Unraveling the molecular landscape of chronic radiation injury: From oxidative stress signaling to translational modeling (Review)

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Abstract. The expanding footprint of human radiation exposure, driven by advances in interventional diagnostics, the resurgence of the nuclear industry and the deep-space exploration, has necessitated a paradigm shift from understanding acute syndromes to the biological effects of chronic, low-dose-rate irradiation. Unlike acute injury, chronic radiation injury (CRI) is a distinct biological entity characterized by the progressive accumulation of sublethal damage, niche remodeling and the propagation of the senescence-associated secretory phenotype, which collectively drive systemic inflammaging. Deciphering these non-linear dose-response dynamics requires high-fidelity animal models that deconstruct mechanisms often obscured by latency in human epidemiological studies. The present review critically synthesizes the methodological evolution of CRI modeling, contrasting continuous external beam paradigms with internal radionuclide contamination systems. The present study aimed to summarize the pathophysiology of multi-organ exhaustion, specifically detailing the mechanisms of hematopoietic niche senescence, pulmonary fibrosis and stochastic carcinogenesis, and propose a multidimensional validation framework integrating deep phenotyping, digital pathology and circulating biomarkers to establish rigorous construct validity. Finally, the present study aimed to bridge the translational gap by aligning preclinical screening with the Food and Drug Administration Animal Rule-a regulatory pathway permitting the approval of medical countermeasures based on animal efficacy data when human trials are unethical, advocating a future defined

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Key words: chronic radiation injury, low-dose-rate, genomic instability, inflammaging, senescence-associated secretory phenotype, medical countermeasure, Food and Drug Administration animal rule, precision radioprotection

by single-cell spatial omics and artificial intelligence-driven precision radioprotection.

Contents

1. Introduction

Human interaction with ionizing radiation has evolved from passive environmental exposure to a complex interface defined by advanced medical diagnostics, nuclear industry expansion and long-duration space exploration (1). While acute radiation syndrome (ARS) resulting from high-dose exposure is characterized, the biological consequences of chronic, low-dose-rate (LDR) exposure represent a knowledge gap (2). It is necessary to distinguish CRI from the delayed effects of acute radiation exposure (DEARE). While DEARE refers to late-onset pathology emerging months to years following an acute high-dose/high-dose-rate exposure, CRI results from protracted LDR irradiation over months to years, characterized by continuous sublethal damage accumulation, cell senescence and inflammaging (3).

Unlike the rapid cell ablation seen in acute scenarios, CRI is characterized by persistent, progressive pathological changes (4). LDR exposure triggers a unique interplay of mitochondrial dysfunction and cytosolic DNA sensing pathways (cyclic GMP-AMP-STING (cGAS/STING), leading to a Senescence-Associated Secretory Phenotype (SASP, a complex pro-inflammatory secretome produced by senescent cells) (5). This inflammaging microenvironment drives progressive fibrosis, immune dysregulation and genomic instability distinct from acute injury patterns (6). Consequently, the linear no-threshold model-which assumes that biological risk is directly proportional to radiation dose without any safe lower limit-often fails to predict the non-linear, stochastic risks of chronic exposure, necessitating re-evaluation through dedicated experimental systems (7).

Animal models of CRI are key tools for deconvoluting these complex biological responses (8). They provide the only rigorous means to isolate the effects of dose rate from total absorbed dose, enabling the study of temporal damage accumulation vs. repair kinetics (9). Moreover, these models serve as the platforms for the rigorous validation of next-generation medical countermeasures (MCMs) targeting late-onset effects of both CRI and acute high-dose irradiation (DEARE), such as radiation-induced lung fibrosis and secondary malignancy (10). However, the fidelity of current CRI models faces scrutiny (11). Many historical models using fractionated acute irradiation inadequately mimic the continuous, low-intensity stress of environmental LDR (12-14). Furthermore, translating findings from inbred rodent strains to genetically diverse human populations is challenging due to species-specific differences in telomere biology and immune surveillance (13). Future models must integrate humanized systems and reflect the heterogeneity of real-world exposure (14).

Complementing experimental data with epidemiological evidence from human cohorts provides a foundational understanding of the long-term risks associated with chronic radiation. Long-term follow-up studies of Chernobyl liquidators and Fukushima cleanup workers have revealed elevated risks of non-cancerous pathologies, such as cataracts and circulatory disease, alongside increased incidences of leukemia and thyroid cancer (15-17). Similarly, occupational cohorts of nuclear power plant workers and healthcare professionals, particularly interventional radiologists and cardiologists, demonstrate an association between cumulative low-dose exposure and hematopoietic dysregulation or genomic instability (16,17). However, human studies are typically confounded by lifestyle variables, inaccurate retrospective dosimetry and the substantial latency period between exposure and symptomatic manifestation. These limitations highlight the translational gap that necessitates the development of high-fidelity animal models (17). By accurately simulating human exposure paradigms under controlled conditions, these models enable the identification of insidious molecular mechanisms such as niche remodeling and SASP-driven inflammaging that remain elusive in retrospective human analyses. Thus, integrating human epidemiological findings with mechanistic animal studies is key for establishing evidence-based occupational safety thresholds and precision radioprotection strategies (18).

The present review provides a comprehensive critique of the methodological and conceptual evolution of CRI animal models. The present study collected literature across major databases, including PubMed (pubmed.ncbi.nlm.nih.gov/), Scopus (scopus.com/), and Web of Science (webofscience.com/) from inception up to December 2025, specifically focusing on LDR irradiation, mechanistic modeling (SASP, oxidative stress) and translational countermeasures. The present study aimed to summarize advances in continuous external exposure and internal radionuclide contamination models, highlighting their relevance to modern radiobiology. The present study aimed to address the identification of robust cross-species biomarkers, including circulating microRNAs (miRs) and inflammatory signatures, as well as the integration of single-cell multi-omics into model validation, proposing a forward-looking framework to enhance the translational power of chronic radiation research (Fig. 1).

