Review

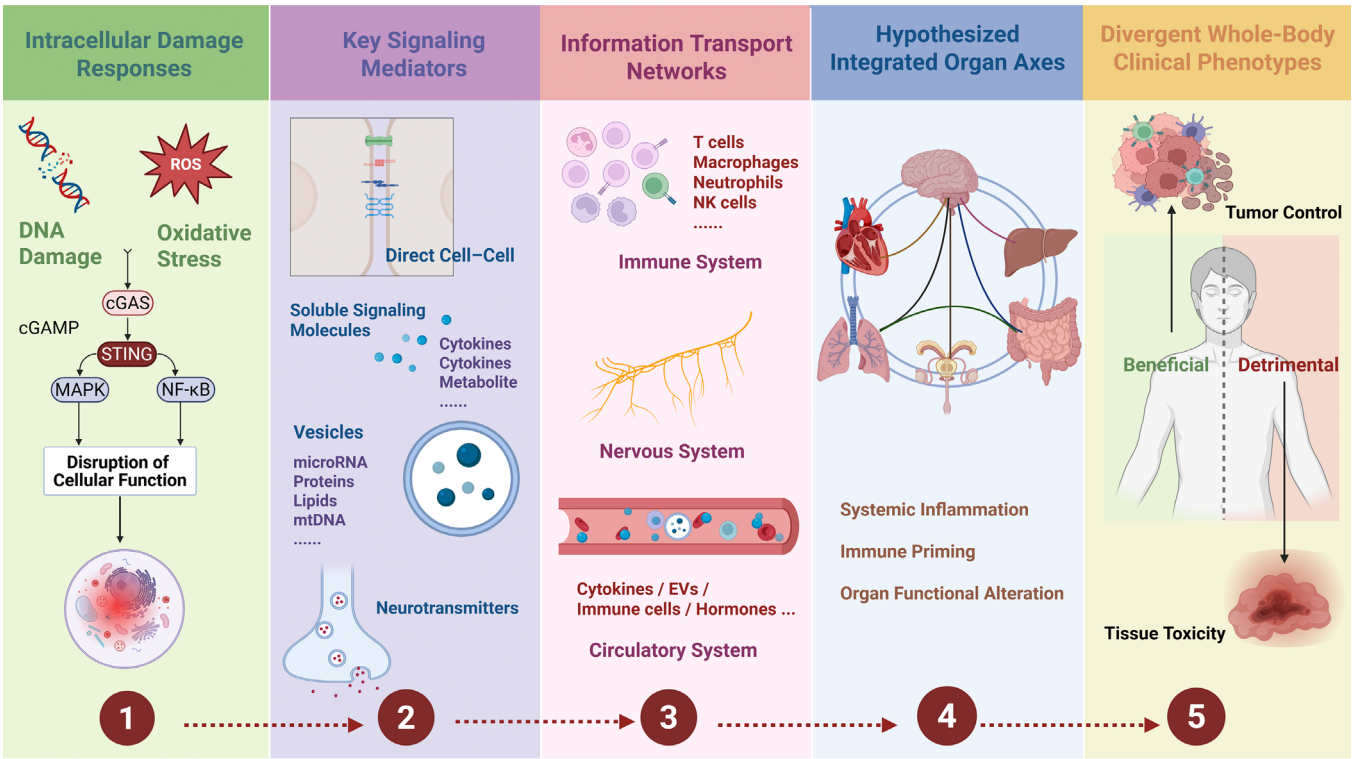
http://dx.doi.org/10.20517/element.2026.10

Radiotherapy: cellular stress, inter-organ crosstalk and clinical outcomes

Xinyi Zheng, Jianfeng Wang, Hetian Xue, Yue Zheng, Shengye Yuan, Yan Pan, Jianghong Zhang, Chunlin Shao

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Graphical abstract



Key Points

- Radiotherapy elicits biological effects beyond the irradiated field, reframing localized treatment as a systemic modulator.
- A multi-layered framework integrates intracellular stress, molecular mediators, transport networks, and organ-axis interactions.
- Immune, circulatory, and neural pathways collectively shape radiation-induced communication across cells, tissues, and distant organs.
- The gut-lung-brain axis is proposed as a hypothesis-generating framework for understanding systemic radiation responses.
- Translational strategies are outlined to enhance antitumor effects while mitigating adverse systemic radiation responses.

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Radiotherapy: cellular stress, inter-organ crosstalk and clinical outcomes

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Received: 2 Jun 2026

Accepted: 1 Sep 202

Online: 26 Nov 2026

Open Access

ABSTRACT

Radiotherapy is a cornerstone of oncology yet has long been perceived as an exclusively local therapeutic modality. Emerging evidence suggests that localized irradiation triggers molecular, cellular and immunological cascades outside the irradiated volume. Though overt distant tissue toxicity and clinically significant abscopal regression are uncommon, such systemic effects overturn the conventional perception of radiotherapy. Nevertheless, existing knowledge on this process remains disjointed, with prior work centering on discrete bystander signals or tumor-restricted immune events rather than inter-organ crosstalk. This concept-driven narrative review synthesizes current evidence to provide a conceptual framework for radiation-elicited systemic responses, spanning intracellular triggers to multi-organ communication networks. We delineate key mechanisms, encompassing DNA damage-initiated cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling, oxidative stress, and immunogenic cell death modalities (ferroptosis, cuproptosis, pyroptosis) alongside pivotal signaling carriers including extracellular vesicles, cytokines, metabolites and neurotransmitters. These messengers disseminate via immune, circulatory and neural routes, ultimately converging within interconnected organ axes. Drawing upon validated pairwise organ interactions, we specifically put forward the gut-lung-brain axis as a hypothesis-generating conceptual model to contextualize systemic radiation effects. We further address key translational challenges, including the low clinical incidence of abscopal responses, dual opposing beneficial and adverse systemic outcomes, and poor response predictability. Finally, we outline actionable therapeutic strategies that amplify anti-tumor immunity while alleviating radiation-associated systemic toxicities. By reframing radiotherapy through the perspective of inter-organ systemic signaling, this review delivers a unifying conceptual blueprint to advance next-generation radioimmunotherapy and precision radiation oncology, providing a conceptual basis for future studies and translational development.

Keywords: Radiotherapy, bystander effect, abscopal effect, multi-organ communication, multi-system effect

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INTRODUCTION

Radiotherapy remains a cornerstone of cancer treatment, with approximately half of all cancer patients undergoing radiotherapy[1]. Traditionally, its clinical efficacy has been attributed to localized cytotoxic effects, including DNA damage, mitotic catastrophe, and tumor cell death confined to the irradiated field[2]. Despite continuous technological advances in radiation dose delivery and precision, its therapeutic efficacy is often limited by local recurrence, distant metastasis, and damage to surrounding normal tissues[1,3,4]. These limitations highlight a core contradiction between the localized nature of radiation delivery and the systemic behaviors of cancer progression and treatment-related toxicities.

Against this backdrop, a growing body of clinical observations has challenged the traditional notion that radiotherapy acts solely as a local therapeutic modality. Although clinically uncommon, sporadic yet reproducible cases of tumor regression at non-irradiated sites, termed the radiation-induced abscopal effect (RIAE), have been reported in patients with various tumor types, particularly in immunogenic tumors or in those receiving combination therapy with immune checkpoint inhibitors (ICIs)[5,6]. Notably, a review of clinical reports identified only 46 cases of abscopal effects following radiotherapy alone from 1969 to 2014, underscoring the rarity of clinically apparent distant tumor regression. In contrast, clinical studies combining radiotherapy with immune checkpoint blockade have reported encouraging systemic responses, although the occurrence of abscopal effects has remained heterogeneous and has not been consistently observed across treatment settings[6]. Conversely, radiotherapy is also associated with adverse systemic consequences, including radiation-induced lung fibrosis, neurocognitive impairment following cranial irradiation, and chronic inflammatory syndromes affecting distant organs[7-9]. For example, radiation-induced lung injury has been reported in approximately 5%-25% of patients with lung cancer[7]. Collectively, these observations suggest that the rarity of clinically detectable distant manifestations should not be interpreted as evidence that systemic responses to radiotherapy are themselves uncommon. Rather, accumulating experimental evidence indicates that localized irradiation frequently induces molecular and immunological alterations beyond the irradiated field, whereas only a subset of these responses culminates in clinically observable distant manifestations, including both beneficial abscopal tumor regression and adverse normal-tissue damage.

Over the past three decades, the understanding of radiation responses beyond the irradiated field has evolved from local cellular phenomena to organism-wide biological regulation. The radiation-induced bystander effect (RIBE) describes local communication between irradiated and neighboring non-irradiated cells[10,11], whereas the RIAE refers to regression of distant tumors following localized radiotherapy and is primarily mediated by systemic antitumor immunity[12]. Detailed descriptions of these evolving concepts are provided in Box 1. Conversely, localized irradiation can also induce radiation-associated injury in distant non-irradiated normal tissues, highlighting the phenomenon of abscopal normal tissue toxicities. Although these concepts have greatly advanced our understanding of non-targeted effects of radiotherapy, several important knowledge gaps remain. First, the mechanisms underlying radiation-induced non-targeted effects remain incompletely understood, and the key signals and mediators responsible for initiating and sustaining radiation-induced non-targeted effects remain incompletely defined. Second, how signals generated within or around the irradiated field are transmitted, propagated, and integrated to influence distant tissues and organs remains poorly defined. Third, despite the potential of these systemic effects to influence both therapeutic efficacy and treatment-related toxicity, strategies for selectively enhancing beneficial effects while limiting detrimental systemic responses remain insufficiently explored. Addressing these gaps requires a systems-level perspective that connects local radiation-induced responses with signal transmission and distant biological outcomes.

Building upon these established concepts, we propose the framework of multi-organ systemic communication as an integrative systems-level perspective rather than a new biological phenomenon. Importantly, this framework does not replace established concepts such as RIBE or RIAE; instead, it incorporates them into a unified hierarchical model that spans multiple biological scales. The relationships and conceptual distinctions among these perspectives are summarized in Table 1. Radiation-induced effects can be interpreted as a manifestation of synergistic communication across multiple organs and systems. Rather than acting through a singular mediator or an isolated pathway, localized irradiation triggers a cascade of intracellular stress responses, induces the production of soluble signaling factors and extracellular vesicles (EVs), and activates the immune system. These signals propagate through immune, circulatory, and neural pathways, thereby remodeling the functional states of distant organs. Within this framework, organ axes integrate immune, metabolic, and neuroendocrine signals to form dynamic and radiation-responsive networks that ultimately determine the systemic outcomes. These processes can be conceptualized as a hierarchical cascade spanning intracellular initiation, molecular signal transmission, systemic dissemination, and organ-axis integration.

Accordingly, this review presents an integrated overview of radiation-induced multi-organ systemic communication from micro to macro scales. We first summarize intracellular events and signaling mediators triggered by radiation, then analyze the roles of the immune and circulatory systems as the primary carriers of systemic information, subsequently examine the interactions of representative organ axes, discuss current challenges and unresolved controversies, and predict emerging research directions. This review interprets the RIAE at the level of multi-organ communication, providing a systems-level framework for understanding radiotherapy beyond its localized effects and highlighting the translational potential of targeting systemic communication networks to enhance radiosensitization, mitigate treatment-related toxicities, and improve control of distant lesions.

As a narrative concept-driven review, this article does not follow a formal systematic-review methodology. Relevant literatures were searched across PubMed and Web of Science using combination keywords including “radiotherapy”, “ionizing radiation”, “radiation-induced bystander effect”, “radiation-induced abscopal effect”, “multi-organ systemic communication”, “organ axis”, “immune signaling”, “extracellular vesicles”, “cytokines”, “neuroimmune communication”, “gut-lung axis”, and “lung-brain axis”. Further relevant papers were retrieved via manual screening of reference lists from landmark publications. Instead of pursuing comprehensive inclusion of all available records, we prioritized seminal mechanistic work, high-quality clinical trials, and cutting-edge research offering mechanistic elucidation or translational implications for radiation-triggered inter-organ crosstalk.

Text Box

Box 1. Evolution of radiation responses beyond the target

Radiotherapy has traditionally been regarded as a local treatment whose biological effects are restricted to the irradiated field. Over the past three decades, however, accumulating evidence has progressively expanded this view, revealing that radiation can trigger biological responses far beyond the targeted tissue. This conceptual evolution has progressed through several distinct stages, each broadening the spatial scale and mechanistic understanding of radiation responses.

The first milestone was the discovery of the RIBE[13], which demonstrated that irradiated cells can transmit damage signals to neighboring non-irradiated cells. As a predominantly cellular and tissue-level phenomenon, RIBE is mediated by gap junctions[14], soluble mediators[15], and oxidative signaling[16], establishing the concept of local non-targeted effects.

Subsequently, the RIAE[5] extended this paradigm to the whole-organism level, describing the regression of distant, non-irradiated tumors following localized radiotherapy. Unlike RIBE, RIAE is largely driven by systemic antitumor immunity and has become an important rationale for combining radiotherapy with immunotherapy, although clinically meaningful responses remain relatively rare[17].

