, 2019.
133. Shi Z, Yu P, Lin WJ, Chen S, Hu X, Chen S, Cheng J, Liu Q, Yang Y, Li S, *et al*: Microglia drive transient insult-induced brain injury by chemotactic recruitment of CD8(+) T lymphocytes. Neuron 111: 696-710.e9, 2023.
134. Lodermann B, Wunderlich R, Frey S, Schorn C, Stangl S, Rodel F, Keilholz L, Fietkau R, Gaipl US and Frey B: Low dose ionising radiation leads to a NF-kappaB dependent decreased secretion of active IL-1beta by activated macrophages with a discontinuous dose-dependency. Int J Radiat Biol 88: 727-734, 2012.
135. Prakash H, Klug F, Nadella V, Mazumdar V, Schmitz-Winnenthal H and Umansky L: Low doses of gamma irradiation potentially modifies immunosuppressive tumor microenvironment by retuning tumor-associated macrophages: lesson from insulinoma. Carcinogenesis 37: 301-313, 2016.
136. Wu Q, Allouch A, Paoletti A, Leteur C, Mirjolet C, Martins I, Voisin L, Law F, Dakhli H, Mintet E, *et al*: NOX2-dependent ATM kinase activation dictates pro-inflammatory macrophage phenotype and improves effectiveness to radiation therapy. Cell Death Differ 24: 1632-1644, 2017.
137. Teresa Pinto A, Laranjeiro Pinto M, Patricia Cardoso A, Monteiro C, Teixeira Pinto M, Filipe Maia A, Castro P, Figueira R, Monteiro A, Marques M, *et al*: Ionizing radiation modulates human macrophages towards a pro-inflammatory phenotype preserving their pro-invasive and pro-angiogenic capacities. Sci Rep 6: 18765, 2016.
138. Stary V, Wolf B, Unterleuthner D, List J, Talic M, Laengle J, Beer A, Strobl J, Stary G, Dolznig H and Bergmann M: Short-course radiotherapy promotes pro-inflammatory macrophages via extracellular vesicles in human rectal cancer. J Immunother Cancer 8: e000667, 2020.
139. Crittenden MR, Cottam B, Savage T, Nguyen C, Newell P and Gough MJ: Expression of NF-kappaB p50 in tumor stroma limits the control of tumors by radiation therapy. PLoS One 7: e39295, 2012.
140. Rodriguez-Ruiz ME, Vitale I, Harrington KJ, Melero I and Galluzzi L: Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. Nat Immunol 21: 120-134, 2020.
141. Choi JY, Seok HJ, Lee DH, Kwon J, Shin US, Shin I and Bae IH: miR-1226-5p is involved in radioresistance of colorectal cancer by activating M2 macrophages through suppressing IRF1. J Transl Med 22: 980, 2024.
142. Chiang Y, Tsai YC, Wang CC, Hsueh FJ, Huang CY, Chung SD, Chen CH, Pu YS and Cheng JC: Tumor-Derived C-C motif ligand 2 induces the recruitment and polarization of tumor-associated macrophages and increases the metastatic potential of bladder cancer cells in the postirradiated microenvironment. Int J Radiat Oncol Biol Phys 114: 321-333, 2022.
143. Lee HL, Tsai YC, Pikatan NW, Yeh CT, Yadav VK, Chen MY and Tsai JT: Tumor-Associated macrophages affect the tumor microenvironment and radioresistance via the upregulation of CXCL6/CXCR2 in hepatocellular carcinoma. Biomedicines 11: 2081, 2023.
144. Li W, Xing X, Shen C and Hu C: Tumor cell-derived exosomal miR-193b-3p promotes tumor-associated macrophage activation to facilitate nasopharyngeal cancer cell invasion and radioresistances. Heliyon 10: e30808, 2024.
145. Gu X, Shi Y, Dong M, Jiang L, Yang J and Liu Z: Exosomal transfer of tumor-associated macrophage-derived hsa_circ_0001610 reduces radiosensitivity in endometrial cancer. Cell Death Dis 12: 818, 2021.
146. Sheng Y, Zhang B, Xing B, Liu Z, Chang Y, Wu G and Zhao Y: Cancer-associated fibroblasts exposed to high-dose ionizing radiation promote M2 polarization of macrophages, which induce radiosensitivity in cervical cancer. Cancers (Basel) 15: 1620, 2023.

147. Meng Y, Beckett MA, Liang H, Mauceri HJ, van Rooijen N, Cohen KS and Weichselbaum RR: Blockade of tumor necrosis factor alpha signaling in tumor-associated macrophages as a radiosensitizing strategy. Cancer Res 70: 1534-1543, 2010.
148. Fu E, Liu T, Yu S, Chen X, Song L, Lou H, Ma F, Zhang S, Hussain S, Guo J, *et al*: M2 macrophages reduce the radiosensitivity of head and neck cancer by releasing HB-EGF. Oncol Rep 44: 698-710, 2020.
149. Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, Pfirschke C, Voss RH, Timke C, Umansky L, *et al*: Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell 24: 589-602, 2013.
150. Zhu L, Hu S, Chen Q, Zhang H, Fu J, Zhou Y, Bai Y, Pan Y and Shao C: Macrophage contributes to radiation-induced anti-tumor abscopal effect on transplanted breast cancer by HMGB1/TNF-α signaling factors. Int J Biol Sci 17: 926-941, 2021.
151. Zhan S, Cao Z, Li J, Chen F, Lai X, Yang W, Teng Y, Li Z, Zhang W and Xie J: Iron oxide nanoparticles induce macrophage secretion of ATP and HMGB1 to enhance irradiation-led immunogenic cell death. Bioconjug Chem 36: 80-91, 2025.