2. Pathophysiological characteristics of CRI

Dosimetric profile: Protracted LDR exposure. The fundamental pathophysiology of CRI diverges from ARS (19). While ARS is driven by immediate, massive cellular ablation following high-dose-rate insult, CRI is the consequence of protracted exposure to LDR ionizing radiation (20). The biological outcome is governed not only by the total absorbed dose but also by DR (21). Under LDR conditions, the continuous induction of DNA damage engages adaptive

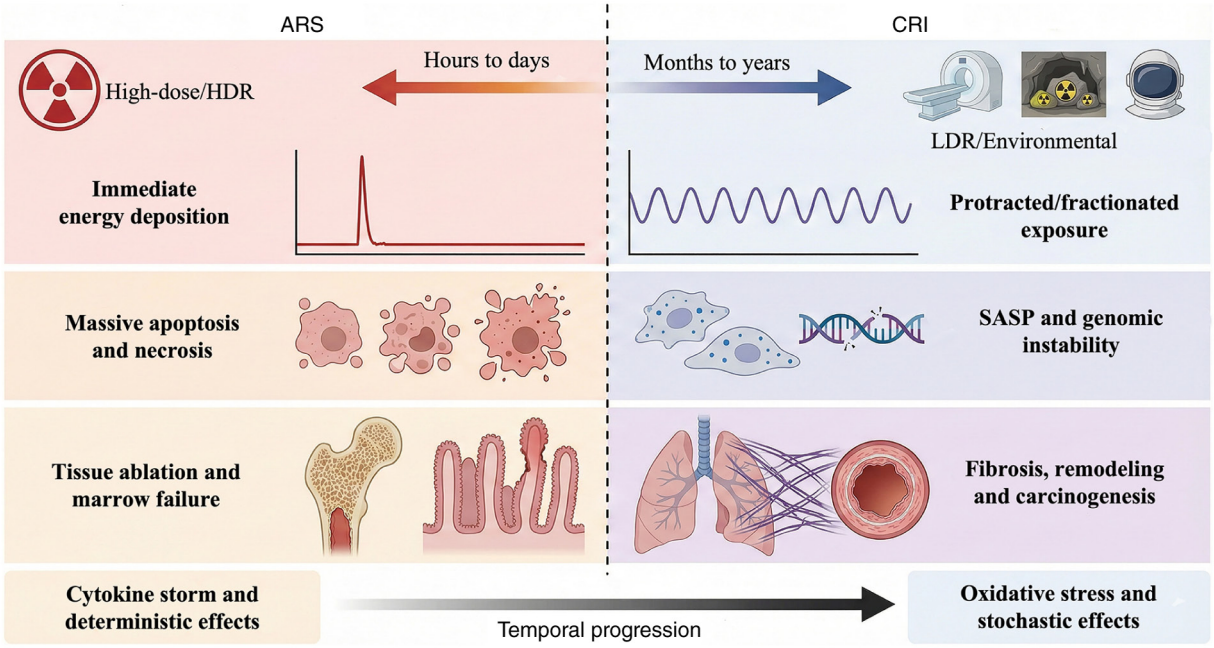

Figure 1. Distinction between ARS and CRI: Dose-rate-dependent temporal and pathobiological divergence. Schematic of the radiobiological trajectories underlying ARS and CRI as a function of dose rate, exposure pattern and temporal evolution. ARS results from HD or HDR irradiation, characterized by immediate energy deposition over hours to days, leading to apoptosis and necrosis, rapid tissue ablation, bone marrow failure and pronounced deterministic effects, such as gastrointestinal mucosal breakdown, cutaneous burns and neurovascular collapse-driven by acute cytokine release and systemic inflammatory responses. CRI arises from prolonged LDR or environmental exposure over months to years, typically delivered in a continuous or fractionated manner. This favors the accumulation of sublethal DNA damage, cellular senescence with activation of the SASP and persistent genomic instability. These processes promote chronic oxidative stress, tissue remodeling, progressive fibrosis, immune dysregulation and increased stochastic risks of carcinogenesis. ARS, acute radiation syndrome; CRI, chronic radiation injury; HDR, high-dose-rate; LDR, low-dose-rate; SASP, senescence-associated secretory phenotype.

response mechanisms, however, the persistent stress eventually overwhelms cellular fidelity, leading to the accumulation of sublethal damage rather than immediate cell death (22).

Populations at risk extend beyond traditional nuclear industry workers to include interventional radiologists, astronauts exposed to galactic cosmic rays and residents in high background radiation areas (23). Unlike the rapid onset of acute symptoms, CRI is characterized by a latent window, in which sub-clinical metabolic reprogramming and oxidative fluctuations occur prior to symptomatic manifestation (24). This progression complicates early risk stratification, rendering traditional biodosimetry markers ineffective and posing a challenge for precision radiation protection (Table I) (25).