More recently, increasing evidence has highlighted that radiotherapy induces widespread systemic immune modulation, including alterations in circulating immune cells, inflammatory mediators, and metabolic networks that affect both tumors and normal tissues[18]. Consistent with this evolving understanding, the 2006 report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) broadened the definition of the abscopal effect to "a significant response in a tissue that is physically separate from the region of the body exposed to radiation", thereby extending the concept beyond the classical interpretation of distant tumor regression. The growing recognition of abscopal normal tissue toxicities further supports this expanded view, indicating that radiation-induced systemic responses encompass both beneficial and detrimental effects in distant organs. Collectively, these observations suggest that radiation responses cannot be fully explained by either local bystander signaling or tumor-centered abscopal effects alone.

The emerging concept of multi-organ systemic communication represents the next stage in this conceptual evolution. Rather than describing a single biological phenomenon, it provides an integrative framework in which molecular, immune, circulatory, metabolic, and neural signals are coordinated through interconnected biological information highways to orchestrate dynamic communication among multiple organs. By incorporating both therapeutic responses and radiation-induced toxicities into the same systems-level network, this framework offers a broader, more comprehensive perspective on radiation responses beyond the target.

INTRACELLULAR STRESS RESPONSES TO IONIZING RADIATION

The systemic effects induced by radiotherapy arise from perturbations in molecular events during the microscopic initiation phase within cells. At this stage, the core molecular dysregulations include DNA damage and the explosive generation of reactive oxygen species (ROS)[23]. As initial triggering signals, both factors synergistically disrupt cellular genomic integrity and endogenous redox homeostasis. These early microscopic perturbations rapidly initiate aberrant intracellular signaling cascades, among which key pathways, including cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING), mitogen-activated protein kinase (MAPK), and nuclear factor κB (NF-κB), are significantly activated[24-26]. A direct outcome of signal activation is the dysregulation of inflammatory cytokine and chemokine production[27], accompanied by coordinated transcriptional reprogramming of metabolic enzyme and immune-related molecule activity[28,29]. Persistent imbalance of downstream signals further elicits a cascade of molecular alterations, such as organelle dysfunction, metabolic reprogramming, and immunogenic remodeling, ultimately resulting in global impairment of cellular function[30,31]. Importantly, these intracellular molecular changes during the microscopic initiation phase drive the synthesis and secretion of signal mediators, thereby laying a fundamental cytological basis for subsequent intercellular and interorgan signal communication.

During the microscopic initiation phase, ionizing radiation induces DNA damage through two principal mechanisms that serve as upstream triggers of subsequent signaling. First, radiation energy is directly deposited onto DNA molecules, causing strand breaks. Second, radiation generates reactive species through water radiolysis, which indirectly damage DNA and other cellular macromolecules[32,33]. Among the resulting lesions, DNA double-strand breaks (DSBs) are considered the most biologically consequential because they have a major influence on cell fate decisions and activate the DNA damage response and repair machinery[32,34]. In cases of incomplete damage repair, nuclear-derived DNA fragments [including micronuclear DNA and aberrantly released mitochondrial DNA (mtDNA)][35] as well as abnormal nucleic acid molecules, such as repeat-derived transcripts, accumulate in the cytosol by breaching normal subcellular localization barriers[36,37]. These nucleic acids are specifically recognized by intracellular pattern recognition receptors, such as cyclic GMP-AMP synthase (cGAS) and retinoic acid-inducible gene I/melanoma differentiation-associated gene 5 (RIG-I/MDA5), thereby activating the STING-TBK1-IRF3/NF-κB pathway or mitochondrial antiviral signaling protein (MAVS) dependent signaling pathway[38-40]. Subsequent induction of type I interferons (IFN-I)[20], production of chemokines [e.g., C-X-C motif chemokine ligand 10 (CXCL10)][41], and extensive transcriptional and epigenetic remodeling amplify intracellular inflammatory signaling[42]. This process renders cells in an immunologically sensitized state, laying the groundwork for radiation-induced signals to propagate beyond irradiated sites to distant regions.

Concurrently, during the microscopic initiation phase, radiation-induced radiolysis of intracellular water generates excessive amounts of ROS, including hydroxyl radicals (•OH) and superoxide anions ($O_2^{\cdot-}$)[43,44]. As core oxidative stress signals, ROS not only

Table 1. Hierarchical comparison of current conceptual frameworks describing radiation responses beyond the target

Perspectives	Definition	Spatial scale	Biological outcome	Representative evidence/examples	Limitation
RIBE	Responses in neighboring non-irradiated cells[13]	Adjacent cells	Adjacent cellular stress and injury	Azzam *et al.* (2001): Verified Cx43 gap junctions transfer radiation damage signals to bystander cells[14]	Restricted to local signaling
RIAE	Regression of distant non-irradiated tumors[5]	Distant tumors	Distant tumor regression	Postow *et al.* (2012): reported immune-mediated regression of distant melanoma metastases following radiotherapy plus ipilimumab[15]	Tumor-centric; focuses mainly on beneficial responses
Systemic immune modulation	Systemic immune activation or suppression[16]	Whole organism immune system	Immune activation, immune suppression	Deng *et al.* (2014): identified the cGAS-STING/type I IFN pathway underlying radiation-induced systemic antitumor immunity[17]	Immune-centric; excludes other physiological systems
Abscopal normal tissue toxicities	Radiation-induced injury in non-irradiated normal organs[18]	Distant normal organs	inflammatory, fibrotic, degenerative pathological lesions	Hu *et al.* (2021): demonstrated localized thoracic irradiation disrupts the blood-testis barrier in distant non-irradiated testes[19]	Usually studied separately from antitumor effects
Multi-organ systemic communication	Hierarchical multi-scale communication network following localized irradiation	Multiple interconnected organs	Both beneficial and harmful responses	Integrative conceptual framework supported by multiple lines of evidence	Requires further validation of coordinated Organ Axes mechanisms

RIBE: Radiation-induced bystander effect; RIAE: radiation-induced abscopal effect; cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; IFN: interferon.

exacerbate DNA damage through mechanisms such as oxidative base modification but also directly target cell membrane lipids and intracellular proteins, thereby inducing lipid peroxidation, oxidative modification of proteins, and protein misfolding[45,46]. These processes provoke endoplasmic reticulum stress and mitochondrial dysfunction, further activating MAPK and NF-κB pathways[30], forming an oxidative stress-driven signal amplification loop. Together, during the microscopic initiation phase, DNA damage-dependent and redox-driven signaling pathways do not operate independently; instead, they converge synergistically and engage in crosstalk, collectively establishing a pro-inflammatory and immunomodulatory intracellular molecular microenvironment. This microenvironment provides a critical molecular basis for the intercellular and interorgan transmission of radiation-induced signals[46].

Importantly, the ultimate fate of irradiated cells is frequently the induction of cell death once accumulated molecular damage exceeds the cellular repair capacity [Figure 1A]. Ionizing radiation can trigger multiple forms of regulated cell death[47], including apoptosis[48], ferroptosis[49], cuproptosis[50] and pyroptosis[51]. Among these, apoptosis has traditionally been considered the dominant radiation-induced death pathway[52]. However, apoptotic cell death is generally regarded as immunologically silent or tolerogenic, as phagocytes rapidly clear apoptotic bodies with minimal release of inflammatory mediators[53]. Consequently, apoptosis alone is often insufficient to generate the strong systemic immune activation required for long-distance antitumor responses.

In contrast, emerging evidence suggests that several forms of regulated necrotic cell death exhibit stronger immunostimulatory properties[54]. Ferroptosis and cuproptosis, two recently characterized forms of regulated necrotic death driven by metabolic dysregulation[55], together with inflammasome-dependent pyroptosis, have attracted increasing attention in the context of radiotherapy-induced immune responses.

Ferroptosis is an iron-dependent form of cell death characterized by excessive lipid peroxidation of polyunsaturated phospholipids within cellular membranes[49]. Mechanistically, ferroptosis is initiated by the accumulation of intracellular ROS and redox imbalance, leading to iron-catalyzed lipid peroxide generation through the Fenton reaction. Failure of antioxidant defense systems particularly the glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis results in uncontrolled lipid peroxidation, membrane damage, and cell death[56-58]. Recent studies further suggest that ferroptosis plays a pivotal role in mediating the abscopal effect of radiotherapy. Ferroptotic tumor cells can release tumor antigens, oxidized lipid mediators, and damage-associated molecular patterns (DAMPs), which promote dendritic cell (DC) maturation and antigen presentation, thereby enhancing $CD8^+$ T-cell-mediated immune responses[59-61]. Several approaches have been developed to potentiate ferroptosis during radiotherapy. For example, activation of Toll-like receptor 3 (TLR3) signaling can promote ferroptosis by initiating NF-κB and type I interferon (IFN) signaling pathways, which subsequently induce intracellular ROS production[62]. In addition, targeting the tripartite motif-containing protein 14 (TRIM14)/ubiquitin-specific protease 14 (USP14) axis