152. Wan C, Sun Y, Tian Y, Lu L, Dai X, Meng J, Huang J, He Q, Wu B, Zhang Z, *et al*: Irradiated tumor cell-derived microparticles mediate tumor eradication via cell killing and immune reprogramming. Sci Adv 6: eaay9789, 2020.
153. Connolly KA, Belt BA, Figueroa NM, Murthy A, Patel A, Kim M, Lord EM, Linehan DC and Gerber SA: Increasing the efficacy of radiotherapy by modulating the CCR2/CCR5 chemokine axes. Oncotarget 7: 86522-86535, 2016.
154. Xu J, Escamilla J, Mok S, David J, Priceman S, West B, Bollag G, McBride W and Wu L: CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer. Cancer Res 73: 2782-2794, 2013.
155. Park I, Yang H, Park JS, Koh GY and Choi EK: VEGF-Grab enhances the efficacy of radiation therapy by blocking VEGF-A and treatment-induced PlGF. Int J Radiat Oncol Biol Phys 102: 609-618, 2018.
156. Fulda S: Smac mimetics as IAP antagonists. Semin Cell Dev Biol 39: 132-138, 2015.
157. Feng Y, Mu R, Wang Z, Xing P, Zhang J, Dong L and Wang C: A toll-like receptor agonist mimicking microbial signal to generate tumor-suppressive macrophages. Nat Commun 10: 2272, 2019.
158. Rodell CB, Arlauckas SP, Cuccarese MF, Garris CS, Li R, Ahmed MS, Kohler RH, Pittet MJ and Weissleder R: TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. Nat Biomed Eng 2: 578-588, 2018.
159. Zhang Y, Feng Z, Liu J, Li H, Su Q, Zhang J, Huang P, Wang W and Liu J: Polarization of tumor-associated macrophages by TLR7/8 conjugated radiosensitive peptide hydrogel for overcoming tumor radioresistance. Bioact Mater 16: 359-371, 2022.
160. Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, Pajarinen JS, Nejadnik H, Goodman S, Moseley M, *et al*: Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol 11: 986-994, 2016.
161. Hu Y, Sun Y, Liao Z, An D, Liu X, Yang X, Tian Y, Deng S, Meng J, Wang Y, *et al*: Irradiated engineered tumor cell-derived microparticles remodel the tumor immune microenvironment and enhance antitumor immunity. Mol Ther 32: 411-425, 2024.
162. Shang Q, Zhang P, Lei X, Du L and Qu B: Insights into CSF-1/CSF-1R signaling: the role of macrophage in radiotherapy. Front Immunol 16: 1530890, 2025.
163. De Ruysscher D, Niedermann G, Burnet NG, Siva S, Lee AWM and Hegi-Johnson F: Radiotherapy toxicity. Nat Rev Dis Primers 5: 13, 2019.
164. Makale MT, McDonald CR, Hattangadi-Gluth JA and Kesari S: Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 13: 52-64, 2017.
165. Zhang P, Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, Abdelmohsen K, Bohr VA, Misra Sen J, Gorospe M and Mattson MP: Senolytic therapy alleviates Abeta-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nat Neurosci 22: 719-728, 2019.
166. Ji J, Ding K, Cheng B, Zhang X, Luo T, Huang B, Yu H, Chen Y, Xu X, Lin H, *et al*: Radiotherapy-Induced astrocyte senescence promotes an immunosuppressive microenvironment in glioblastoma to facilitate tumor regrowth. Adv Sci (Weinh) 11: e2304609, 2024.
167. Xu A, Li R, Ren A, Jian H, Huang Z, Zeng Q, Wang B, Zheng J, Chen X, Zheng N, *et al*: Regulatory coupling between long noncoding RNAs and senescence in irradiated microglia. J Neuroinflammation 17: 321, 2020.
168. Luo N, Zhu W, Li X, Fu M, Zhang Y, Yang F, Zhang Y, Chen Z, Zhang Q, Peng B, *et al*: Defective autophagy of pericytes enhances radiation-induced senescence promoting radiation brain injury. Neuro Oncol 26: 2288-2304, 2024.
169. Kalm M, Fukuda A, Fukuda H, Ohrfelt A, Lannering B, Bjork-Eriksson T, Blennow K, Marky I and Blomgren K: Transient inflammation in neurogenic regions after irradiation of the developing brain. Radiat Res 171: 66-76, 2009.
170. Blomstrand M, Kalm M, Grander R, Bjork-Eriksson T and Blomgren K: Different reactions to irradiation in the juvenile and adult hippocampus. Int J Radiat Biol 90: 807-815, 2014.
171. Ungvari Z, Podlutsky A, Sosnowska D, Tucsek Z, Toth P, Deak F, Gautam T, Csiszar A and Sonntag WE: Ionizing radiation promotes the acquisition of a senescence-associated secretory phenotype and impairs angiogenic capacity in cerebromicrovascular endothelial cells: role of increased DNA damage and decreased DNA repair capacity in microvascular radiosensitivity. J Gerontol A Biol Sci Med Sci 68: 1443-1457, 2013.
172. Brincat SL and Miller EK: Frequency-specific hippocampal-prefrontal interactions during associative learning. Nat Neurosci 18: 576-581, 2015.
173. Wang Y, Zhou K, Li T, Xu Y, Xie C, Sun Y, Rodriguez J, Zhang S, Song J, Wang X, *et al*: Selective neural deletion of the Atg7 gene reduces irradiation-induced cerebellar white matter injury in the juvenile mouse brain by ameliorating oligodendrocyte progenitor cell loss. Front Cell Neurosci 13: 241, 2019.
174. Leeman DS, Hebestreit K, Ruetz T, Webb AE, McKay A, Pollina EA, Dulken BW, Zhao X, Yeo RW, Ho TT, *et al*: Lysosome activation clears aggregates and enhances quiescent neural stem cell activation during aging. Science 359: 1277-1283, 2018.