Systemic cross-talk and multi-organ exhaustion. CRI is a systemic disease, propagated by complex inter-organ signaling rather than isolated tissue injury. The hematopoietic system serves as the most sensitive biological indicator and primary responsive target of LDR toxicity (26). Beyond direct DNA damage to hematopoietic stem cells (HSCs), chronic exposure remodels the bone marrow microenvironment (27). Radiation-induced stromal senescence and adipogenesis (fatty marrow) create a hostile niche that fails to support HSC self-renewal, leading to HSC exhaustion, persistent cytopenia and a pre-leukemic state of clonal instability (28). The immune system undergoes a paradoxical shift termed inflammaging. While radiation depletes naïve lymphocyte pools (immunosenescence), damage-associated molecular patterns released from stressed cells trigger the cGAS/STING pathway, driving a sustained release of pro-inflammatory cytokines (IL-6, TNF-α) (29). This chronic low-grade inflammation not only impairs pathogen clearance but also creates a tumor-permissive microenvironment (30). The central nervous system (CNS), previously considered radioresistant, exhibits vulnerability through neuroinflammation and the inhibition of hippocampal neurogenesis, manifesting as cognitive rigidity (diminished mental flexibility and impaired adaptation to changing environmental demands) and autonomic dysregulation (31). Furthermore, reproductive toxicity involves germline DNA fragmentation and endocrine axis disruption, creating a cycle of systemic physiological decline amplified by oxidative stress (32).

Genomic instability and epigenetic drift. The molecular hallmark of CRI is genomic instability, a state where the genome acquires an increased tendency to alteration. Unlike the transient reactive oxygen species (ROS) burst in acute exposure, CRI establishes a cycle of chronic oxidative stress driven by mitochondrial dysfunction (33). Leakage of electrons from damaged electron transport chains generates persistent ROS, causing continuous oxidative base damage-specifically the formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine (34). Damage is not confined to directly irradiated cells (35). Through the radiation-induced bystander effect, irradiated cells transmit distress signals (via exosomes and gap junctions) to non-irradiated neighbors, propagating genomic instability (36). Studies highlight the role of epigenetic drift (aberrant DNA methylation and histone modifications) in locking cells into a dysfunctional state (37,38). These heritable epigenetic marks explain why radiation effects persist after

Table I. Comparative pathophysiology: ARS vs. CRI.

Feature	ARS	CRI
Exposure pattern	High-dose, short duration (minutes to hours)	Low-dose-rate, protracted (months to years)
Primary cell fate	Apoptosis, necrosis (rapid cell loss)	Senescence, genomic instability, clonal expansion
Dominant mechanism	Direct DNA double-strand breaks, stem cell ablation	Oxidative stress cycles, inflammaging (SASP)
Latency period	Hours to weeks (immediate toxicity)	Months to decades
Hematopoietic response	Rapid pancytopenia (bone marrow failure)	Lineage skewing (myeloid bias), fatty marrow remodeling
Tissue remodeling	Acute inflammation, edema	Progressive fibrosis, extracellular matrix deposition
Carcinogenic risk	Deterministic (severity increases with dose)	Stochastic (probability increases with dose) accumulation

ARS, acute radiation syndrome; CRI, chronic radiation injury; SASP, senescence-associated secretory phenotype.

exposure ceases, potentially affecting unexposed offspring via transgenerational inheritance (Fig. 2) (38).

Stochastic carcinogenesis and clonal evolution. A key long-term consequence of CRI is the elevation of stochastic carcinogenic risk (39). According to the LNT model, chronic accumulation of DNA mis-repairs increases the probability of malignant transformation (40).

Under continuous immune pressure and oxidative stress, somatic cells with advantageous mutations (in TP53 or DNA methyltransferase 3A) may undergo clonal expansion, a phenomenon known as clonal hematopoiesis of indeterminate potential (41). This clonal evolution serves as a precursor to radiation-induced leukemias and solid tumors (42).

Compared with spontaneous cancer, radiation-associated malignancies exhibit distinct mutational signatures and extended latency periods (43). The spectrum includes leukemia, thyroid papillary carcinoma and lung fibrosis-associated cancers (44). These mechanistic insights underscore the need for refined radiobiological models that recapitulate these stochastic events to guide international occupational safety standards (Fig. 3; Table II).

3. Methodological paradigms for modeling CRI

The translational validity of animal models hinges on the fidelity with which they replicate the physics and dosimetry of human exposure (45). While acute high-dose models are well-established, simulating the protracted nature of CRI requires precise control over dose accumulation, temporal distribution and linear energy transfer (LET) (46-48). Existing methodological approaches use X-ray and γ-ray sources (^{60}Co, ^{137}Cs) due to their stable energy output and tissue penetration profiles (47,48). However, the field is evolving from static exposures to sophisticated dynamic systems that decouple DR from total absorbed dose, enabling the differentiation between repairable sublethal damage and cumulative irreversible injury (48).

External beam irradiation: From systemic to targeted precision. External beam irradiation is the cornerstone of radiobiological modeling, categorized by the extent of anatomical coverage. Whole-body irradiation (WBI) is the standard for simulating systemic catastrophe, such as large-scale nuclear accidents or prolonged occupational exposure in unshielded environments (49). By delivering a homogeneous dose across all physiological compartments, WBI effectively reproduces the syndromic nature of RI, capturing the interplay between bone marrow failure (hematopoietic syndrome) and systemic immune collapse (50). A challenge in WBI is achieving dosimetric homogeneity (51). Variations in animal geometry can lead to hot spots (overdose) or cold spots (underdose), potentially confounding survival data (52). Furthermore, WBI typically induces lethal acute GI toxicity before chronic fibrotic phenotypes manifest (53). To address this, fractionated low-dose regimens are employed to allow animals to survive the acute phase and develop late-onset pathology (54). To mimic scenarios such as localized radiotherapy toxicity or partial shielding, partial body irradiation selectively targets specific organs (thorax, brain) while sparing the bone marrow (55). Research has moved beyond lead shielding to use small animal radiation research platforms (56). These systems employ micro-CT guidance to deliver conformal radiation beams with sub-millimeter precision (57). This allows the study of organ-specific radiosensitivity (radiation-induced lung fibrosis) without the confounding variable of systemic hematopoietic collapse (Fig. 4) (58).