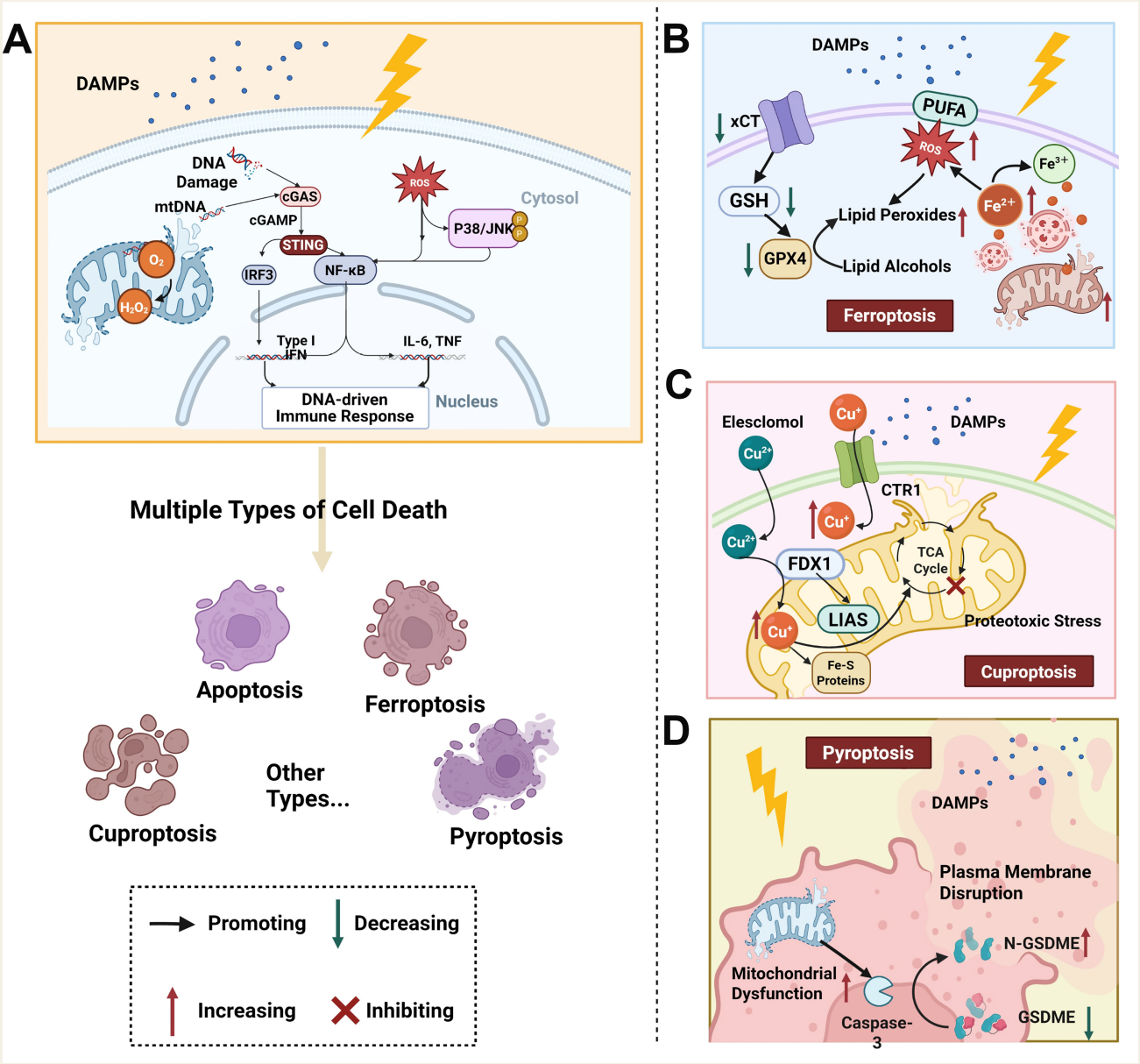


Figure 1. Intracellular initiation of radiation-induced signaling and cell death.
(A) Ionizing radiation induces DNA damage and mitochondrial dysfunction, leading to cytosolic DNA accumulation and activation of the cGAS-STING pathway. This triggers downstream IRF3 and NF-κB signaling, promoting the production of type I IFNs and pro-inflammatory cytokines (e.g., IL-6 and TNF). Concurrent ROS generation activates MAPK pathways (e.g., p38/JNK). Collectively, these responses initiate DNA damage-driven immune signaling and ultimately induce multiple forms of regulated cell death, including apoptosis, ferroptosis, cuproptosis and pyroptosis; (B) Radiation-induced oxidative stress promotes ferroptosis by disrupting cellular redox homeostasis. ROS accumulation and iron overload enhance lipid peroxidation, while inhibition of the system xCT-GSH-GPX4 axis impairs detoxification of lipid peroxides, leading to irreversible membrane damage; (C) Radiation can also induce cuproptosis through copper-dependent mitochondrial dysfunction. Elevated intracellular Cu^{2+} is transported via CTR1 and reduced to Cu^{+}, which binds lipoylated components of the TCA cycle via FDX1 and LIAS, causing proteotoxic stress and ultimately inducing cuproptotic cell death; (D) Radiation can also induce pyroptosis through the caspase-3/GSDME pathway. Radiation-induced DNA damage activates the intrinsic apoptotic cascade, leading to caspase-3 activation, which cleaves GSDME to release its pore-forming N-terminal fragment. GSDME-N oligomerizes on the plasma membrane to form pores, causing cell swelling, membrane rupture, and the release of inflammatory mediators, thereby promoting inflammatory cell death. This figure was created in BioRender. Zheng, X. (2026) https://BioRender.com/smf5aey. DAMPs: Damage-associated molecular patterns; mtDNA: mitochondrial DNA; cGAS: cyclic GMP-AMP synthase; cGAMP: cyclic GMP-AMP; STING: stimulator of interferon genes; IRF3: interferon regulatory factor 3; NF-κB: nuclear factor kappa B; ROS: reactive oxygen species; MAPK: mitogen-activated protein kinase; p38: p38 mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; IFN: interferon; IL-6: interleukin-6; TNF: tumor necrosis factor; xCT: cystine/glutamate antiporter; GSH: glutathione; GPX4: glutathione peroxidase 4; CTR1: copper transporter 1; FDX1: ferredoxin 1; TCA: tricarboxylic acid cycle; LIAS: lipoic acid synthetase; Fe-S: iron-sulfur; GSDME: gasdermin E; GSDME-N: N-terminal gasdermin E.

disrupts ferroptosis resistance by inducing degradation of GPX4, thereby sensitizing tumors to radiation-induced ferroptosis[63]. Moreover, targeting hypoxia-derived exosomal angiopoietin-like 4 (ANGPTL4) can downregulate GPX4 and solute carrier family 7 member 11 (SLC7A11) expression in neighboring tumor cells, restore lipid peroxidation, and promote ferroptosis[64]. Nanotherapeutic strategies can also trigger ferroptosis by inducing lysosomal membrane permeabilization, leading to overload and release of intracellular iron ions[65,66] [Figure 1B].

Cuproptosis is a recently defined form of copper-dependent regulated cell death[50]. Unlike apoptosis or ferroptosis, it is driven by copper directly binding to lipoylated tricarboxylic acid (TCA) cycle proteins in mitochondria, leading to proteotoxic stress and mitochondrial dysfunction[67]. Although this mechanism has attracted increasing interest, its contribution to radiation-induced systemic communication remains preliminary and is supported mainly by preclinical studies. Research demonstrates that copper-based nanoplatforms can trigger immunogenic cell death by inducing mitochondrial copper overload[68,69], a process further enhanced when combined with ferroptosis or metabolic interventions[70,71]. This targeted approach promotes the release of DAMPs, which subsequently activate DCs and $CD8^+$ T cells, effectively converting localized irradiation into a potent systemic antitumor immune response[68,69,72] [Figure 1C].

Pyroptosis is an inflammatory form of regulated cell death characterized by gasdermin-mediated plasma membrane pore formation and the release of intracellular pro-inflammatory mediators[73]. Increasing evidence demonstrates that ionizing radiation activates the caspase-3/gasdermin E (GSDME) signaling pathway to induce pyroptotic tumor cell death, thereby enhancing radiosensitivity and promoting antitumor immunity[51,74]. The major intracellular events associated with radiation-induced pyroptosis are illustrated in Figure 1D. Emerging evidence further indicates that pyroptosis and ferroptosis are not independent processes but exhibit extensive molecular crosstalk, with shared regulation by autophagy, oxidative stress, and inflammatory signaling[75]. Their coordinated activation may amplify immunogenic cell death and strengthen antitumor immune responses. Notably, pyroptosis may exert both beneficial and detrimental systemic effects. Beyond promoting antitumor immunity, sustained release of inflammatory mediators during pyroptosis has the potential to amplify systemic inflammatory signaling and perturb distant tissue homeostasis[76], raising the possibility that pyroptosis contributes to both therapeutic responses and radiation-associated toxicities within the framework of multi-organ systemic communication.

Collectively, these immunogenic forms of regulated necrotic cell death may represent critical mechanistic links between local tumor irradiation and systemic immune activation[77]. By releasing diverse molecular signals, dying irradiated cells provide the primary source of intercellular communication cues. These signals subsequently propagate beyond the irradiated microenvironment, mediating the transmission of radiotherapy-induced effects between neighboring cells and even distant organs.

MOLECULAR MEDIATORS OF INTERCELLULAR SIGNAL TRANSMISSION

Following intracellular initiation, radiation-induced signals are encoded into diverse molecular mediators that orchestrate both local intercellular crosstalk and systemic communication. These dynamic alterations are not confined to the irradiated cells but are actively transmitted to non-irradiated neighbors and distant organs through an integrated regulatory network. This process primarily relies on four major categories of mediators and delivery mechanisms. First, direct cell-cell communication (CCC) through gap junctions enables efficient, rapid short-range signal transfer. Second, vesicle-mediated communication is mediated by EVs, such as exosomes, which package nucleic acids and proteins for intermediate- to long-range delivery. Third, CCC is mediated by soluble signaling molecules, such as ROS, inflammatory cytokines, metabolites, and ions. Fourth, neurotransmitter-based signaling serves as a paramount layer of systemic integration, linking localized radiation stress to distal responses. These molecules diffuse through the extracellular microenvironment and exert extensive synergistic regulatory effects on intercellular signal transduction[78-80]. Collectively, these mechanisms constitute an integrated regulatory network that serves as the core molecular basis for radiation-induced cross-cellular communication. Representative signaling molecules and their principal modes of intercellular transmission are summarized in Figure 2. The representative mediators, their biological characteristics, and their reported roles in radiation-induced intercellular communication are further summarized in Table 2.

Direct cell-to-cell communication via gap junctions

Direct intercellular communication relies on physical contact structures between adjacent cells, primarily gap junctions composed of connexin proteins. Studies have demonstrated that irradiation can upregulate the expression and stability of connexins, particularly connexin 43 (Cx43), thereby enhancing gap junctional communication[101]. Furthermore, small-molecule signaling factors such as ROS and calcium ions (Ca^{2+}) generated in irradiated cells can rapidly enter neighboring non-irradiated cells through these channels, enabling efficient transmission of damage signals[102]. This mode of communication is especially prominent in densely packed tissues, facilitating synchronized signaling propagation within local cellular networks and representing a critical route for the rapid spread of RIBEs in the tissue microenvironments[11,16]. Notably, gap junction-mediated signal transduction appears particularly relevant under low-dose irradiation, as it effectively propagates radiation-derived signals generated by directly irradiated cells to the surrounding milieu[14].

Vesicle-mediated long-range communication

EVs, including exosomes, constitute a central vehicle for intermediate- and long-range intercellular communication under radiation. Irradiation stimulates the robust release of EVs, which encapsulate diverse functional cargoes such as microRNAs, proteins, lipids, and damaged mitochondrial components, thereby protecting these molecules from extracellular degradation[81]. EVs diffuse via bodily fluids, fuse with recipient cells, and deliver their contents to elicit functional responses[103]. For example, exosomes carrying miR-21 can induce DNA damage phenotypes in bystander cells, including micronucleus formation and an increase in 53BP1 repair foci, ultimately reducing cell survival[104]. Furthermore, exosomes released from irradiated bronchial epithelial cells transfer miR-7-5p to neighboring cells, where it induces autophagy through the EGFR-Akt-mTOR signaling pathway and mediates RIBEs[84]. Although microRNAs are the most extensively studied cargo of EVs, accumulating evidence indicates that EVs also transfer a broad spectrum of other bioactive signals. EV-mediated transfer of immunoregulatory proteins [e.g., heat shock protein 70 (HSP70)] and mitochondrial components has been reported to modulate immune cell function and cellular metabolism, thereby contributing to immunosuppressive effects within the tumor microenvironment[105-107]. These findings underscore that EVs represent a class of multifunctional mediators that act as

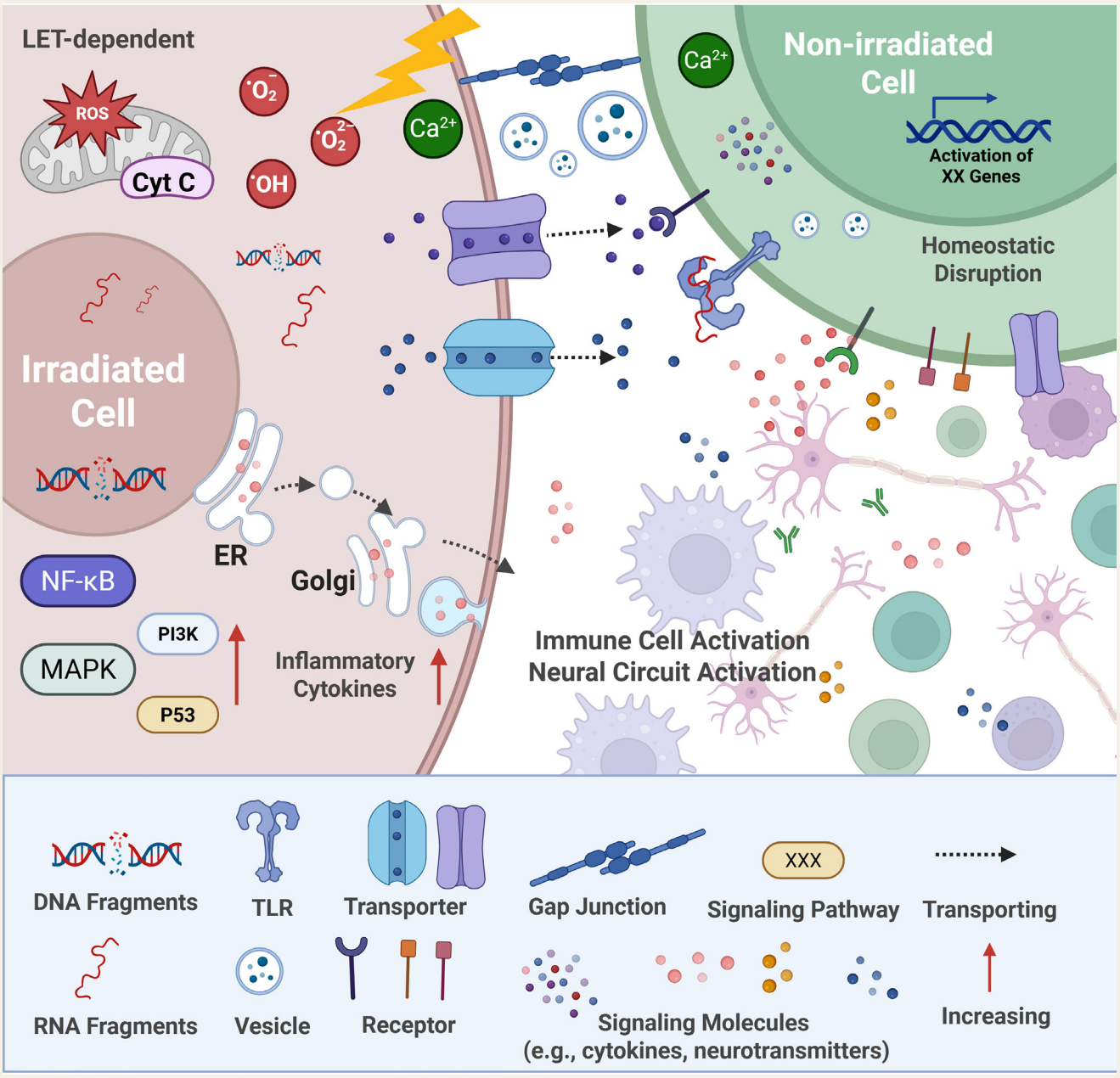


Figure 2. Molecular mediators and routes of radiation-induced intercellular signal transmission. Ionizing radiation triggers intracellular stress responses in irradiated cells, including DNA damage, ROS accumulation, and activation of signaling pathways, resulting in the release of diverse signaling mediators that transmit damage signals to non-irradiated cells. These mediators are broadly classified into four categories: direct contact-dependent signals, vesicle-mediated cargo, soluble factors, and neurotransmitter-like signals, and are conveyed via gap junctions, ligand-receptor interactions, and vesicle trafficking (endocytosis/exocytosis). Together, these interconnected routes enable radiation-derived signals to propagate locally and systemically while engaging immune and neural circuits to coordinate intercellular communication. This figure was created in BioRender. Zheng, X. (2026) https://BioRender.com/twf4nnj. LET: Linear energy transfer; ROS: reactive oxygen species; Cyt C: cytochrome c; NF-κB: nuclear factor kappa B; PI3K: phosphoinositide 3-kinase; MAPK: mitogen-activated protein kinase; ER: endoplasmic reticulum; TLR: Toll-like receptor.

a bridge linking intracellular damage induced by radiotherapy to systemic biological consequences.