175. Shakhbazau A, Danilkovich N, Seviaryn I, Ermilova T and Kosmacheva S: Effects of minocycline and rapamycin in gamma-irradiated human embryonic stem cells-derived cerebral organoids. Mol Biol Rep 46: 1343-1348, 2019.
176. Juricic P, Lu YX, Leech T, Drews LF, Paulitz J, Lu J, Nespital T, Azami S, Regan JC, Funk E, *et al*: Long-lasting geroprotection from brief rapamycin treatment in early adulthood by persistently increased intestinal autophagy. Nat Aging 2: 824-836, 2022.
177. Rao E, Hou Y, Huang X, Wang L, Wang J, Zheng W, Yang H, Yu X, Yang K, Bugno J, *et al*: All-trans retinoic acid overcomes solid tumor radioresistance by inducing inflammatory macrophages. Sci Immunol 6: eaba8426, 2021.
178. Martin N, Ma X and Bernard D: Regulation of cellular senescence by retinoid X receptors and their partners. Mech Ageing Dev 183: 111131, 2019.
179. Zhang Z, Jiang J, He Y, Cai J, Xie J, Wu M, Xing M, Zhang Z, Chang H, Yu P, *et al*: Pregabalin mitigates microglial activation and neuronal injury by inhibiting HMGB1 signaling pathway in radiation-induced brain injury. J Neuroinflammation 19: 231, 2022.
180. Lastra Romero A, Seitz T, Zisiadis GA, Jeffery H and Osman AM: EDA2R reflects the acute brain response to cranial irradiation in liquid biopsies. Neuro Oncol 26: 1617-1627, 2024.
181. Bilgic SN, Domaniku A, Toledo B, Agca S, Weber BZC, Arabaci DH, Ozornek Z, Lause P, Thissen JP, Loumaye A and Kir S: EDA2R-NIK signalling promotes muscle atrophy linked to cancer cachexia. Nature 617: 827-834, 2023.
182. Jia N, Jia Y, Yang F and Du W: Knockdown of EDA2R alleviates hyperoxia-induced lung epithelial cell injury by inhibiting NF-κB pathway. Allergol Immunopathol (Madr) 50: 84-90, 2022.
183. Colonna M and Butovsky O: Microglia function in the central nervous system during health and neurodegeneration. Annu Rev Immunol 35: 441-468, 2017.
184. Kalm M, Lannering B, Bjork-Eriksson T and Blomgren K: Irradiation-induced loss of microglia in the young brain. J Neuroimmunol 206: 70-75, 2009.
185. Osman AM, Sun Y, Burns TC, He L, Kee N, Oliva-Vilarnau N, Alevyzaki A, Zhou K, Louhivuori L, Uhlen P, *et al*: Radiation triggers a dynamic sequence of transient microglial alterations in juvenile brain. Cell Rep 31: 107699, 2020.
186. Monje ML, Toda H and Palmer TD: Inflammatory blockade restores adult hippocampal neurogenesis. Science 302: 1760-1765, 2003.

187. Trott KR, Herrmann T and Kasper M: Target cells in radiation pneumopathy. Int J Radiat Oncol Biol Phys 58: 463-469, 2004.
188. Rube CE, Wilfert F, Palm J, Konig J, Burdak-Rothkamm S, Liu L, Schuck A, Willich N and Rube C: Irradiation induces a biphasic expression of pro-inflammatory cytokines in the lung. Strahlenther Onkol 180: 442-448, 2004.
189. Ozturk B, Egehan I, Atavci S and Kitapci M: Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: A double-blind randomized trial. Int J Radiat Oncol Biol Phys 58: 213-219, 2004.
190. Kasmann L, Dietrich A, Staab-Weijnitz CA, Manapov F, Behr J, Rimner A, Jeremic B, Senan S, De Ruysscher D, Lauber K and Belka C: Radiation-induced lung toxicity-cellular and molecular mechanisms of pathogenesis, management, and literature review. Radiat Oncol 15: 214, 2020.
191. Venkatesulu BP, Mahadevan LS, Aliru ML, Yang X, Bodd MH, Singh PK, Yusuf SW, Abe JI and Krishnan S: Radiation-induced endothelial vascular injury: A review of possible mechanisms. JACC Basic Transl Sci 3: 563-572, 2018.
192. Cytlak UM, Dyer DP, Honeychurch J, Williams KJ, Travis MA and Illidge TM: Immunomodulation by radiotherapy in tumour control and normal tissue toxicity. Nat Rev Immunol 22: 124-138, 2022.
193. Liu X, Zhang T, Zhou J, Xiao Z, Li Y, Zhang Y, Yue H, Li Z and Tian J: β-Catenin/Lin28/let-7 regulatory network determines type II alveolar epithelial stem cell differentiation phenotypes following thoracic irradiation. J Radiat Res 62: 119-132, 2021.
194. House IG, Savas P, Lai J, Chen AXY, Oliver AJ, Teo ZL, Todd KL, Henderson MA, Giuffrida L, Petley EV, *et al*: Macrophage-derived CXCL9 and CXCL10 are required for antitumor immune responses following immune checkpoint blockade. Clin Cancer Res 26: 487-504, 2020.
195. Ni J, Guo T, Zhou Y, Jiang S, Zhang L and Zhu Z: STING signaling activation modulates macrophage polarization via CCL2 in radiation-induced lung injury. J Transl Med 21: 590, 2023.
196. Kishore A and Petrek M: Roles of macrophage polarization and macrophage-derived miRNAs in pulmonary fibrosis. Front Immunol 12: 678457, 2021.
197. Zhou BW, Liu HM, Xu F and Jia XH: The role of macrophage polarization and cellular crosstalk in the pulmonary fibrotic microenvironment: A review. Cell Commun Signal 22: 172, 2024.