Non-targeted effects (NTEs) and bystander models. Emerging evidence suggests CRI is not solely the result of direct energy deposition but is also mediated by NTEs (59). Models of indirect irradiation focus on how radiation signals are propagated through the microenvironment (60-63). Bystander and abscopal models investigate how irradiated cells communicate with non-irradiated neighbors via gap junctions, exosomes and soluble factors (ROS, cytokines) (61). By irradiating a specific volume (such as the liver) and assessing damage in distant organs (such as the lung), researchers can elucidate the systemic propagation of inflammatory signals (62). In ecological toxicology contexts, indirect exposure also refers to the interaction with irradiated media (water or soil) (63). These models are essential for distinguishing between direct radiotoxicity and the

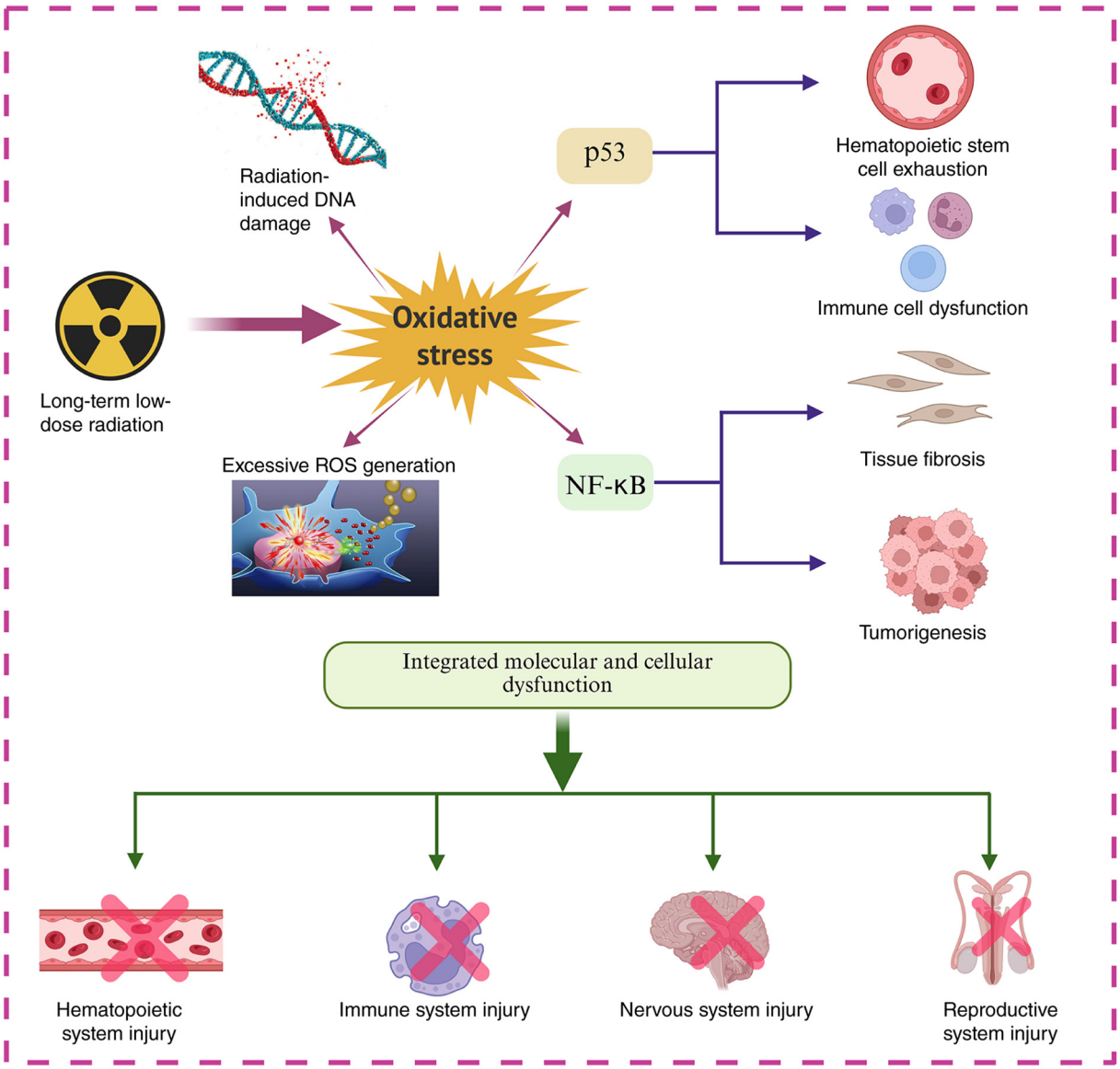

Figure 2. Role of oxidative stress signaling in mediating chronic radiation-induced systemic toxicity. Molecular cascades connecting chronic low-dose exposure to multi-organ pathology. Prolonged exposure to low-dose ionizing radiation drives the sustained accumulation of ROS, establishing a state of persistent oxidative stress and cumulative DNA damage. This oxidative burden serves as a master switch, concurrently activating distinct stress-response pathways: Upregulation of p53 signaling mediates cell cycle arrest and senescence, primarily contributing to hematopoietic stem cell exhaustion and immune dysfunction. Chronic activation of NF-κB propagates a pro-inflammatory microenvironment, driving tissue fibrosis and stochastic tumorigenesis. These molecular perturbations culminate in widespread cellular dysfunction, manifesting as clinical injury across the hematopoietic, immune, nervous and reproductive systems. ROS, reactive oxygen species.

secondary toxicity of radiation-induced chemical species (radiolysis products) (64).