Biochemical and metabolic mediators in the microenvironment

Soluble signaling molecules represent the most diverse and broadly distributed class of mediators in radiation-induced intercellular communication. They diffuse through the extracellular fluids to coordinate responses across various cell types and multiple tissues[108]. ROS generated following irradiation readily diffuse into the surrounding microenvironment, further inducing oxida-

Table 2. Key mediators of radiation-induced intercellular communication

Mediator category	Representative mediator	Mode of transmission/range	Key pathways or molecules	Major biological effects
Gap junction-mediated mediators	ROS[11,81]	Gap junction	Cx43	Induction of oxidative DNA damage and propagation of bystander signaling
Gap junction-mediated mediators	Ca^{2+}[81,82]	Gap junctions	Cx43, calcium signaling pathways	Promotion of stress signal amplification and synchronization
Extracellular vesicle cargo	miR-21[78]	Extracellular vesicles	DDR (e.g., 53BP1)	Induction of DNA damage responses and reduction of cell survival
Extracellular vesicle cargo	miR-7-5p[83,84]	Extracellular vesicles	EGFR-Akt-mTOR pathway	Induction of autophagy and bystander responses in recipient cells
Extracellular vesicle cargo	Extracellular dsDNA[24,85]	Extracellular vesicles	cGAS-STING pathway	Activation of antitumor immune responses
Soluble signaling molecules	ROS[86-88]	Diffusion	Oxidative stress-responsive inflammatory pathways (e.g., NF-κB)	Initiation of inflammatory cascades and bystander responses
Soluble signaling molecules	TNF-α[89,90]	Diffusion	TNFR/NF-κB pathway	Amplification of inflammation and distant tissue injury
Soluble signaling molecules	IL-6[91,92]	Diffusion	IL-6/JAK-STAT3 pathway	Promotion of inflammatory activation and immune microenvironment remodeling
Nucleic acid-based signals	Mitochondrial DNA fragments[93-95]	Free or EV-associated	DNA-sensing innate immune pathways (e.g., TLR9)	Activation of innate immunity and transcriptional reprogramming
Metabolic mediators	ATP[21,96]	Diffusion	Purinergic receptors (P2X/P2Y)	Activation of acute stress signaling and inflammatory responses
Metabolic mediators	Kynurenine[97,98]	Diffusion	AhR	Promotion of immune suppression and metabolic reprogramming
Metabolic mediators	Lactate[99,100]	Diffusion	GPR81/HCAR1 receptors	Promotion of radioresistance and M2 macrophage polarization

ROS: Reactive oxygen species; Cx43: connexin 43; miR-21: microRNA-21; DDR: DNA damage response; 53BP1: p53-binding protein 1; miR-7-5p: microRNA-7-5p; EGFR: epidermal growth factor receptor; Akt: protein kinase B; mTOR: mechanistic target of rapamycin; dsDNA: double-stranded DNA; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; NF-κB: nuclear factor kappa B; TNF-α: tumor necrosis factor alpha; TNFR: tumor necrosis factor receptor; IL-6: interleukin-6; JAK: Janus kinase; STAT3: signal transducer and activator of transcription 3; EV: extracellular vesicle; TLR9: Toll-like receptor 9; ATP: adenosine triphosphate; P2X/P2Y: purinergic receptor families 2X and 2Y; AhR: aryl hydrocarbon receptor; GPR81: G protein-coupled receptor 81; HCAR1: hydroxycarboxylic acid receptor 1.

tive damage to DNA, lipids, and proteins in target cells[43]. Beyond activating inflammatory pathways such as NF-κB, ROS interact with Ca^{2+} and other signaling mediators to amplify the cascades, enhancing the propagation of radiation damage. Consequently, ROS have emerged as a key initiator of RIBEs[109]. Cytochrome c release serves as a critical upstream event triggering ROS burst by impairing mitochondrial respiratory chain function. It can also act as a key signal for intercellular communication upon secretion into the extracellular space, thereby mediating RIBEs[110].

In addition, inflammatory cytokines play a pivotal role. Irradiation activates intracellular signaling axes, such as extracellular signal-regulated kinase (ERK)/early growth response 1 (EGR1), leading to the secretion of cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8)[108,111]. By engaging cognate receptors on target cells, these cytokines initiate downstream inflammatory signaling, contributing to local and systemic inflammatory responses and participating in the pathogenesis of radiation-associated distant tissue injury[22,112].

Nucleic acid-based signals arise from radiation-induced DNA damage, resulting in the release of mtDNA and genomic DNA (gDNA) fragments, as well as altered expression and extracellular transfer of microRNAs[32,113]. These nucleic acids can be transmitted either encapsulated within EVs or as extracellular soluble entities[113,114]. Extracellular DNA fragments can activate pattern recognition receptors, including TLR9, whereas extracellular microRNAs regulate gene expression in recipient cells. Together, these nucleic acid-based signals convey damage information, reshape cellular phenotypes, and contribute to radiation-induced inflammatory activation and transcriptional reprogramming[115,116].

Furthermore, radiation disrupts intracellular homeostasis, promoting the release of adenosine triphosphate (ATP) and uric acid crystals, and driving extensive metabolic reprogramming of amino acid, lipid, and glucose metabolism[108,117]. This leads to the abundant secretion of metabolites such as glutamate, kynurenine, prostaglandin E_2 (PGE_2), lysophosphatidic acid (LPA), and lactate, forming an integrated metabolic signaling network[118]. Extracellular ATP activates purinergic signaling, whereas uric acid contributes to TLR4/NF-κB and NLR family pyrin domain containing 3 (NLRP3)-mediated inflammatory responses, linking acute stress responses to chronic inflammation[119,120]. Glutamate and kynurenine modulate tumor proliferation and immune suppression. PGE_2 and LPA can promote radioresistance, angiogenesis, and tumor invasion[121]. Lactate further remodels the tumor microenvironment by reducing radiosensitivity and driving M2 macrophage polarization via G protein-coupled receptor 81 (GPR81)[100]. Beyond these, ionic signaling, particularly Ca^{2+} flux, constitutes the rapid-response component of radiation-induced communication. Irradiation disrupts membrane ion homeostasis, leading to Ca^{2+} efflux, which can directly trigger stress responses in neighboring cells[122]. Calcium signaling further modulates ROS production and inflammatory cytokine release, establishing an "ion-oxidative stress-inflammation" cascade that facilitates the rapid dissemination of radiation-induced damage signals[123]. In addition, nitric oxide (NO), a small gaseous metabolite produced by inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) under radiation stress, can directly transmit damage signals to adjacent non-irradiated cells[124]; meanwhile, it also mediates intracellular signaling cascades to upregulate the expression and secretion of transforming growth factor-β1 (TGF-β1)[15], thereby amplifying intercellular damage communication.

Neurotransmitter-driven integration of systemic signaling

In recent years, cancer neuroscience has rapidly emerged as a central focus in oncology research[125]. Radiotherapy can influence neural signaling not only through direct neuronal injury, particularly in the context of cranial or thoracic irradiation[8,126] but also through reshaping the tumor and immune microenvironment[127-130], thereby modulating the synthesis and release of neurotransmitters. Classical neurotransmitters such as norepinephrine and acetylcholine, as well as neuropeptides including calcitonin gene-related peptide (CGRP) and substance P, extend beyond synaptic transmission and function as systemic soluble signaling molecules[131,132]. For instance, glutamate accumulating within the tumor microenvironment may disseminate via humoral circulation or neural pathways to activate N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) receptors on tumor cells in distant organs, promoting their proliferation and invasiveness[133-135]. Altered norepinephrine release not only regulates tumor angiogenesis but also reshapes immune cell metabolic programming through β-adrenergic signaling, thereby modulating systemic antitumor immune responses[136-138]. Moreover, imbalances in acetylcholine and γ-aminobutyric acid (GABA) signaling have been implicated in multi-organ systemic communication networks associated with metastasis, including the gut-liver and breast-brain axes[139,140]. Together, these findings suggest that neurotransmitters constitute an additional class of radiation-responsive mediators contributing to multi-organ and systemic communication beyond the irradiated field.

SYSTEMIC SIGNAL HIGHWAYS: IMMUNE, CIRCULATORY, AND NEURAL NETWORKS

Local intercellular signaling does not represent the endpoint of radiation-mediated multi-organ systemic communication. To exert regulatory effects across tissues and organs, radiation-induced signals must be disseminated through efficient systemic carriers and integrated transport networks. Immune cells function as highly dynamic "mobile signal carriers", capable of sensing, loading, and transporting radiation-associated information throughout the body via the circulatory system[141]. In parallel, humoral circulation itself constitutes the principal infrastructure for long-distance signal dissemination, enabling cytokines, metabolites, nucleic acids, and EVs to escape local microenvironmental constraints[142-145]. Importantly, as the most rapid and precisely regulated control network in the body, the nervous system serves as a critical conduit linking the central nervous system (CNS) with peripheral organs[125,146]. It is capable of converting localized radiation-induced stress into electrochemical signals that are rapidly transmitted to distant sites. Critically, the nervous system does not operate in isolation; rather, it engages in dynamic and reciprocal interactions with both the immune and circulatory systems[147,148], forming an integrated regulatory network that coordinates systemic responses to local injury [Figure 3]. This systemic propagation is not indiscriminate; instead, it is finely regulated by multiple physiological barriers. These barriers modulate signal entry and spatial reach through selective permeability and immune surveillance[149,150]. The coordinated interplay among the immune system, circulatory system, nervous system, and physiological barriers ultimately determines whether localized radiation injury evolves into organ-specific and systemic multi-organ responses.

Immune system: mobile signal carriers

Immune cells are central mediators of radiation-induced multi-organ systemic signaling and represent the dominant mobile carriers of systemic antitumor immunity[12,151]. Ionizing radiation induces immunogenic cell death in tumor cells, resulting in the release of tumor-associated antigens (TAAs), double-stranded DNA (dsDNA), and other DAMPs[152]. These signals are captured by antigen-presenting cells (APCs), particularly DCs[153], which migrate to tumor-draining lymph nodes and activate type I interferon (IFN-I) signaling via the cGAS-STING pathway. This process enables efficient cross-presentation and priming of $CD8^+$ T cells[94]. Once activated, $CD8^+$ T cells circulate systemically and mediate cytotoxic responses not only against locally irradiated tumors but also against distant, non-irradiated metastatic lesions, constituting the cellular basis of the abscopal effect[93,154].

Beyond T cells, radiation can promote macrophage polarization toward a pro-inflammatory M1 phenotype[141], enhancing cytokine production and tumoricidal activity, while natural killer (NK) cells contribute to distant tumor control by recognizing radiation-induced upregulation of natural killer group 2 member D (NKG2D) ligands on tumor cells[155]. Importantly, the combination of radiotherapy with ICIs [e.g., anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies] can reverse T cell exhaustion[156,157], suppress regulatory T cell (Treg)-mediated immunosuppression, and further amplify the systemic signaling capacity of immune cells[158,159], thereby coupling local irradiation with global immune activation.