198. Inoue T, Fujishima S, Ikeda E, Yoshie O, Tsukamoto N, Aiso S, Aikawa N, Kubo A, Matsushima K and Yamaguchi K: CCL22 and CCL17 in rat radiation pneumonitis and in human idiopathic pulmonary fibrosis. Eur Respir J 24: 49-56, 2004.
199. Strandberg J, Louie A, Lee S, Hahn M, Srinivasan P, George A, De La Cruz A, Zhang L, Hernandez Borrero L, Huntington KE, *et al*: TRAIL agonists rescue mice from radiation-induced lung, skin, or esophageal injury. J Clin Invest 135: e173649, 2025.
200. Ban Y, Markowitz GJ, Zou Y, Ramchandani D, Kraynak J, Sheng J, Lee SB, Wong STC, Altorki NK, Gao D and Mittal V: Radiation-activated secretory proteins of Scgb1a1(+) club cells increase the efficacy of immune checkpoint blockade in lung cancer. Nat Cancer 2: 919-931, 2021.
201. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, Barriger RB, Moreno-Jimenez M, Kim TH, Ramella S, *et al*: Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: An individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 87: 690-696, 2013.
202. Gomez DR, Tucker SL, Martel MK, Mohan R, Balter PA, Lopez Guerra JL, Liu H, Komaki R, Cox JD and Liao Z: Predictors of high-grade esophagitis after definitive three-dimensional conformal therapy, intensity-modulated radiation therapy, or proton beam therapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 84: 1010-1016, 2012.
203. Bradley JD, Bae K, Graham MV, Byhardt R, Govindan R, Fowler J, Purdy JA, Michalski JM, Gore E and Choy H: Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol 28: 2475-2480, 2010.
204. Kitamura H, Tanigawa T, Kuzumoto T, Nadatani Y, Otani K, Fukunaga S, Hosomi S, Tanaka F, Kamata N, Nagami Y, *et al*: Interferon-alpha exerts proinflammatory properties in experimental radiation-induced esophagitis: Possible involvement of plasmacytoid dendritic cells. Life Sci 289: 120215, 2022.
205. Fries PN and Griebel PJ: Mucosal dendritic cell diversity in the gastrointestinal tract. Cell Tissue Res 343: 33-41, 2011.
206. Fitzgerald-Bocarsly P, Dai J and Singh S: Plasmacytoid dendritic cells and type I IFN: 50 years of convergent history. Cytokine Growth Factor Rev 19: 3-19, 2008.
207. Reizis B: Plasmacytoid dendritic cells: Development, regulation, and function. Immunity 50: 37-50, 2019.
208. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P and van Lin EN: Chronic radiation proctitis: Tricks to prevent and treat. Int J Colorectal Dis 30: 1293-1303, 2015.
209. Lu W, Xie Y, Huang B, Ma T, Wang H, Deng B, Zou S, Wang W, Tang Q, Yang Z, *et al*: Platelet-derived growth factor C signaling is a potential therapeutic target for radiation proctopathy. Sci Transl Med 13: eabc2344, 2021.
210. Ge Z, Chen C, Chen J, Jiang Z, Chen L, Wei Y, Chen H, He L, Zou Y, Long X, *et al*: Gut microbiota-derived 3-hydroxybutyrate blocks GPR43-Mediated IL6 signaling to ameliorate radiation proctopathy. Adv Sci (Weinh) 11: e2306217, 2024.
211. Lei R, Li J, Liu F, Li W, Zhang S, Wang Y, Chu X and Xu J: HIF-1α promotes the keloid development through the activation of TGF-beta/Smad and TLR4/MyD88/NF-κB pathways. Cell Cycle 18: 3239-3250, 2019.
212. Ramakrishnan S, Anand V and Roy S: Vascular endothelial growth factor signaling in hypoxia and inflammation. J Neuroimmune Pharmacol 9: 142-160, 2014.
213. Bedini N, Cicchetti A, Palorini F, Magnani T, Zuco V, Pennati M, Campi E, Allavena P, Pesce S, Villa S, *et al*: Evaluation of mediators associated with the inflammatory response in prostate cancer patients undergoing radiotherapy. Dis Markers 2018: 9128128, 2018.
214. Hamade DF, Epperly MW, Fisher R, Hou W, Shields D, van Pijkeren JP, Mukherjee A, Yu J, Leibowitz BJ, Vlad AM, *et al*: Release of Interferon-β (IFN-β) from probiotic limosilactobacillus reuteri-IFN-β (LR-IFN-β) mitigates gastrointestinal acute radiation syndrome (GI-ARS) following whole abdominal irradiation. Cancers (Basel) 15: 1670, 2023.
215. Xie LW, Cai S, Lu HY, Tang FL, Zhu RQ, Tian Y and Li M: Microbiota-derived I3A protects the intestine against radiation injury by activating AhR/IL-10/Wnt signaling and enhancing the abundance of probiotics. Gut Microbes 16: 2347722, 2024.
216. Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, Fox JL, Mah D, Garg MK, Han-Chih Chang J and Lee NY: Proton beam reirradiation for recurrent head and neck cancer: Multi-institutional report on feasibility and early outcomes. Int J Radiat Oncol Biol Phys 95: 386-395, 2016.
217. Lin L, Yao JJ, Zhou GQ, Guo R, Zhang F, Zhang Y, Xu L, Zhang LL, Lin AH, Ma J and Sun Y: The efficacy and toxicity of individualized intensity-modulated radiotherapy based on the tumor extension patterns of nasopharyngeal carcinoma. Oncotarget 7: 20680-20690, 2016.
218. Elad S, Yarom N, Zadik Y, Kuten-Shorrer M and Sonis ST: The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. CA Cancer J Clin 72: 57-77, 2022.