Internal contamination: Challenge of internal emitters. While external beams simulate prompt exposure, internal contamination is the most biologically faithful model for occupational hazards (such as uranium mining) or post-accident fallout (65). The pathology is dictated by the chemical nature of the radionuclide (66). For example, osteotropic isotopes (^{90}Sr, ^{226}Ra) accumulate in the bone matrix, causing chronic marrow suppression and osteosarcoma, whereas radioiodine (^{131}I) targets the thyroid (67). These models require precise calculation of body burden (the total amount of a radionuclide present in the organism at a given time) and effective half-life (68). Internal models are key for studying high-LET radiation (α-particles from plutonium or radon) (69). Unlike low-LET γ-rays, α-particles cause dense ionization tracks and complex DNA double-strand breaks that are refractory to repair (70). This biological insult highlights the limitation of using external X-rays to mimic internal α-emitter contamination (71).

Complex exposure scenarios: Combined injury (CI) and LDR. To bridge the gap between laboratory conditions and real-world catastrophes, advanced models integrate multiple stressors (72,73). Real-world exposure typically co-occurs with trauma or burns (73-75). Specialized facilities-such as gamma gardens (open-field irradiation facilities equipped with a central radioactive source) or prolonged housing near radioactive sources (^{60}Co or ^{137}Cs)-allow continuous exposure over months (0.05-0.50 Gy/week) (75). These models are

Table II. Progression of chronic radiation injury.

Phase	Time post-exposure	Biological events	Clinical manifestations	Detectable biomarkers
Initial/latent	0-6 months	Mitochondrial dysfunction; ROS accumulation; DNA mis-repair; initiation of epigenetic drift	Largely asymptomatic; sub-clinical metabolic shifts; mild fatigue	γ-H2AX foci (lymphocytes); 8-oxo-dG (urine); transient lymphocyte dip
Inflammatory	6-12 months	Onset of senescence-associated secretory phenotype; macrophage activation (M1 polarization); endothelial activation	Decreased exercise tolerance; recurrent mild infections; gut dysbiosis	Plasma IL-6, TNF-α; elevated CRP; upregulation of ICAM-1/VCAM-1
Fibrotic	1-2 years	Myofibroblast differentiation; excessive ECM deposition; capillary rarefaction; tissue stiffening	Pulmonary fibrosis (dyspnea); nephropathy (hypertension); malabsorption	TGF-β1; pro-collagen peptides (PIIINP); micro-albuminuria; circulating miR (miR-21)
Degenerative	>2 years	Stem cell exhaustion (senescence); clonal hematopoiesis; genomic instability threshold breached	Bone marrow failure (refractory anemia); cognitive decline; secondary malignancies (leukemia/solid tumors)	Shortened telomeres; $p16^{INK4a}$ expression; clonal mutations (DNMT3A); high frailty index score

ROS, reactive oxygen species; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; ECM, extracellular matrix; PIIINP, procollagen III N-terminal peptide; miR, microRNA; Dnmt3a, DNA methyltransferase 3A.

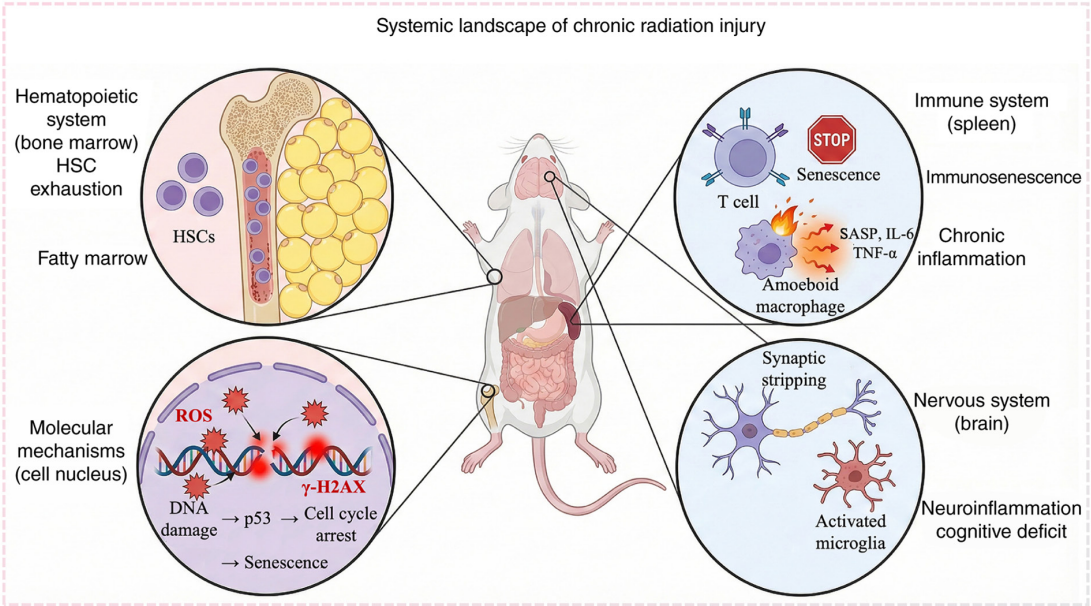

Figure 3. Chronic radiation injury: Organ-specific pathology and molecular drivers. Pathophysiological sequelae of protracted low-dose-rate exposure compared to acute injury. The hematopoietic compartment acts as the primary most sensitive biological indicator and early responder to radiation toxicity. Chronic stress drives HSC exhaustion and remodels the niche into an adipogenic (fatty marrow) state, leading to persistent cytopenia and regenerative failure. The immune microenvironment shifts toward a pro-inflammatory inflammaging state. Activated macrophages and senescent cells secrete SASP factors (IL-6, TNF-α) via the cGAS/STING pathway, creating a tumor-permissive environment. The unifying molecular mechanism involves a self-perpetuating cycle of mitochondrial dysfunction (ROS leakage) and genomic instability (γ-H2AX accumulation). This triggers p53-mediated cell cycle arrest, driving the cell senescence that underlies systemic tissue dysfunction. The central nervous system exhibits microglial-mediated neuroinflammation. This results in synaptic stripping (loss of dendritic spines) in the hippocampus, manifesting clinically as cognitive rigidity and behavioral deficit. HSC, hematopoietic stem cell; SASP, senescence-associated secretory phenotype; TNF, tumor necrosis factor; ROS, reactive oxygen species; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

suited to test the dose-rate effect (the phenomenon where the biological effectiveness of a radiation dose decreases as the rate of delivery is reduced, primarily due to ongoing cellular repair), providing key data for setting occupational