Conversely, immune cells can also act as negative signal carriers that propagate systemic toxicity and therapeutic resistance. Figure 3B uses distinct color coding to differentiate immune cell populations with beneficial and detrimental effects, highlighting their dual roles in mediating systemic responses following radiotherapy. Radiation-induced secretion of cytokines such as

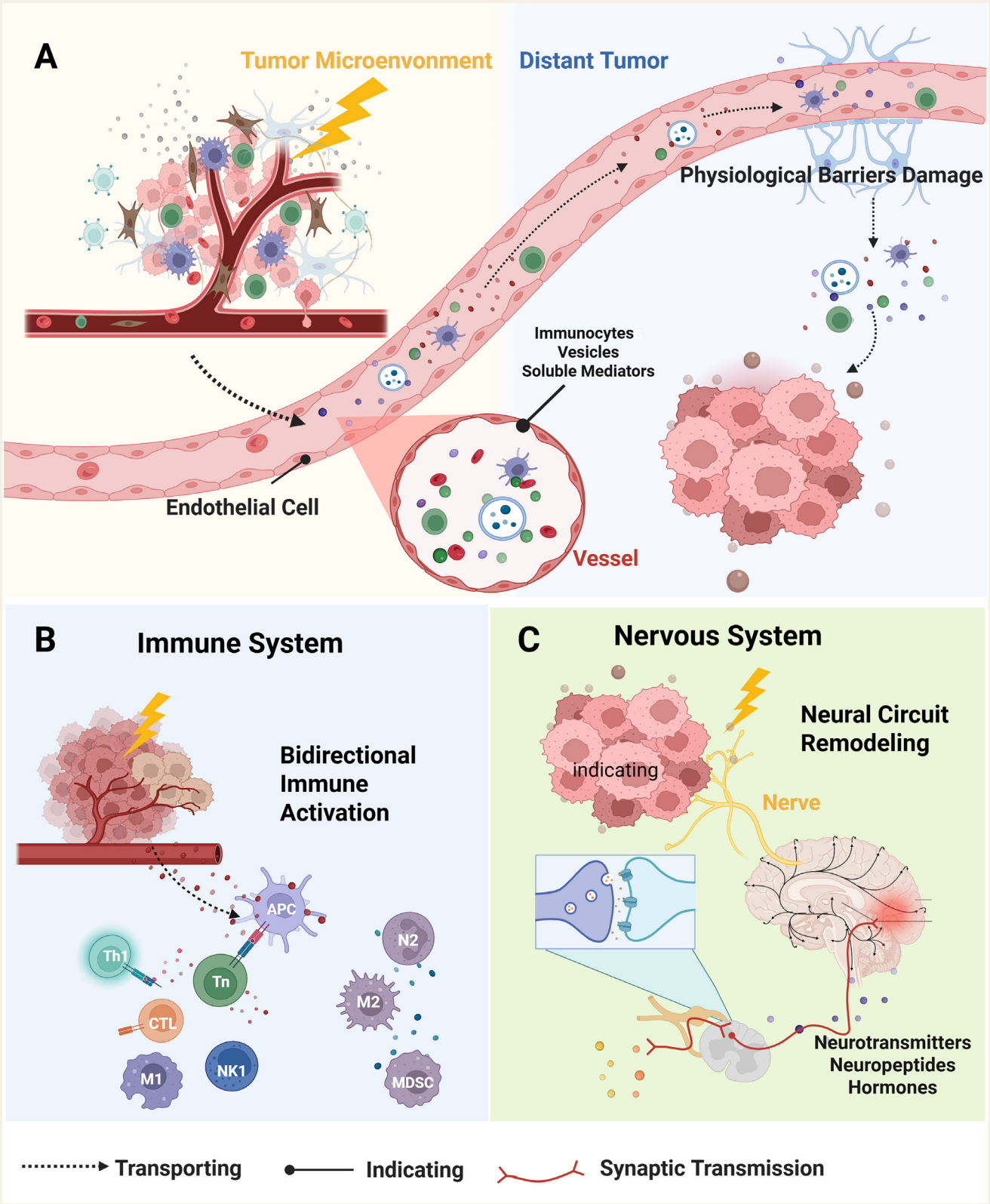


Figure 3. Integrated systemic network mediating radiation-induced multi-organ communication.
(A) Circulatory dissemination as a central signaling hub. Localized irradiation triggers the release of immune- and nerve-derived signals, including immune cells, soluble mediators, EVs, and neuroactive factors, into the circulation. The vascular system serves as a central conduit integrating signals from the immune and nervous systems to enable long-range communication. Radiation-induced endothelial activation

and barrier disruption further facilitate signal propagation to distant tumor sites; (B) Immune system: bidirectional activation. Radiation-induced ICD promotes DAMP and antigen release, driving APC-mediated activation of CD8+ T cells, NK cells, and M1 macrophages for systemic antitumor immunity. Conversely, recruitment of MDSCs and M2 macrophages contributes to systemic immunosuppression and radiation-associated toxicities; (C) Nervous system: neural circuit remodeling and systemic regulation. Radiation-induced stress is translated into neural signals that remodel local and central neural circuits. Through neurotransmitters, neuropeptides, and neuroendocrine pathways (e.g., HPA and sympathetic axes), the nervous system regulates tumor progression and systemic physiological responses. This figure was created in BioRender. Zheng, X. (2026) https://BioRender.com/3xuw6it. EVs: Extracellular vesicles; ICD: immunogenic cell death; DAMP: damage-associated molecular pattern; APC: antigen-presenting cell; Th1: T helper 1 cell; Tn: naive T cell; CTL: cytotoxic T lymphocyte; M1: classically activated macrophage; NK1: natural killer cell type 1; N2: N2-polarized neutrophil; M2: alternatively activated macrophage; MDSCs: myeloid-derived suppressor cells; HPA: hypothalamic-pituitary-adrenal axis.

TGF-β promotes immunosuppressive microenvironment remodeling[160], including myeloid-derived suppressor cells (MDSCs)[161] and M2-polarized macrophages[162,163], which disseminate to distant organs. These cells suppress effector T cell function through IL-10 and TGF-β release, promote angiogenesis and fibrosis, and dampen cross-organ antitumor signaling[164]. Evidence indicates that M2 macrophages secrete IL-10, which activates the IL-10/STAT3/GPX4 axis in bystander tumor cells to suppress ferroptosis and enhance their radioresistance[165]. Under specific conditions, neutrophils may acquire immunosuppressive phenotypes, inhibiting T cell proliferation through arginase and ROS or forming neutrophil extracellular traps (NETs) that degrade chemokines and physically impede T cell infiltration[166,167]. Additionally, radiation-induced upregulation of PD-L1 on tumor and immune cells can drive T cell exhaustion at distant sites, reducing therapeutic efficacy while increasing the risk of immune-related adverse events[168,169]. Tumor hypoxia following irradiation further distorts immune trafficking and function via hypoxia-inducible factor 1 alpha (HIF-1α) signaling, impairing APC maturation and T cell infiltration and ultimately favoring tumor progression and radioresistance[170,171].

Circulatory system: distribution and amplification

Humoral circulation, encompassing both blood and lymphatic systems, provides the structural basis for long-range dissemination of radiation-induced signals while simultaneously transporting immune cells and interacting with physiological barriers to form a "transport-filtering-targeting" cascade. Blood circulation enables the rapid systemic distribution of soluble mediators, some of which associate with plasma proteins, such as albumin, to enhance stability and persistence[172]. Radiation-induced EVs are particularly well-suited for circulatory transport, as their lipid bilayers protect enclosed miRNAs, proteins, and DNA fragments from enzymatic degradation, thereby enabling efficient whole-body dissemination[173].

Activated immune cells enter the bloodstream and migrate to distant tumor sites or normal tissues, where they exert either protective or pathogenic effects[174]. The lymphatic system complements blood circulation by facilitating local signal drainage and immune activation[175]. Soluble mediators and EVs from irradiated tissues enter lymphatic capillaries and are delivered to regional lymph nodes[176], where they are captured by immune cells, leading to further immune priming before re-entry into systemic circulation[177,178]. As illustrated in Figure 3A, the circulatory system serves as a central communication highway that disseminates activated immune cells and circulating signaling molecules to distant organs, including non-irradiated tumors, thereby linking local irradiation to systemic biological responses.

Nervous system: rapid signal integration

Beyond the circulatory and immune systems, the nervous system serves as an indispensable pathway for radiation-mediated multi-organ systemic communication, providing a critical conduit that integrates the CNS with peripheral organs[146,179] [Figure 3C]. Its multifaceted roles in orchestrating cross-tissue communication are manifested through three core mechanisms, supported by accumulating evidence in cancer neuroscience and radiotherapy research.

First, in the oncologic context, growing evidence supports the existence of a neural-tumor axis[180] that may be reshaped following irradiation. Within this network, direct neuro-cancer communication is facilitated by perineural invasion (PNI) and neurogenesis[181] within the tumor microenvironment: tumor cells secrete neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) to recruit peripheral nerve axons[182], which in turn release neurotransmitters to modulate tumor proliferation, invasion, and metastasis[183]. For instance, prostate cancer cells induce neurite outgrowth from dorsal root ganglia (DRG) neurons, establishing direct synaptic-like contacts[184,185] that promote tumor colony expansion and nerve-dependent metastasis. In brain tumors such as glioblastoma, tumor cells integrate into neural circuits via glutamatergic synapses with CNS neurons, hijacking neural signaling to support intracranial progression[186].

Second, the nervous system engages in integrated regulation with the immune system, forming a neuro-immune crosstalk network that modulates systemic immune responses and cross-organ immunity[187-189]. Peripheral sensory neurons can respond to radiation-induced inflammatory mediators and transmit signals to central integrative centers, while autonomic efferents in turn regulate immune cell trafficking and cytokine production in distant organs[190,191]. For instance, sympathetic nerve-derived norepinephrine influences macrophage polarization and T cell activity[138,192], whereas vagal signaling participates in the inflammatory reflex to constrain excessive cytokine release[193]. Radiation-induced neuroinflammation may therefore modulate systemic immune tone, shaping whether local irradiation culminates in abscopal immune activation or systemic inflammatory toxicity.

Third, the nervous system interfaces closely with the circulatory system through two pathways: neurotransmitter and neuropeptide dissemination via humoral circulation and hormone release through neuroendocrine axes. Many neurotransmitters and neuropeptides, acting as soluble signaling molecules, escape local neural circuits to enter the bloodstream, facilitating long-distance multi-organ communication, such as norepinephrine, glutamate, and CGRP[131,132]. In clinical settings, cranial radiotherapy can disrupt neuroendocrine regulation, particularly the hypothalamic-pituitary-adrenal (HPA) axis[194] and the sympathetic-adrenal-medullary axis[195], leading to systemic release of glucocorticoids and catecholamines into the bloodstream. These hormones circulate to regulate immune function, vascular permeability, and tissue metabolism across organs[196-198].

Physiological barriers: gatekeepers of signal propagation

Physiological barriers impose structural and functional constraints on circulating signals and immune cells, thereby protecting tissue-specific microenvironments through selective filtration[199,200]. Radiation dose is a critical determinant of barrier integrity. Clinical studies suggest that, under appropriately designed low-dose radiotherapy regimens, physiological barriers generally remain functionally preserved[201]. In contrast, high-dose irradiation disrupts barrier architecture, increases permeability, and facilitates infiltration of aberrant signals, thereby contributing to radiation-induced distant organ injury[202].

The blood-brain barrier (BBB), composed of brain microvascular endothelial cells, tight junction complexes, and astrocytic endfeet, represents the principal defense of the CNS[203]. When intact, the BBB restricts the entry of most circulating molecules, allowing passive diffusion of small lipophilic molecules, while only a limited proportion of EVs can traverse the barrier through active transport mechanisms, such as receptor-mediated transcytosis and endothelial uptake[204,205]. Activated $CD8^+$ T cells and macrophages may also traverse the BBB through adhesion molecule-mediated interactions [e.g., intercellular adhesion molecule 1 (ICAM-1)/vascular cell adhesion molecule 1 (VCAM-1)][206]. Under conditions of high-dose irradiation, brain metastasis, or external interventions such as focused ultrasound, BBB permeability increases, permitting peripheral cytokines and EVs to infiltrate the brain parenchyma[207]. Clinical studies have demonstrated the feasibility of therapeutic strategies aimed at preserving or restoring BBB integrity for the treatment of radiation-induced brain injury[208,209].

The blood-testis barrier (BTB), formed by tight junctions between Sertoli cells and the basement membrane, maintains immune privilege within the seminiferous epithelium[210]. Radiation exerts a dual influence on BTB function. On the one hand, the barrier effectively restricts the infiltration of systemic inflammatory mediators and immune cells, thereby protecting germ cells from immune-mediated damage[211]. On the other hand, the BTB is highly sensitive to radiation-induced systemic signals[212,213]. Evidence indicates that irradiation at distant sites can trigger the transport of TNF-α via the bloodstream, activating p38 MAPK/Rac1 signaling in Sertoli cells and promoting degradation of tight junction proteins, ultimately compromising barrier integrity[22]. Radiation-induced hormonal perturbations further modulate BTB permeability; for example, elevated luteinizing hormone (LH) levels can disrupt Sertoli cell polarity and cytoskeletal organization, indirectly increasing barrier leakage[214,215]. Together, these mechanisms position physiological barriers as active regulators rather than passive obstacles to radiation-induced multi-organ communication.

ORGAN-AXIS INTEGRATION OF RADIATION-INDUCED RESPONSES

Biological complexity arises from the fact that organs do not function in isolation but are connected via highly specialized functional linkages established during evolution[216]. Therefore, signals transmitted by systemic transport networks are not randomly distributed but tend to converge on specific organ circuits, initiating coordinated cross-organ cascades[217]. In recent years, the concept of "organ axes" has emerged as a powerful framework for interpreting systemic biological communication following tissue injury, including radiation-induced effects[218]. Further details are presented in Box 2. Emerging evidence further suggests that cancer should be viewed as a multi-organ disease shaped by neuroimmune-metabolic co-evolution between the tumor microenvironment and the systemic macroenvironment[226]. Notably, the establishment of such organ-axis communication often presupposes the disruption or functional loosening of physiological barriers, which permits the translocation of signals and mediators across otherwise compartmentalized tissues[227,228]. Among these, the gut-lung-brain axis, a cross-organ circuit jointly mediated by immune, metabolic, and neural signals, has gained increasing attention[229] [Figure 4]. However, a critical caveat must be acknowledged: while this tri-organ network is presented as a central conceptual model, direct experimental evidence demonstrating a fully coordinated, simultaneous three-organ communication framework specifically under radiotherapy remains severely limited and partly speculative. Most current understanding relies on parallel insights from critical care or independent bidirectional axis studies that have provided a solid mechanistic foundation for constructing this integrated network.