219. Potrich AR, So BB, Schuch LF, Wagner VP, Silveira FM, de Abreu Alves F, Prado-Ribeiro AC, Santos-Silva AR, Treister NS, Martins MD and Martins MAT: Impact of photobiomodulation for prevention of oral mucositis on the quality of life of patients with head and neck cancer: A systematic review. Lasers Med Sci 39: 1, 2023.
220. Sonis ST: The pathobiology of mucositis. Nat Rev Cancer 4: 277-284, 2004.
221. Logan RM, Stringer AM, Bowen JM, Gibson RJ, Sonis ST and Keefe DM: Serum levels of NFkappaB and pro-inflammatory cytokines following administration of mucotoxic drugs. Cancer Biol Ther 7: 1139-1145, 2008.
222. Vasconcelos RM, Sanfilippo N, Paster BJ, Kerr AR, Li Y, Ramalho L, Queiroz EL, Smith B, Sonis ST and Corby PM: Host-Microbiome cross-talk in oral mucositis. J Dent Res 95: 725-733, 2016.
223. Thaiss CA, Zmora N, Levy M and Elinav E: The microbiome and innate immunity. Nature 535: 65-74, 2016.
224. Bonan PR, Kaminagakura E, Pires FR, Vargas PA and De Almeida OP: Histomorphometry and immunohistochemical features of grade I (WHO) oral radiomucositis. Oral Diseases 13: 170-176, 2007.
225. Imam T, Park S, Kaplan MH and Olson MR: Effector T helper cell subsets in inflammatory bowel diseases. Front Immunol 9: 1212, 2018.

226. Krebs CF, Schmidt T, Riedel JH and Panzer U: T helper type 17 cells in immune-mediated glomerular disease. Nat Rev Nephrol 13: 647-659, 2017.
227. Oronsky B, Goyal S, Kim MM, Cabrales P, Lybeck M, Caroen S, Oronsky N, Burbano E, Carter C and Oronsky A: A review of clinical radioprotection and chemoprotection for oral mucositis. Transl Oncol 11: 771-778, 2018.
228. Lozano A, Marruecos J, Rubio J, Farre N, Gomez-Millan J, Morera R, Planas I, Lanzuela M, Vazquez-Masedo MG, Cascallar L, *et al*: Randomized placebo-controlled phase II trial of high-dose melatonin mucoadhesive oral gel for the prevention and treatment of oral mucositis in patients with head and neck cancer undergoing radiation therapy concurrent with systemic treatment. Clin Transl Oncol 23: 1801-1810, 2021.
229. Giralt J, Tao Y, Kortmann RD, Zasadny X, Contreras-Martinez J, Ceruse P, Arias de la Vega F, Lalla RV, Ozsahin EM, Pajkos G, *et al*: Randomized phase 2 trial of a novel clonidine mucoadhesive buccal tablet for the amelioration of oral mucositis in patients treated with concomitant chemoradiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 106: 320-328, 2020.
230. Flanders CA, Rocke AS, Edwardson SA, Baillie JK and Walsh TS: The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: A systematic review of animal and human studies. Crit Care 23: 402, 2019.
231. Marques LJ, Zheng L, Poulakis N, Guzman J and Costabel U: Pentoxifylline inhibits TNF-alpha production from human alveolar macrophages. Am J Respir Crit Care Med 159: 508-511, 1999.
232. Sayed R, El Wakeel L, Saad AS, Kelany M and El-Hamamsy M: Pentoxifylline and vitamin E reduce the severity of radiotherapy-induced oral mucositis and dysphagia in head and neck cancer patients: A randomized, controlled study. Med Oncol 37: 8, 2019.
233. Wei H, Wei J and Dong X: A prospective interventional study of recombinant human interleukin-11 mouthwash in chemotherapy-induced oral mucositis. BMC Oral Health 22: 313, 2022.
234. Zhang Y, Li Y, He A, Wang J, Zhang P, Lei B, Huang Z, Zhang L, Zhao W and Ma X: Efficacy of recombinant human interleukin-11 in preventing and treating oral mucositis after chemotherapy for patients with acute leukemia. BMC Oral Health 23: 476, 2023.
235. Aggarwal BB, Gupta SC and Sung B: Curcumin: An orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 169: 1672-1692, 2013.
236. Thomas PL, Kang HK and Rishi KS: Randomized control study of the effects of turmeric mouthwash on oral health status, treatment-induced mucositis, and associated oral dysfunctions among patients with head and neck cancer. Cancer Nurs 46: 36-44, 2023.
237. Ramezani V, Ghadirian S, Shabani M, Boroumand MA, Daneshvar R and Saghafi F: Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: A preliminary randomized controlled clinical trial. BMC Cancer 23: 354, 2023.
238. Wagner VP, Curra M, Webber LP, Nor C, Matte U, Meurer L and Martins MD: Photobiomodulation regulates cytokine release and new blood vessel formation during oral wound healing in rats. Lasers Med Sci 31: 665-671, 2016.
239. Zadik Y, Arany PR, Fregnani ER, Bossi P, Antunes HS, Bensadoun RJ, Gueiros LA, Majorana A, Nair RG, Ranna V, *et al*: Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 27: 3969-3983, 2019.
240. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, Bowen J, Gibson R, Saunders DP, Zadik Y, *et al*: MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 126: 4423-4431, 2020.
241. Robijns J, Nair RG, Lodewijckx J, Arany P, Barasch A, Bjordal JM, Bossi P, Chilles A, Corby PM, Epstein JB, *et al*: Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. Front Oncol 12: 927685, 2022.
242. Cox PB and Gupta R: Contemporary computational applications and tools in drug discovery. ACS Med Chem Lett 13: 1016-1029, 2022.
243. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, *et al*: Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 18: 41-58, 2019.
244. Kim J and Jung Y: Radiation-induced liver disease: Current understanding and future perspectives. Exp Mol Med 49: e359, 2017.
245. Guha C and Kavanagh BD: Hepatic radiation toxicity: Avoidance and amelioration. Semin Radiat Oncol 21: 256-263, 2011.