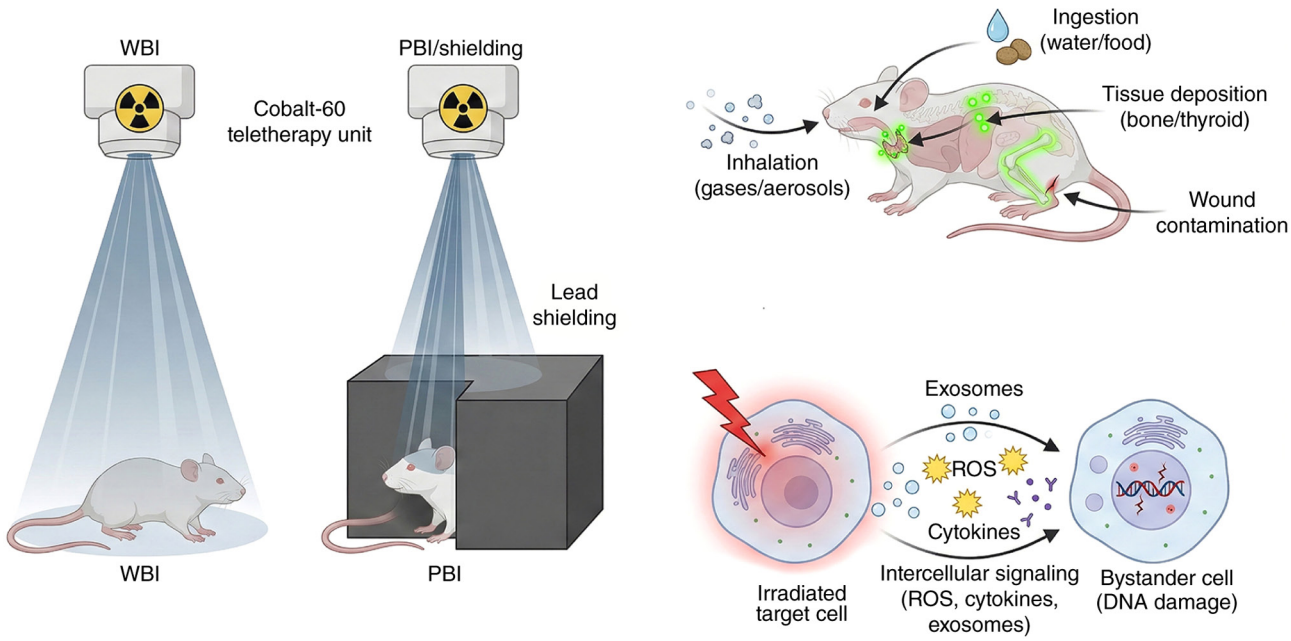

Figure 4. Methodological paradigms for modeling CRI: External beam irradiation, internal radionuclide exposure and non-targeted BE. Schematic of the principal experimental strategies used to model CRI *in vivo*, highlighting complementary approaches that capture distinct physical, dosimetric and biological dimensions of prolonged radiation exposure. (A) External beam irradiation models. WBI delivers a homogeneous dose to simulate systemic exposure scenarios such as nuclear accidents or unshielded occupational environments, enabling assessment of global hematopoietic and immune failure. PBI, achieved through physical shielding or image-guided precision platforms, restricts radiation to selected anatomical regions, allowing organ-specific injury (lung or brain) to be studied while sparing critical bone marrow compartments. (B) Internal exposure and radionuclide deposition. Internal contamination models reproduce biologically realistic exposure via inhalation, ingestion or wound entry of radionuclides, followed by tissue-specific deposition (bone, thyroid). These systems integrate radionuclide biokinetics, effective half-life, and LET and are indispensable for studying chronic low-dose-rate exposure and high-LET particle effects that cannot be mimicked by external beams. (C) RIBE. Non-targeted effects are demonstrated by intercellular signaling from irradiated target cells to non-irradiated bystander cells through ROS, cytokines and exosome-mediated communication, resulting in DNA damage and persistent stress responses in distal tissue. Collectively, these paradigms underscore the need for integrated modeling frameworks to capture the complexity of CRI, encompassing direct energy deposition, indirect microenvironmental signaling and long-term systemic consequences. CRI, chronic radiation injury; WBI, whole-body irradiation; PBI, partial-body irradiation; LET, linear energy transfer; RIBE, radiation-induced bystander effect; ROS, reactive oxygen species.

safety thresholds and validating environmental risk models (Table III) (76).

4. Biological characteristics and strategic model selection

Phenotypic landscape of CRI. Animal models of CRI are defined by a distinct phenotypic landscape that diverges from acute syndromes (77). These models capture the progressive, multidimensional failure of organ systems driven by the continuous accumulation of sublethal damage and the propagation of SASP (77,78).