Under conditions of radiation exposure, the intestine represents a highly sensitive organ due to its active epithelial turnover. Ionizing radiation can induce intestinal microbial dysbiosis and promote pro-inflammatory responses, thereby contributing to radiation-induced systemic immune dysregulation[230]. Experimental studies have demonstrated that radiation-induced alterations in the gut microbiota exacerbate radiation-associated lung injury[231]. In contrast, modulation of microbial composition or microbial-derived metabolites can partially attenuate pulmonary inflammation[232], implicating the gut-lung axis as a critical regulatory pathway in radiation-induced lung damage. Meanwhile, gut dysbiosis following radiation exposure has been associated with neuroinflammation and alterations in cognitive function[233]. These microbial perturbations may influence brain immune homeostasis through gut-brain axis signaling, as microbiota-derived metabolites, intestinal barrier dysfunction, and immune pathways are recognized regulators of neuroinflammatory responses[234], and targeted manipulation of the gut microbiota has been shown to alleviate radiation-associated neurological dysfunction[235]. Conversely, radiation-induced central neuroinflammation and hypothalamic stress activate the HPA axis, triggering a systemic surge of glucocorticoids. This hormonal flux directly impairs the expression of tight junction proteins in intestinal epithelial cells, thereby driving peripheral gut barrier leakage even in the absence of direct abdominal irradiation. Through this coordinated network of microbial metabolites, circulating immune mediators, and neurogenic signaling, the intestine functions as both an initiator and amplifier of systemic radiation-induced pathology across the lung and brain.

While the gut-brain axis has been thoroughly characterized, direct empirical evidence supporting a radiation-relevant lung-brain axis remains relatively scarce, though emerging work is quickly narrowing this research gap. Existing supporting data predominantly stem from critical care and inflammatory disease models, instead of radiation studies[236-238]. These studies verify bidirectional neuroimmune crosstalk between the lungs and brain triggered by pulmonary damage and inflammation, laying a biological foundation to frame testable hypotheses on radiation-mediated inter-organ signaling. From a neural perspective, the vagus nerve acts as a primary bidirectional signaling highway mediating lung-brain dialogue during acute pulmonary injury and inflammatory pathologies. Specifically, pulmonary inflammatory signals propagate to the CNS through afferent vagal fibers, driving neuroinflammation and shifts in cerebral neurotransmitter profiles. Subsequent functional remodeling of brain nuclei further tunes pulmonary inflammatory status via efferent neural pathways, establishing a reciprocal lung-brain feedback loop[186,239]. In the context of radiation exposure, by contrast, available evidence of lung-brain axis crosstalk is limited to unilat-

eral, preliminary observations. Existing preclinical work mainly characterizes brain-to-lung signaling upon cranial irradiation: radiation-primed microglia secrete effector molecules including miR-9, and irradiation-triggered cerebral periostin may also modulate pulmonary function[240,241]. However, the reverse lung-to-brain signaling cascade and a fully bidirectional lung-brain axis under radiation stress await further experimental verification. We hypothesize that beyond being a primary target of thoracic irradiation and a source of systemic inflammation, the lung transmits neural and humoral signals that influence central immune and neuroinflammatory states. In turn, the brain regulates pulmonary immunity, vascular function, and tissue repair through autonomic and neuroendocrine pathways, thereby shaping the severity and resolution of radiation-induced lung injury[223,242,243].

Taken together, under radiation stress, the interactions among multiple organs, such as the intestine, lung, and brain, are better regarded as a highly coupled, radiation-sensitive functional network rather than a collection of isolated bidirectional pathways[93]. Within this framework, the gut, lung, and brain form a core regulatory axis in which metabolic, immune, circulatory, and neural signals converge. Ionizing radiation rapidly perturbs gut microbiota homeostasis and compromises barrier function, rendering the intestine a persistent upstream source of systemic signals[221]. Current evidence suggests that disruption of intestinal barrier integrity permits the translocation of microbiota-derived products - including lipopolysaccharide (LPS), bacterial DNA, and peptidoglycan fragments - into the circulation, where they activate pattern-recognition receptors and amplify systemic inflammatory signaling[237]. In parallel, radiation-induced alterations in microbial metabolites, such as short-chain fatty acids[244], further modulate immune cell function and contribute to distant organ responses. Inflammatory mediators together with circulating microbiota-derived products and microbiota-derived metabolites collectively shape immune cell activation and contribute to systemic communication following irradiation[245]. The lung functions both as a major target of radiation exposure and as an intermediate amplifier, translating gut-derived inflammatory and metabolic cues into pulmonary immune remodeling and systemic cytokine release[246,247]. Concurrently, the nervous system integrates and coordinates this multi-organ systemic dialogue: gut-derived signals are processed by enteric neural circuits and relayed to the brain through vagal afferent pathways[248,249], pulmonary injury can activate sensory-autonomic reflex circuits[186,250], and central neural outputs modulate immune tone and vascular responses in peripheral tissues. The brain thus serves not only as a vulnerable target of circulating mediators but also as an active regulatory hub that can influence pulmonary and intestinal responses through autonomic and neuroendocrine pathways[219,251]. Although direct experimental evidence for synchronized tri-organ communication upon irradiation remains scarce, the conserved molecular mediators and regulatory pathways identified across these organs provide credible biological plausibility to this conceptual framework. This organ axis acts as a practical system-level model to investigate radiation-induced systemic multi-organ communication and requires further experimental validation.

Text Box 2

Box 2. From individual organ axes to integrated multi-organ communication

Communication between anatomically distant organs is increasingly recognized as a fundamental principle governing physiological homeostasis and disease progression[219,220]. Rather than functioning as isolated entities, organs are interconnected through coordinated immune, neural, endocrine, metabolic, vascular, and microbial signaling, forming functional organ axes that dynamically integrate local responses into systemic physiological regulation.

Several organ axes have been extensively characterized in both physiological and pathological settings. The gut-brain axis coordinates bidirectional communication through the gut microbiota, vagus nerve, immune mediators, and microbial metabolites, thereby regulating neurodevelopment, cognition, and neuroinflammation[221]. The gut-liver axis plays a central role in metabolic homeostasis, linking intestinal barrier integrity, bile acid metabolism, and immune regulation with liver diseases[222]. Increasing evidence also supports the gut-lung axis[223], in which microbial metabolites, circulating immune cells, and inflammatory mediators influence pulmonary infection, chronic lung diseases, and responses to immunotherapy. More recently, the brain-lung axis[186,224,225] has emerged as an important regulatory pathway in stroke, acute lung injury, chronic inflammation, and lung cancer, highlighting reciprocal neuroimmune communication between the CNS and peripheral organs.

Although these organ axes differ in their physiological functions, they share common biological principles. Long-distance communication is mediated by interconnected information highways, including the circulatory, immune, and nervous systems, and coordinated through conserved signaling mediators such as cytokines, EVs, neurotransmitters, hormones, metabolites, and microbial products. Collectively, these findings indicate that multi-organ systemic communication is a general organizational principle of mammalian physiology rather than an exceptional biological event.

Within this context, the proposed gut-lung-brain communication in radiotherapy should currently be regarded as a hypothesis-generating conceptual model rather than an established biological pathway. Radiotherapy simultaneously perturbs immune homeostasis, neural activity, metabolic regulation, and tissue integrity, providing a biologically plausible basis for coordinated signaling across multiple organ axes. Consequently, the multi-organ systemic communication framework extends the concept of individual organ axes from isolated bidirectional interactions to an integrated systems-level network, offering a unified perspective for understanding radiation-induced therapeutic responses and normal tissue toxicities.

CHALLENGES AND CONSTRAINTS

A comprehensive understanding of radiation-induced multi-organ and multi-system communication is critical for advancing translational oncology. However, the translation of these systemic insights into clinically actionable strategies remains constrained by multi-layered challenges, including mechanistic complexity, clinical variability, and technological tool-related limitations.

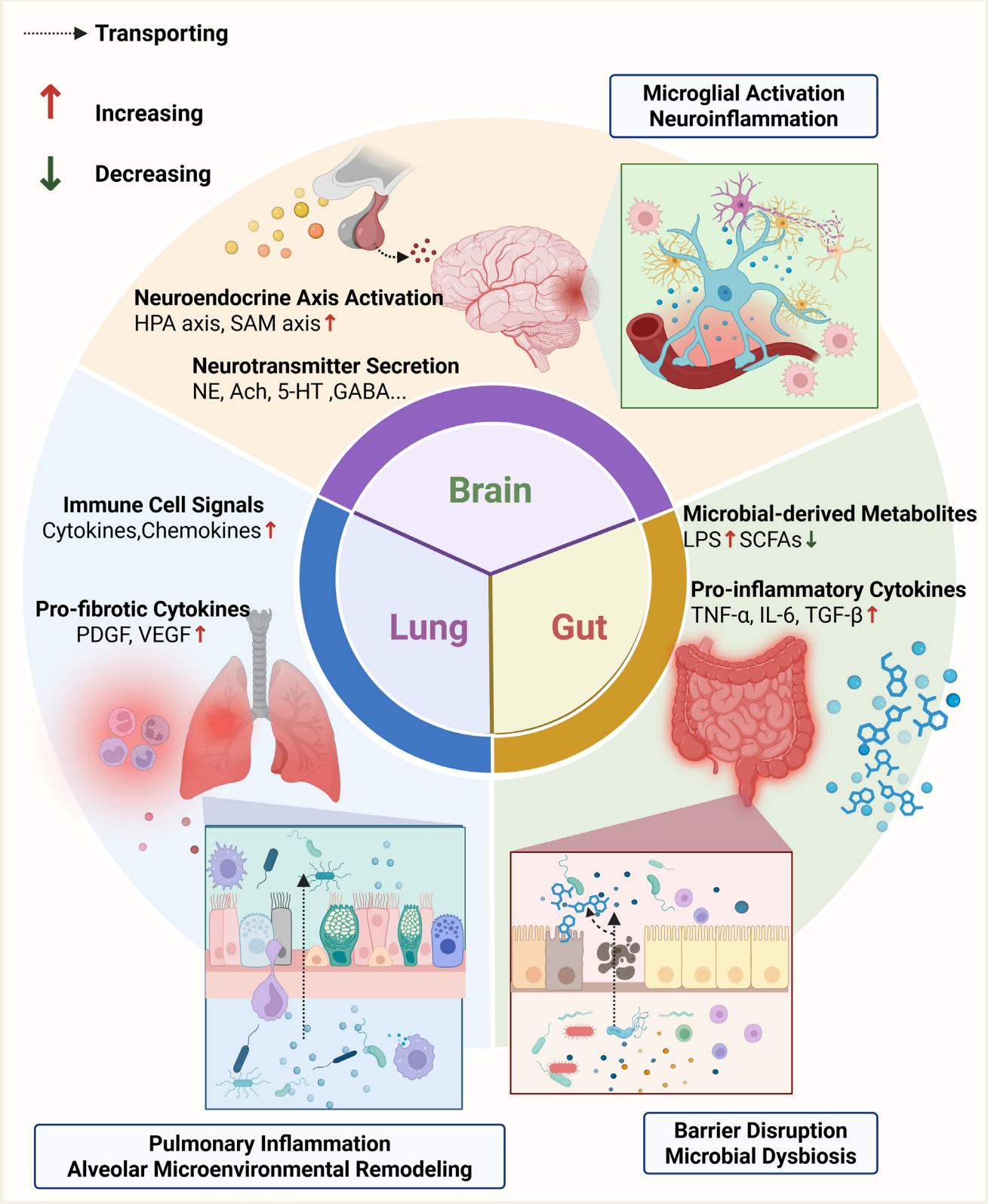


Figure 4. Radiation-induced gut-lung-brain axis as a systemic communication network.
Ionizing radiation induces coordinated biological alterations in the gut, lung, and brain through multiple systemic signaling pathways. Established experimental and clinical evidence demonstrates that irradiation promotes ROS generation, DNA damage, inflammatory

cytokine release, EV-mediated signaling, immune cell activation, and tissue-specific responses, including intestinal dysbiosis and barrier disruption, pulmonary inflammation, and microglial activation. Building upon these established observations, the integrated gut-lung-brain axis illustrated in this figure represents a conceptual framework proposed in this review, synthesizing evidence from radiobiology together with broader studies of gut-lung and gut-brain communication. Although increasing evidence supports interactions among these organs following irradiation, the organization of these responses into a coordinated radiation-induced gut-lung-brain axis remains a conceptual hypothesis that requires further experimental and clinical validation. This figure was created in BioRender. Zheng, X. (2026) https://BioRender.com/d76woz0. HPA: Hypothalamic-pituitary-adrenal axis; SAM: sympathetic-adrenal-medullary axis; NE: norepinephrine; Ach: acetylcholine; 5-HT: 5-hydroxytryptamine (serotonin); GABA: γ-aminobutyric acid; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; LPS: lipopolysaccharide; SCFAs: short-chain fatty acids; TNF-α: tumor necrosis factor alpha; IL-6: interleukin-6; TGF-β: transforming growth factor beta; ROS: reactive oxygen species; EV: extracellular vesicle.