246. Fischietti M, Fratini E, Verzella D, Vecchiotti D, Capece D, Di Francesco B, Esposito G, Balata M, Ioannuci L, Sykes P, *et al*: Low radiation environment switches the overgrowth-induced cell apoptosis toward autophagy. Front Public Health 8: 594789, 2021.
247. Xu B, Jiang M, Chu Y, Wang W, Chen D, Li X, Zhang Z, Zhang D, Fan D, Nie Y, *et al*: Gasdermin D plays a key role as a pyroptosis executor of non-alcoholic steatohepatitis in humans and mice. J Hepatol 68: 773-782, 2018.
248. Lv X, Chen J, He J, Hou L, Ren Y, Shen X, Wang Y, Ji T and Cai X: Gasdermin D-mediated pyroptosis suppresses liver regeneration after 70% partial hepatectomy. Hepatol Commun 6: 2340-2353, 2022.
249. Li J, Zhao J, Xu M, Li M, Wang B, Qu X, Yu C, Hang H, Xia Q, Wu H, *et al*: Blocking GSDMD processing in innate immune cells but not in hepatocytes protects hepatic ischemia-reperfusion injury. Cell Death Dis 11: 244, 2020.
250. Chen G, Zhao Q, Yuan B, Wang B, Zhang Y, Li Z, Du S and Zeng Z: ALKBH5-Modified HMGB1-STING activation contributes to radiation induced liver disease via innate immune response. Int J Radiat Oncol Biol Phys 111: 491-501, 2021.
251. Dong A, Wei G, Liang Z, Di Y, Tang Y, Ling Y, Li S, Chen Y, Zhou Y, Wang X and Peng Z: Gasdermin D aggravates a mouse model of radiation-induced liver disease by promoting chemokine secretion and neutrophil recruitment. Nat Commun 16: 6064, 2025.
252. Deng W, Yang Z, Yue H, Ou Y, Hu W and Sun P: Disulfiram suppresses NLRP3 inflammasome activation to treat peritoneal and gouty inflammation. Free Radic Biol Med 152: 8-17, 2020.
253. Hu S, Wang L, Xu Y, Li F and Wang T: Disulfiram attenuates hypoxia-induced pulmonary hypertension by inhibiting GSDMD cleavage and pyroptosis in HPASMCs. Respir Res 23: 353, 2022.
254. Wu J, Zhang J, Zhao J, Chen S, Zhou T and Xu J: Treatment of severe acute pancreatitis and related lung injury by targeting gasdermin D-Mediated pyroptosis. Front Cell Dev Biol 9: 780142, 2021.
255. Liu M, Liu D, Yu C, Fan HH, Zhao X, Wang H, Zhang C, Zhang M, Bo R, He S, *et al*: Caffeic acid, but not ferulic acid, inhibits macrophage pyroptosis by directly blocking gasdermin D activation. MedComm (2020) 4: e255, 2023.
256. Chatzipapas KP, Papadimitroulas P, Emfietzoglou D, Kalospyros SA, Hada M, Georgakilas AG and Kagadis GC: Ionizing radiation and complex DNA damage: Quantifying the radiobiological damage using monte carlo simulations. Cancers (Basel) 12: 799, 2020.
257. Taysi S, Tascan AS, Ugur MG and Demir M: Radicals, oxidative/nitrosative stress and preeclampsia. Mini Rev Med Chem 19: 178-193, 2019.
258. Taysi S, Algburi FS, Mohammed ZR, Ali OA and Taysi ME: Thymoquinone: A review on its pharmacological importance, and its association with oxidative stress, COVID-19, and radiotherapy. Mini Rev Med Chem 22: 1847-1875, 2022.
259. Dent P, Yacoub A, Fisher PB, Hagan MP and Grant S: MAPK pathways in radiation responses. Oncogene 22: 5885-5896, 2003.
260. Du SS, Qiang M, Zeng ZC, Ke AW, Ji Y, Zhang ZY, Zeng HY and Liu Z: Inactivation of kupffer cells by gadolinium chloride protects murine liver from radiation-induced apoptosis. Int J Radiat Oncol Biol Phys 76: 1225-1234, 2010.
261. Mossanen JC, Krenkel O, Ergen C, Govaere O, Liepelt A, Puengel T. Heymann F, Kalthoff S, Lefebvre E, Eulberg D, *et al*: Chemokine (C-C motif) receptor 2-positive monocytes aggravate the early phase of acetaminophen-induced acute liver injury. Hepatology 64: 1667-1682, 2016.
262. Zigmond E, Samia-Grinberg S, Pasmanik-Chor M, Brazowski E, Shibolet O, Halpern Z and Varol C: Infiltrating monocyte-derived macrophages and resident kupffer cells display different ontogeny and functions in acute liver injury. J Immunol 193: 344-353, 2014.
263. Yuan D, Huang S, Berger E, Liu L, Gross N, Heinzmann F, Ringelhan M, Connor TO, Stadler M, Meister M, *et al*: Kupffer cell-derived tnf triggers cholangiocellular tumorigenesis through JNK due to chronic mitochondrial dysfunction and ROS. Cancer Cell 31: 771-789 e6, 2017.

264. Su L, Li N, Tang H, Lou Z, Chong X, Zhang C, Su J and Dong X: Kupffer cell-derived TNF-alpha promotes hepatocytes to produce CXCL1 and mobilize neutrophils in response to necrotic cells. Cell Death Dis 9: 323, 2018.
265. Natarajan V, Harris EN and Kidambi S: SECs (Sinusoidal Endothelial Cells), liver microenvironment, and fibrosis. Biomed Res Int 2017: 4097205, 2017.