Hematopoietic exhaustion and niche remodeling. The hematopoietic system serves as the primary detector of radiation toxicity (79). Under LDR exposure, the pathology shifts from acute ablation to hematopoietic exhaustion (80). Continuous irradiation imposes replicative stress on HSCs, forcing quiescent cells into the cell cycle to maintain homeostasis (81). This chronic cycling leads to telomere erosion and premature senescence, evidenced by the downregulation of stemness markers (c-Kit, CD34) and lineage skewing toward myelopoiesis (82).

Damage extends to the bone marrow microenvironment (83). Radiation damages mesenchymal stromal cells and sinusoidal endothelium, altering the cytokine milieu (decreased CXCL12, increased TGF-β) (84). This hostile niche fails to support HSC retention and promotes adipogenic differentiation, perpetuating a cycle of pancytopenia and immune incompetence akin to human myelodysplastic syndrome (85).

Immunosenescence and the inflammaging loop. Chronic radiation accelerates immunosenescence, characterized by thymic involution and a functional paralysis of the adaptive immune repertoire (86). Peripheral T cell pools become oligoclonal, dominated by exhausted memory phenotypes (PD-1^{+}) with decreased proliferative capacity (87). Simultaneously, the innate immune system enters a state of hyper-activation known as inflammaging (88). Irradiated macrophages activate the NLRP3 inflammasome and the cGAS/STING pathway, secreting a constant stream of pro-inflammatory cytokines (IL-1β, IL-6) (89). This immune dysregulation creates a permissive microenvironment that impairs pathogen clearance and reduces immunosurveillance against neoplastic transformation (90).

Neuroinflammation and synaptic stripping. The CNS exhibits a delayed response to chronic radiation (91). The primary mechanism is neuroinflammation mediated by activated microglia (92). Chronic exposure prevents the turnover of hippocampal neural progenitor cells, leading to deficits in neurogenesis essential for memory consolidation (93). Structurally, this manifests as synaptic stripping, the loss of dendritic spines in the prefrontal cortex (94).

Table III. Methodological paradigms for modeling chronic radiation exposure.

Modeling paradigm	Methodology description	Strengths (construct validity)	Weaknesses/confounders
Whole-body irradiation	Homogeneous exposure of the entire organism	Simulates systemic fallout/ accidents; captures multi-organ failure	GI toxicity typically precedes chronic fibrosis; uneven dosimetry
Partial-body irradiation	Targeted exposure (such as the thorax) with shielding	Spares bone marrow; allows study of specific organ failure (such as the lung)	Lacks systemic immune-endocrine interaction (abscopal effects)
Internal contamination	Injection/ingestion of radionuclides (^{90}Sr, ^{137}Cs)	Biologically faithful to nuclear inhalation/ingestion scenarios	Complex dosimetry; disposal of radioactive biological waste
Continuous LDR facility	Isodose cages within a γ-source field	Decouples dose-rate from total dose; mimics occupational exposure	Resource-intensive; requires dedicated long-term facilities
Combined injury	Radiation + burn/wound/ sepsis	Replicates real-world catastrophe scenarios (synergistic lethality)	High mortality rate complicates study of late-term chronic effects

GI, gastrointestinal; LDR, low-dose-rate.

Physiologically, these changes translate into sickness behaviors, such as lethargy, anxiety-like thigmotaxis and cognitive rigidity (95). Furthermore, radiation disrupts the hypothalamic-pituitary-adrenal axis, leading to circadian dysregulation (96). This neuro-immune-endocrine crosstalk highlights the systemic nature of CRI, where CNS injury exacerbates peripheral immune suppression (Fig. 5) (97).

Critical appraisal: Face vs. construct validity. The utility of any animal model is determined by the balance between its face (phenotypic similarity to humans) and construct validity (mechanistic similarity). Compared with fractionated acute doses, LDR sources more accurately replicate the continuous radiation exposure patterns associated with occupational hazards and environmental contamination (98). LDR models capture the abscopal interactions between organs (such as the kidney-heart axis), allowing for the evaluation of holistic therapeutics rather than single-organ protectants (99). The latency of CRI requires extended housing (6-24 months), increasing costs (100). The confounding factor of aging becomes critical; distinguishing radiation effects from natural geriatric decline requires robust age-matched controls (101). Rodents possess different metabolic rates and DNA repair kinetics than humans (102). For example, the lethal dose required to kill 50% of the population within 30 days) varies, complicating the direct extrapolation of dose-response associations (103).

Strategic model selection for translational relevance. Selecting the appropriate model involves ensuring a match between the specific biological mechanisms under investigation and the inherent physiological attributes of the chosen animal (104).

Interspecies radiosensitivity and physiological homology. Murine models are the workhorse of mechanistic radiobiology (105). C57BL/6 mice are preferred for fibrosis and inflammation studies (Th1-dominant), while BALB/c mice are used for solid tumor induction (Th2-dominant) (106). While useful for molecular genetics, their small size makes localized organ dosimetry challenging (107). Rats offer a larger physiological volume, facilitating surgical interventions and serial blood sampling without inducing hypovolemic stress (108). They are superior for cardiovascular and renal radiation toxicity models due to hemodynamics closer to those of humans (109). Large animal models (canine/porcine/non-human primates) are the gold standard for preclinical validation. Porcine skin and gastrointestinal tracts are anatomically nearly identical to humans, making them ideal for cutaneous and visceral RI models (110). Non-human primates are essential for pivotal studies assessing complex neurobehavioral outcomes and sophisticated immune responses due to high genetic homology (Fig. 6; Table IV) (111).