Conceptual and mechanistic complexity of systemic radiation responses

At the conceptual level, the notion that radiotherapy functions not only as a local cytotoxic modality but also as a systemic regulatory intervention remains incompletely defined and continues to face fundamental challenges. Although accumulating evidence supports the ability of localized irradiation to reshape distant biological processes, the principles governing these effects are still poorly understood. In particular, the stage-, organ-, and tumor-type specificity of radiation-induced systemic responses remains insufficiently characterized, limiting the establishment of a unified conceptual framework.

A central feature underlying this uncertainty is the system-level complexity of radiation-induced multi-organ systemic communication. Rather than operating through isolated pathways, these responses emerge from an integrated neuro-immune-tumor network, leading to non-linear, context-dependent, and inherently bidirectional outcomes. As illustrated in Figure 5, localized irradiation can initiate the same systemic communication network yet ultimately lead to two distinct trajectories: beneficial systemic antitumor responses, characterized by immune activation, immune memory, and tumor regression, or detrimental systemic consequences, including chronic inflammation and radiation-induced injury across multiple organs.

Consistent with this, while radiotherapy combined with ICIs can enhance systemic antitumor immunity and promote abscopal tumor regression, immune and inflammatory pathways may also contribute to chronic inflammation, tissue remodeling, and normal tissue injury[252,253]. Moreover, the limited penetrance of systemic responses reflects the presence of active negative regulatory barriers within the network[254,255]. Tumor-intrinsic and stromal suppressive programs can restrict the propagation of antitumor signals, with stromal components acting as key regulatory nodes that intercept and reprogram systemic immune responses. For example, plasminogen activator inhibitor-1 (PAI-1)-driven secreted frizzled-related protein 2-positive ($SFRP2^+$) cancer-associated fibroblasts (CAFs) can hijack radioimmunotherapy-induced immunity, thereby preventing effective clearance of distant tumors and contributing to the low incidence of abscopal effects[256].

Clinical variability and translational uncertainty

At the clinical level, radiation-induced systemic effects remain difficult to predict, quantify, and control. Abscopal effects occur infrequently with marked variability, even when combined with radioimmunotherapy[257]. Although combining radiotherapy with immune checkpoint blockade can increase out-of-field response rates in certain settings[258,259], clinically detectable tumor regression likely represents only a subset of radiation-induced systemic responses, with additional molecular and immunological alterations occurring without overt clinical manifestations[257,260,261].

This uncertainty is further compounded by substantial inter-individual and inter-tumoral heterogeneity. Systemic responses vary across patients and cancer types, influenced by baseline immune states and stromal architecture, with a higher incidence observed in immunogenic tumors such as melanoma and renal cell carcinoma compared to "cold" tumors like pancreatic cancer[262,263].

In addition, the lack of robust biomarkers for patient stratification and response monitoring remains a major barrier to clinical translation. Although a variety of candidate biomarkers have been proposed, most remain insufficiently validated for routine clinical use. Representative biomarkers, together with their clinical evidence, predictive value, and current limitations, are summarized in Table 3. Although emerging approaches, such as the assessment of tumor antigen-specific effector T cells (ETASTs), show promise[261], they remain exploratory and not yet clinically validated.

Technological and therapeutic constraints

Beyond biological and clinical challenges, the controllability of radiation-induced multi-organ systemic communication is further limited by both therapeutic modalities and technological gaps.

From a clinical radiotherapy perspective, a major challenge lies in the limited control over treatment parameters that shape systemic responses. Dose, fractionation, and temporal scheduling influence immune activation and cross-organ signaling, yet their effects are highly context-dependent and difficult to standardize. For example, hypofractionated regimens (e.g., 8 Gy × 3) may promote immune priming, whereas high single doses can activate three prime repair exonuclease 1 (TREX1) and suppress IFN-I signaling, thereby limiting systemic immune propagation[271,272]. Consequently, it remains difficult to enhance tumor-suppressive systemic effects without increasing toxicity, particularly given the poorly defined temporal dynamics of these responses.

At the mechanistic level, the dissection of multi-organ communication is constrained by limited technological resolution. Although multi-omics approaches provide descriptive insights into irradiation-induced changes[273-276], they generally rely on static sampling at predefined time points and therefore cannot resolve the dynamic initiation, propagation, and resolution of systemic signaling following irradiation. Moreover, currently available experimental models only partially recapitulate the complexity of human systemic physiology. Conventional in vitro systems lack vascular, lymphatic, immune, and neural interactions, whereas animal models differ substantially from humans in immune composition, microbiota, metabolism, lifespan, and radiation sensitivity. Consequently, long-range bidirectional communication, organ-specific feedback loops, and chronic systemic adaptation remain difficult to model faithfully.

Table 3. Clinical evidence linking radiation-induced systemic molecular mediators to patient outcomes

Molecular mediator	Biological function	Clinical association	Patient outcome	Study type
IFN-β	Type I IFN signaling and $CD8^+$ T-cell priming	Elevated serum IFN-β predicts response to RT + CTLA-4 blockade[264]	Associated with improved response, durable disease control, and abscopal effects	Phase II clinical trial (n = 39)
IL-21	$CD8^+$ T/NK-cell activation	Elevated circulating IL-21 predicts response to SBRT + immunotherapy[265]	Associated with prolonged PFS and OS	Phase II clinical trial (n = 50)
CCL2	Monocyte/macrophage recruitment	Elevated post-RT serum CCL2 predicts poor prognosis[266]	Associated with shorter PFS and OS	Prospective observational cohort (n = 75)
TGF-β	Immune suppression and fibrosis	TGF-β blockade enhances RT efficacy; elevated plasma TGF-β predicts lung toxicity[267,268]	Associated with enhanced antitumor immunity or increased radiation pneumonitis/fibrosis	Phase I clinical trial (n = 23); Prospective observational cohort (n = 142)
IL-6	Systemic inflammation and MDSC/Treg expansion	Elevated baseline IL-6 predicts poor response to immune check-point blockade and radiation pneumonitis[269,270]	Associated with reduced response, shorter PFS, and increased radiation pneumonitis	Phase II clinical trial (n = 106); Prospective observational cohort (n = 96)

IFN-β: Interferon beta; RT: radiotherapy; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; IL-21: interleukin-21; NK: natural killer; SBRT: stereotactic body radiotherapy; PFS: progression-free survival; OS: overall survival; CCL2: C-C motif chemokine ligand 2; TGF-β: transforming growth factor beta; MDSC: myeloid-derived suppressor cells; Treg: regulatory T cells.

TRANSLATIONAL STRATEGIES

Current translational strategies span a broad spectrum of evidence, ranging from clinically implemented approaches to exploratory preclinical interventions. To facilitate interpretation, the following section first summarizes strategies with established or emerging clinical evidence, followed by experimental approaches that provide mechanistic insights and future therapeutic opportunities.

Combined radiotherapy and immunotherapy

Among currently available approaches, the combination of radiotherapy with ICIs represents the most clinically advanced strategy for harnessing radiation-induced multi-organ systemic communication. Radiotherapy promotes immunogenic cell death, enhances tumor antigen release, activates the cGAS-STING pathway, and facilitates DC priming and T-cell activation, thereby converting irradiated tumors into in situ vaccines. Immune checkpoint blockade further amplifies these radiation-induced immune responses by restoring T-cell function and promoting systemic antitumor immunity. Clinical studies across multiple tumor types have demonstrated improved survival and durable responses in selected patients. However, clinically meaningful abscopal responses remain uncommon and are influenced by tumor type, immune status, treatment sequencing, and radiation dose/fractionation.

Clinical stratification and predictive biomarkers

Addressing clinical heterogeneity requires robust biomarkers for patient stratification. Candidate indices, including blood-based biomarkers[277,278], liquid biopsy-derived molecular signatures[279], and the Radiosensitivity Index (RSI)[280], show potential in predicting response and toxicity. Furthermore, quantifying tumor-antigen-specific T cells provides functional insights into systemic immune activation[261]. These metrics are essential for precise patient selection and guiding personalized combination strategies. As summarized in Table 4, although no single biomarker has yet demonstrated sufficient predictive performance for routine clinical implementation, several candidates have undergone clinical evaluation. Among them, circulating cytokine signatures and liquid biopsy-based biomarkers currently represent the most promising approaches because of their favorable balance between clinical feasibility, translational maturity, and predictive potential.

Overcoming negative regulatory barriers

Increasing evidence indicates that the efficacy of radiotherapy depends not only on the strength of immune activation but also on the ability to overcome active negative regulatory barriers within the tumor microenvironment. Among these, stromal components, particularly CAFs, have emerged as key regulators. Beyond secreting immunosuppressive factors, CAFs remodel the extracellular matrix and establish physical barriers that restrict immune-cell infiltration, making stromal architecture and spatial immune exclusion major focuses of current radioimmunotherapy research.

Accordingly, therapeutic strategies targeting these inhibitory networks have attracted increasing interest. Approaches such as TGF-β blockade, fibroblast activation protein (FAP)-directed therapies, C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C motif chemokine receptor 4 (CXCR4) inhibition, and extracellular matrix normalization are currently under clinical or early translational investigation. They may enhance immune cell infiltration and restore systemic antitumor immunity. Rather than indiscriminately amplifying immune activation, future interventions should aim to selectively relieve these inhibitory barriers, thereby facilitating beneficial multi-organ systemic communication while minimizing treatment-related toxicity.

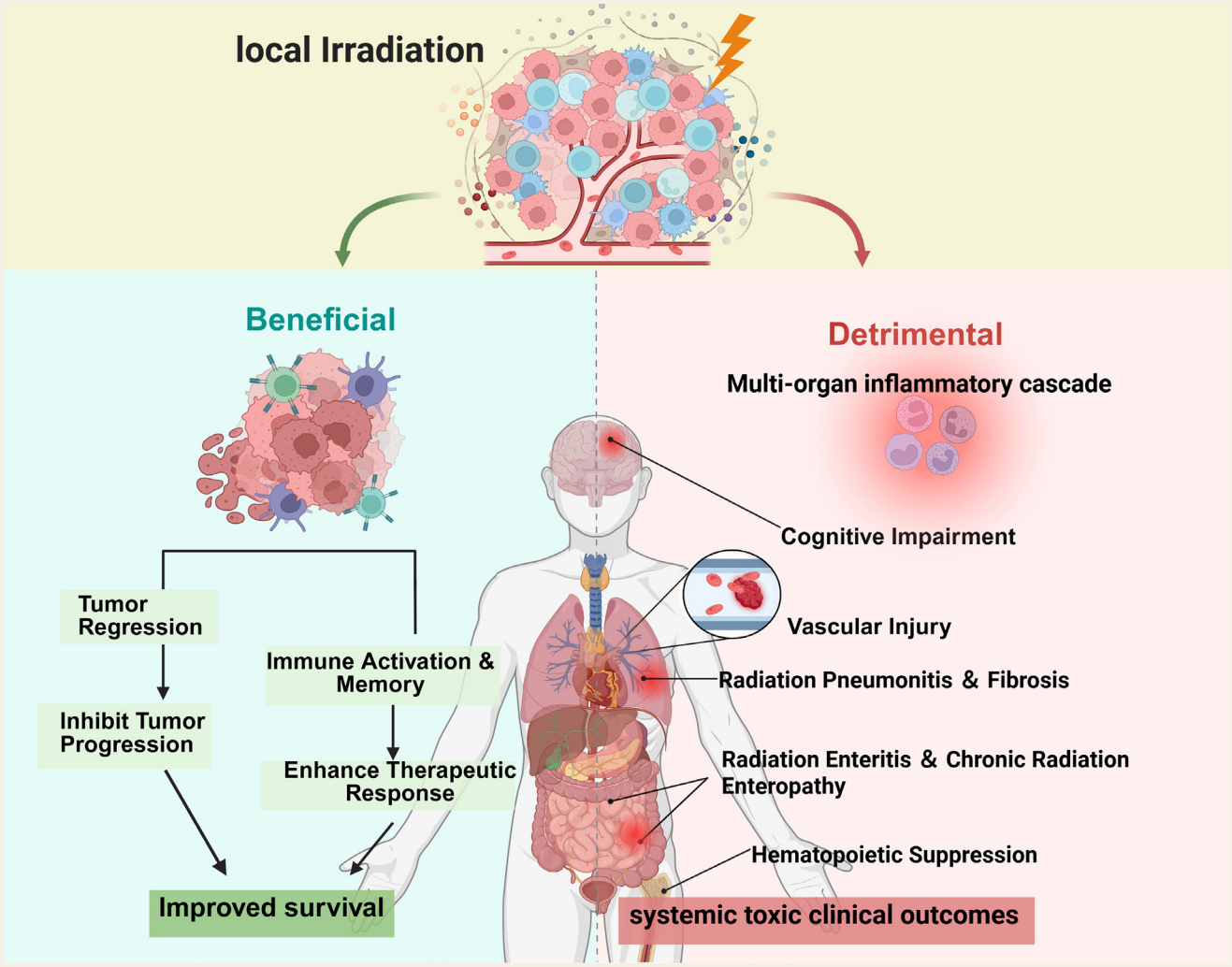


Figure 5. Bidirectional clinical outcomes of radiation-induced multi-organ systemic communication.
Localized irradiation initiates integrated multi-organ systemic communication through coordinated molecular, immune, circulatory, and neural signaling. Depending on the balance between stimulatory and suppressive regulatory mechanisms, these systemic signals can lead to two distinct yet interconnected clinical trajectories. Beneficial systemic communication promotes systemic antitumor immunity, immune memory, tumor regression, inhibition of tumor progression, and ultimately improved survival. In contrast, detrimental systemic communication amplifies chronic inflammation and propagates injury to distant normal organs, contributing to radiation-induced toxicities, including cognitive impairment, vascular injury, radiation pneumonitis and fibrosis, radiation enteritis and chronic enteropathy, and hematopoietic suppression. These bidirectional outcomes are not mutually exclusive but represent two interconnected manifestations of the same systemic communication network, highlighting the need for therapeutic strategies that selectively enhance beneficial signaling while suppressing harmful responses. This figure was created in BioRender. Zheng, X. (2026) https://BioRender.com/2jpoh9b.