266. Chen YX, Zeng ZC, Sun J, Zeng HY, Huang Y and Zhang ZY: Mesenchymal stem cell-conditioned medium prevents radiation-induced liver injury by inhibiting inflammation and protecting sinusoidal endothelial cells. J Radiat Res 56: 700-708, 2015.
267. Yuan B, Chen Y, Wu Z, Zhang L, Zhuang Y, Zhao X, Niu H, Cheng JC and Zeng Z: Proteomic profiling of human hepatic stellate cell line LX2 responses to irradiation and TGF-β1. J Proteome Res 18: 508-521, 2019.
268. Seong J, Kim SH, Chung EJ, Lee WJ and Suh CO: Early alteration in TGF-beta mRNA expression in irradiated rat liver. Int J Radiat Oncol Biol Phys 46: 639-643, 2000.
269. Meng XM, Nikolic-Paterson DJ and Lan HY: TGF-β: The master regulator of fibrosis. Nat Rev Nephrol 12: 325-338, 2016.
270. Wu Y, Wang W, Peng XM, He Y, Xiong YX, Liang HF, Chu L, Zhang BX, Ding ZY and Chen XP: Rapamycin upregulates connective tissue growth factor expression in hepatic progenitor cells through TGF-β-Smad2 dependent signaling. Front Pharmacol 9: 877, 2018.
271. Du SS, Qiang M, Zeng ZC, Zhou J, Tan YS, Zhang ZY, Zeng HY and Liu ZS: Radiation-induced liver fibrosis is mitigated by gene therapy inhibiting transforming growth factor-β signaling in the rat. Int J Radiat Oncol Biol Phys 78: 1513-1523, 2010.
272. Zhu W, Zhang X, Yu M, Lin B and Yu C: Radiation-induced liver injury and hepatocyte senescence. Cell Death Discov 7: 244, 2021.
273. Marampon F, Gravina GL, Festuccia C, Popov VM, Colapietro A, Sanita P, Musio D, De Felice F, Lenzi A, Jannini EA, *et al*: Vitamin D protects endothelial cells from irradiation-induced senescence and apoptosis by modulating MAPK/SirT1 axis. J Endocrinol Invest 39: 411-422, 2016.
274. Chen YX, Zeng ZC, Sun J, Zhang ZY, Zeng HY and Hu WX: Radioprotective effect of kupffer cell depletion on hepatic sinusoidal endothelial cells. Radiat Res 183: 563-570, 2015.
275. Sun YW, Zhang YY, Ke XJ, Wu XJ, Chen ZF and Chi P: Pirfenidone prevents radiation-induced intestinal fibrosis in rats by inhibiting fibroblast proliferation and differentiation and suppressing the TGF-β1/Smad/CTGF signaling pathway. Eur J Pharmacol 822: 199-206, 2018.
276. Xie Y, Zhang J, Xu Y and Shao C: SirT1 confers hypoxia-induced radioresistance via the modulation of c-Myc stabilization on hepatoma cells. J Radiat Res 53: 44-50, 2012.
277. Mahmoud Moustafa E, Rashed ER, Rashed RR and Omar NN: Piceatannol promotes hepatic and renal AMPK/SIRT1/PGC-1alpha mitochondrial pathway in rats exposed to reserpine or gamma-radiation. Int J Immunopathol Pharmacol 35: 20587384211016194, 2021.
278. Srinivasan M, Sudheer AR, Rajasekaran KN and Menon VP: Effect of curcumin analog on gamma-radiation-induced cellular changes in primary culture of isolated rat hepatocytes in vitro. Chem Biol Interact 176: 1-8, 2008.
279. Li W, Jiang L, Lu X, Liu X and Ling M: Curcumin protects radiation-induced liver damage in rats through the NF-κB signaling pathway. BMC Complement Med Ther 21: 10, 2021.
280. Zhang J, Zhou S, Zhou Y, Feng F, Wang Q, Zhu X, Ai H, Huang X and Zhang X: Hepatocyte growth factor gene-modified adipose-derived mesenchymal stem cells ameliorate radiation induced liver damage in a rat model. PLoS One 9: e114670, 2014.
281. Lee YH, Tai D, Yip C, Choo SP and Chew V: Combinational immunotherapy for hepatocellular carcinoma: Radiotherapy, immune checkpoint blockade and beyond. Front Immunol 11: 568759, 2020.
282. Yi M, Li T, Niu M, Mei Q, Zhao B, Chu Q, Dai Z and Wu K: Exploiting innate immunity for cancer immunotherapy. Mol Cancer 22: 187, 2023.
283. De Ridder M, Jiang H, Van Esch G, Law K, Monsaert C, Van den Berge DL, Verellen D, Verovski VN and Storme GA: IFN-gamma+ CD8+ T lymphocytes: possible link between immune and radiation responses in tumor-relevant hypoxia. Int J Radiat Oncol Biol Phys 71: 647-651, 2008.
284. He K, Puebla-Osorio N, Barsoumian HB, Sezen D, Rafiq Z, Riad TS, Hu Y, Huang A, Voss TA, Leyton CSK, *et al*: Novel engineered IL-2 Nemvaleukin alfa combined with PD1 checkpoint blockade enhances the systemic anti-tumor responses of radiation therapy. J Exp Clin Cancer Res 43: 251, 2024.
285. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC and Demaria S: DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 8: 15618, 2017.
286. Wang Y, Chen Z, Liang K, Wang W, Hu Z, Mao Y, Liang X, Jiang L, Liu Z and Ma Z: AGO2 mediates immunotherapy failure via suppressing tumor IFN-gamma response-dependent CD8(+) T cell immunity. Cell Rep 44: 115445, 2025.
287. Trovo M, Giaj-Levra N, Furlan C, Bortolin MT, Muraro E, Polesel J, Minatel E, Tedeschi R, Filippi AR, Alongi F and Ricardi U: Stereotactic body radiation therapy and intensity modulated radiation therapy induce different plasmatic cytokine changes in non-small cell lung cancer patients: A pilot study. Clin Transl Oncol 18: 1003-1010, 2016.