Optimization of radiotherapy parameters and therapeutic window

Optimizing physical parameters is critical to maximizing the therapeutic window. Novel fractionation strategies, such as personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR)[290], align radiation with dynamic immune states to boost systemic responses[291]. Spatially fractionated radiotherapy (SFRT)[292] (e.g., GRID/Lattice) has shown the potential to promote bystander signaling and facilitate abscopal responses in preclinical and selected clinical settings[293,294]. In contrast, FLASH radiotherapy minimizes normal tissue damage through ultra-high dose rates[295,296]. Additionally, proton and heavy-ion therapies offer superior conformality[297]. Together, these technologies shift radiotherapy from simple dose escalation toward biologically informed, spatio-temporal optimization.

Systemic integration: the neuro-immune-cancer axis

Beyond traditional radio-immunotherapy, the nervous system has emerged as a critical regulatory layer. Localized irradiation can reshape the neuro-immune microenvironment by inducing persistent immune reprogramming in neural tissues[298]. Since most tumor-associated neural signals, such as neuron-to-cancer synapses or sympathetic innervation, promote immunosuppression and resistance[299], targeting this axis offers a synergistic

Table 4. Comparison of candidate biomarkers for predicting systemic radiotherapy responses

Biomarker modality	Representative biomarkers	Sample source	Clinical feasibility	Predictive value	Current limitations
Circulating cytokines/chemokines	IFN-β[264], IL-6[270], TGF-β[268]	Plasma or serum	Routine blood sampling with standardized immunoassays	Predicts immune activation, treatment response, abscopal effects, and radiation toxicity	Limited by biological variability and assay standardization
Immune cell profiling (T-cell assays)	Peripheral T-cell clonal expansion[281], immune subset characterization[282]	PBMCs	Requires PBMC isolation and flow cytometry/CyTOF/TCR sequencing	Predicts systemic immune activation and response to RT-immunotherapy	Limited by labor-intensive workflows and the need for fresh samples
Liquid biopsy	ctDNA (VAF)[269]	Plasma	Requires EDTA plasma extraction and molecular assays	Supports response assessment and prognostic monitoring	Limited by low analyte abundance and assay sensitivity
Radiomics	CD8 radiomics signature[283]	CT/PET/MRI images	Non-invasive and based on routinely acquired CT, MRI, or PET images.	Predicts treatment response, survival, and potential abscopal responses	Limited by imaging variability and insufficient external validation
Circulating damage and tissue injury biomarkers	GFAP, NfL[284], HMGB1[285], ICAM-1[286]	Plasma or serum	Measured using standard immunoassays	Reflects radiation injury, neurotoxicity, and systemic toxicity	Limited by non-radiation-related tissue injury and comorbidities
Extracellular vesicles	Exosomal miRNAs (e.g., miR-7-5p[287], miR-208a[80])	Plasma	Requires EV isolation and characterization	Reflects intercellular communication and therapeutic response	Limited by non-standardized isolation methods and limited clinical validation
Peripheral immune cell counts	ALC[288], NLR[252]	Whole blood (CBC)	Routinely available from the CBC	Predicts immune status, prognosis, treatment response, and abscopal effects	Limited by low specificity and confounding systemic conditions
Transcriptomic signatures	RSI[289]	Tumor or PBMCs	Requires RNA sequencing or gene-expression profiling	Identifies radiosensitivity and immune activation signatures	Limited by specialized sequencing requirements and bioinformatic analysis

IFN-β: Interferon beta; IL-6: interleukin-6; TGF-β: transforming growth factor beta; PBMCs: peripheral blood mononuclear cells; CyTOF: cytometry by time of flight; TCR: T-cell receptor; RT: radiotherapy; VAF: variant allele frequency; EDTA: ethylenediaminetetraacetic acid; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; GFAP: glial fibrillary acidic protein; NfL: neurofilament light chain; HMGB1: high mobility group box 1; ICAM-1: intercellular adhesion molecule 1; EV: extracellular vesicle; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; CBC: complete blood count; RSI: radiosensitivity index.

opportunity. Combining radiotherapy with neuro-active drugs[190] (e.g., beta-blockers) may alleviate the neural brake on the immune system, thereby potentially improving systemic antitumor responses.

Targeted modulation of key molecules and immunogenic cell death

Advanced nanotherapeutic strategies offer a versatile platform to modulate cell death pathways and improve radiotherapy's systemic efficacy. Nanoplatforms can be engineered to trigger ferroptosis via lysosomal membrane permeabilization and subsequent lipid peroxidation, or promote cuproptosis through mitochondrial copper overload and proteotoxic stress. These targeted approaches not only enhance local cytotoxicity but also transform the tumor into a source of DAMPs, thereby potentially promoting systemic immune activation. However, evidence supporting these strategies remains largely confined to preclinical studies.

Advanced technologies and emerging research tools

Integrative multi-omics (transcriptomic, proteomic, and spatial profiling) and organ-on-a-chip/3D organoid models are essential for deciphering complex systemic interactions[300-302]. These platforms bridge high-throughput screening with clinical observation, aiding in the mechanistic understanding of abscopal effects and long-term toxicities. Future progress relies on developing high-resolution, temporally resolved tools to capture real-time cross-organ crosstalk during and after radiotherapy.

Looking ahead, three research priorities are most likely to accelerate the clinical translation of radiation-induced multi-organ

Glossary

Radiation-induced bystander effect (RIBE)

A radiation-induced biological response in non-irradiated cells that arises through signals transmitted from irradiated cells, despite the absence of direct radiation exposure.

Radiation-induced abscopal effect (RIAE)

A systemic biological response in which distant, non-irradiated tumors exhibit regression or other treatment-related responses following localized radiotherapy, often associated with systemic antitumor immune activation.

Multi-organ systemic communication

A hierarchical communication network integrating intracellular signaling, molecular mediators, systemic transport pathways, physiological barriers, and organ-axis interactions following localized irradiation.

Immunogenic cell death (ICD)

A regulated form of cell death that can stimulate adaptive immune responses through the coordinated exposure or release of damage-associated molecular patterns and other immunostimulatory signals.

Damage-associated molecular patterns (DAMPs)

Endogenous molecules released, exposed, or secreted by stressed or dying cells that activate innate immune receptors and contribute to inflammation, immune activation, and tissue responses following cellular injury.

Ferroptosis

An iron-dependent form of regulated cell death characterized by the accumulation of lipid peroxides, resulting from disruption of cellular redox homeostasis and insufficient detoxification of oxidized phospholipids.

Cuproptosis

A copper-dependent form of regulated cell death associated with mitochondrial metabolism and the aggregation of lipoylated mitochondrial proteins, leading to proteotoxic stress and subsequent cellular dysfunction.

Pyroptosis

A highly inflammatory form of lytic programmed cell death mediated by inflammasomes and the caspase family, characterized by cellular swelling, rapid plasma membrane lysis, and the massive release of pro-inflammatory cytokines.

Tumor immune microenvironment (TIME)

The heterogeneous immune cell composition and signaling network within the tumor microenvironment dynamically shape tumor progression, immune evasion, and therapeutic response.

Physiological barriers

Specialized structural membranous boundaries (e.g., the blood-brain barrier or blood-testis barrier) that selectively filter circulating radiation-induced signals; exposure to high-dose radiotherapy can disrupt their structural integrity, subsequently inducing out-of-field normal tissue damage.

Extracellular vesicles (EVs)

Cell-secreted membrane-bound vesicles (including exosomes and microvesicles) that encapsulate diverse bioactive payloads such as miRNAs, DNA fragments, lipids, and proteins.

Cancer neuroscience

An emerging, interdisciplinary field focused on exploring how the central, peripheral, and enteric nervous systems reciprocally interact with cancer cells and the tumor microenvironment to regulate oncogenesis, progression, metastasis, and therapeutic resistance.

Neuroimmune interactions

The bidirectional, reciprocal communication between the nervous system and the immune system, wherein neural-derived factors modulate immune cell functions, and immune-derived factors retroactively shape neural activity and neuroinflammation.

Organ axis

A functional, long-distance communication network linking two or more anatomically separate organs through immune, neural, endocrine, or metabolic pathways to maintain systemic homeostasis or propagate pathological stress.

Gut-lung-brain axis

A proposed multi-organ communication network linking the gut, lung, and brain through interconnected immune, neural, endocrine, metabolic, and microbial pathways, although direct evidence specifically demonstrating coordinated radiation-induced signaling across all three organs remains limited.

systemic communication over the next 5-10 years. First, the development of robust biomarker-guided patient stratification strategies will be essential to identify individuals most likely to benefit from beneficial systemic communication while minimizing treatment-related toxicities. Second, further optimization of radioimmunotherapy aimed at strengthening systemic antitumor immunity represents the most promising therapeutic direction. Future efforts should focus on rational optimization of radiotherapy dose, fractionation, treatment sequencing, and combination with ICIs or other immune-modulating strategies to maximize beneficial systemic immune communication while limiting treatment-related toxicity. Third, increasing attention should be directed toward overcoming active negative regulatory barriers that constrain multi-organ systemic communication. In particular, emerging evidence indicates that immunosuppressive CAFs, together with other inhibitory components such as TGF-β signaling, extracellular matrix remodeling, and suppressive immune cell populations, actively restrict the propagation of beneficial systemic responses. Therapeutic strategies targeting these barriers may therefore represent a promising avenue for converting

ineffective systemic signaling into durable clinical benefit.

CONCLUSION AND PROSPECTS

In summary, radiation-induced biological responses stretch well beyond the targeted treatment volume, driven by coordinated signaling across individual cells, discrete organs and whole physiological systems. These sequential events form a multi-layered biological cascade, encompassing intracellular signaling initiation, secretion of heterogeneous molecular messengers, systemic distribution via interconnected circulatory, immune and neural transport routes, and ultimate integration at the organ-axis level. Framing radiotherapy not merely as a localized treatment but as a systemic biological modulator establishes a unified conceptual paradigm to boost anti-tumor therapeutic potency, alleviate off-target normal tissue toxicities, and rationally exploit multi-organ crosstalk in clinical workflows.

Notably, this inter-organ signaling network operates in a bidirectional fashion, concurrently orchestrating systemic anti-tumor immunity and propagating radiation-mediated normal tissue damage. Reinterpreting radiotherapy within a systemic biological framework may expand our comprehension of its full-spectrum biological outcomes and inform the design of combinatorial therapeutic regimens targeting cross-organ signaling axes. Future investigations are warranted to focus on disentangling these opposing effects and developing strategies that selectively amplify beneficial systemic antitumor responses while minimizing harmful side effects. Advancing from descriptive characterization to precise, tunable regulation of radiation-triggered multi-organ systemic communication will be critical to harnessing systemic radiation responses, including the rare but clinically meaningful abscopal effect.

DECLARATIONS

Acknowledgments

The authors would like to express their gratitude to all members of the Shao Laboratory, Institute of Radiation Medicine, Fudan University, for their invaluable support and critical comments. The Graphic Abstract was created in BioRender. Zheng, X. (2026) https://BioRender.com/8h930pr.

Authors' contributions

Drafted the manuscript and performed figure preparation: Zheng, X.
Participated in conceptualization and original draft writing: Wang, J.; Xue, H.; Zheng, Y.; Pan, Y.; Yuan, S.
Provided overall supervision and secured funding acquisition: Shao, C.
Critically revised the manuscript: Shao, C.; Zhang, J.
All the authors have read and approved the final manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version GPT-5.5, released 2026-06) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

This research was funded by the National Natural Science Foundation of China (Nos. 12235004, 12175044, and 12375338).

Conflicts of interest

Shao, C. is an Editorial Board Member of the journal *Element*. Shao, C. was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling, or decision-making. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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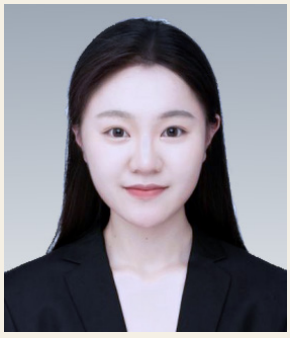
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