288. Mills BN, Connolly KA, Ye J, Murphy JD, Uccello TP, Han BJ, Zhao T, Drage MG, Murthy A, Qiu H, *et al*: Stereotactic body radiation and interleukin-12 combination therapy eradicates pancreatic tumors by repolarizing the immune microenvironment. Cell Rep 29: 406-421 e5, 2019.
289. Jiang K, Yin X, Zhang Q, Yin J, Tang Q, Xu M, Wu L, Shen Y, Zhou Z, Yu H and Yan S: STC2 activates PRMT5 to induce radioresistance through DNA damage repair and ferroptosis pathways in esophageal squamous cell carcinoma. Redox Biol 60: 102626, 2023.
290. Berquist BR and Wilson DM III: Pathways for repairing and tolerating the spectrum of oxidative DNA lesions. Cancer Lett 327: 61-72, 2012.
291. Mladenov E, Magin S, Soni A and Iliakis G: DNA double-strand-break repair in higher eukaryotes and its role in genomic instability and cancer: Cell cycle and proliferation-dependent regulation. Semin Cancer Biol 37-38: 51-64, 2016.
292. Zong C, Zhu T, He J, Huang R, Jia R and Shen J: PARP mediated DNA damage response, genomic stability and immune responses. Int J Cancer 150: 1745-1759, 2022.
293. Li T, Cheng H, Yuan H, Xu Q, Shu C, Zhang Y, Xu P, Tan J, Rui Y, Li P and Tan X: Antitumor activity of cGAMP via stimulation of cGAS-cGAMP-STING-IRF3 mediated innate immune response. Sci Rep 6: 19049, 2016.
294. Zhao X, Ma Y, Li J, Sun X, Sun Y, Qu F, Shi X, Xie Y, Liu S, Ma Y, *et al*: The AEG-1-USP10-PARP1 axis confers radioresistance in esophageal squamous cell carcinoma via facilitating homologous recombination-dependent DNA damage repair. Cancer Lett 577: 216440, 2023.
295. Liu W, Miao C, Zhang S, Liu Y, Niu X, Xi Y, Guo W, Chu J, Lin A, Liu H, *et al*: VAV2 is required for DNA repair and implicated in cancer radiotherapy resistance. Signal Transduct Target Ther 6: 322, 2021.
296. Liu YG, Chen JK, Zhang ZT, Ma XJ, Chen YC, Du XM, Liu H, Zong Y and Lu GC: NLRP3 inflammasome activation mediates radiation-induced pyroptosis in bone marrow-derived macrophages. Cell Death Dis 8: e2579, 2017.
297. Ortiz F, Acuna-Castroviejo D, Doerrier C, Dayoub JC, Lopez LC, Venegas C, Garcia JA, Lopez A, Volt H, Luna-Sanchez M and Escames G: Melatonin blunts the mitochondrial/NLRP3 connection and protects against radiation-induced oral mucositis. J Pineal Res 58: 34-49, 2015.
298. Feldmeyer L, Keller M, Niklaus G, Hohl D, Werner S and Beer HD: The inflammasome mediates UVB-induced activation and secretion of interleukin-1beta by keratinocytes. Curr Biol 17: 1140-1145, 2007.
299. Anand PK, Malireddi RK and Kanneganti TD: Role of the nlrp3 inflammasome in microbial infection. Front Microbiol 2: 12, 2011.
300. Francois A, Milliat F, Guipaud O and Benderitter M: Inflammation and immunity in radiation damage to the gut mucosa. Biomed Res Int 2013: 123241, 2013.
301. DeBo RJ, Lees CJ, Dugan GO, Caudell DL, Michalson KT, Hanbury DB, Kavanagh K, Cline JM and Register TC: Late effects of total-body gamma irradiation on cardiac structure and function in male rhesus macaques. Radiat Res 186: 55-64, 2016.
302. De Palma M, Coukos G and Hanahan D: A new twist on radiation oncology: Low-dose irradiation elicits immunostimulatory macrophages that unlock barriers to tumor immunotherapy. Cancer Cell 24: 559-561, 2013.
303. Ratikan JA, Micewicz ED, Xie MW and Schaue D: Radiation takes its toll. Cancer Lett 368: 238-245, 2015.

304. Curti B, Crittenden M, Seung SK, Fountain CB, Payne R, Chang S, Fleser J, Phillips K, Malkasian I, Dobrunick LB and Urba WJ: Randomized phase II study of stereotactic body radiotherapy and interleukin-2 versus interleukin-2 in patients with metastatic melanoma. J Immunother Cancer 8: e000773, 2020.
305. Ng SSW, Zhang H, Wang L, Citrin D and Dawson LA: Association of pro-inflammatory soluble cytokine receptors early during hepatocellular carcinoma stereotactic radiotherapy with liver toxicity. NPJ Precis Oncol 4: 17, 2020.
306. McBride WH and Schaue D: In situ tumor ablation with radiation therapy: Its effect on the tumor microenvironment and anti-tumor immunity. In: Tumor ablation: Effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Keisari Y (ed). Springer, Dordrecht, pp109-119, 2013.
307. Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, Miller W, Payne R, Glenn L, Bageac A and Urba WJ: Phase 1 study of stereotactic body radiotherapy and interleukin-2-tumor and immunological responses. Sci Transl Med 4: 137ra74, 2012.
308. Hughson AL, Hannon G, Salama NA, Vrooman TG, Stockwell CA, Mills BN, Garrett-Larsen J, Qiu H, Katerji R, Benoodt L, *et al*: Integrating IL-12 mRNA nanotechnology with SBRT eliminates T cell exhaustion in preclinical models of pancreatic cancer. Mol Ther Nucleic Acids 35: 102350, 2024.