Genetic diversity: Humanized and outbred models. Genetic background dictates the trajectory of chronic injury (112). While inbred strains (C57BL/6) offer reproducibility, they fail to capture human heterogeneity. Strains such as ataxia telangiectasia mutated-deficient or p53-heterozygous mice accelerate the onset of stochastic effects such as carcinogenesis, compressing decades of human latency into months (113). One approach involves using diversity outbred populations to map the genetic architecture of individual radiosensitivity, mimicking the diverse human response more effectively than traditional, genetically homogeneous inbred strains (114). Humanized mouse models, such as the NSG-SGM3 strain [NOD.Cg-Prkdc^{scid} Il2^{rgtm1Wjl} Tg(Prfg-IL3,CSF2,KITLG)1Eav/MloySzJ, which expresses human cytokines to support myeloid engraftment], reconstituted with human HSCs allow the study of human immune responses to chronic radiation *in vivo*, bridging the translational gap (61,89,115).

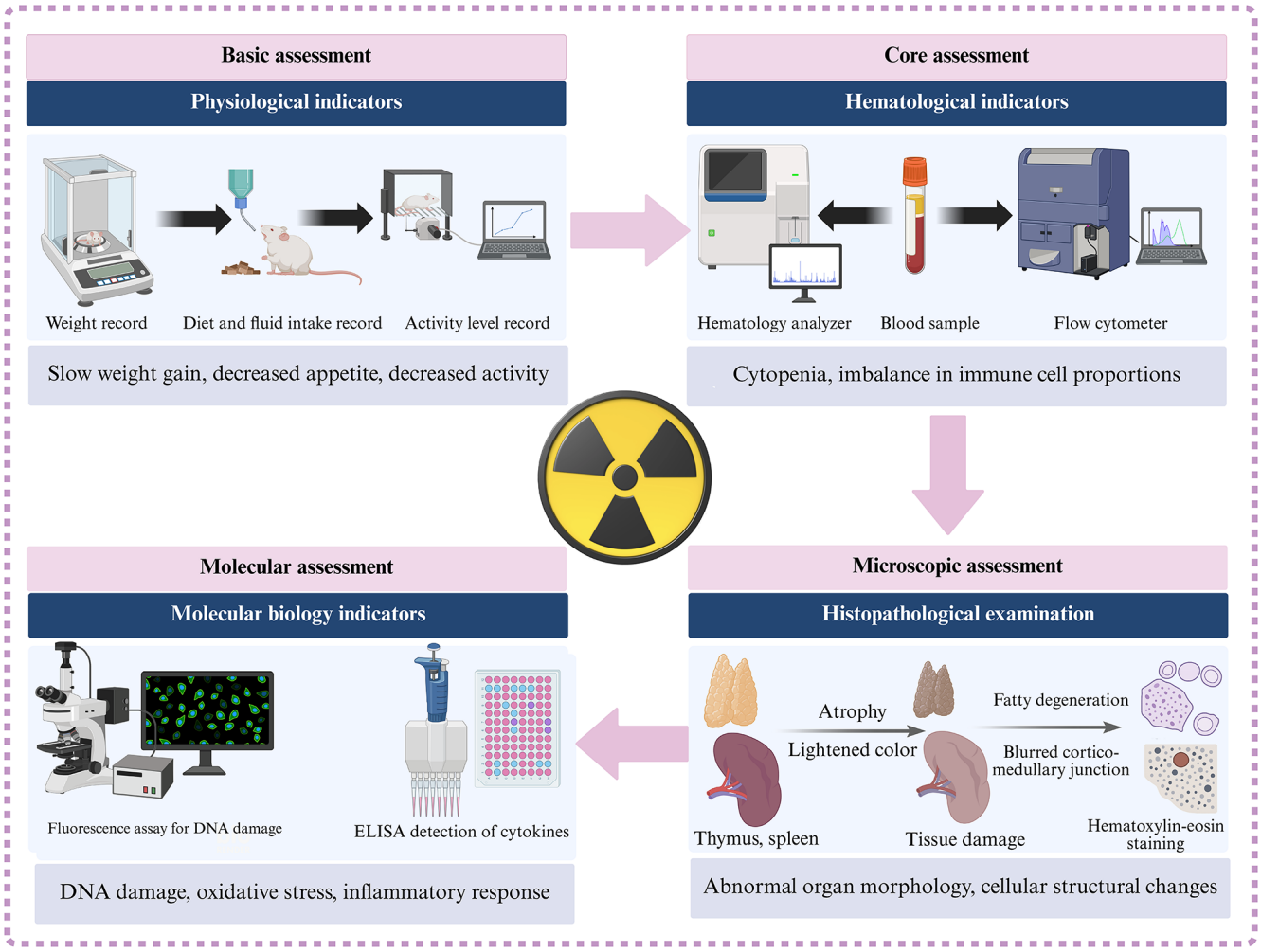

Figure 5. Multilevel assessment hierarchy for characterizing systemic toxicity and hematopoietic dysfunction in chronic radiation injury models. Hierarchical strategy for evaluating the spectrum of radiation-induced injury across biological dimensions. Basic assessment (systemic health) monitors macroscopic physiological indicators including body weight trajectory, nutritional intake and locomotor activity, serving as early warning signs of functional decline and sickness behavior. Core assessment (hematological status) surveils the circulating compartment. Complete blood counts and flow cytometric profiling are used to identify specific cytopenias and lineage skewing within immune cell subsets, reflecting bone marrow integrity. Microscopic assessment (organ architecture) visualizes structural abnormalities in radiosensitive parenchymal organs (thymus, spleen, kidney). Histopathological analysis identifies defining morphological hallmarks, such as organ atrophy, fatty degeneration and the disruption of cortico-medullary boundaries. Molecular assessment (mechanistic drivers) assesses underlying biological initiators of toxicity. Assays for DNA damage (phosphorylated histone H2AX), oxidative stress and inflammatory cytokine profiles (ELISA) link observed phenotypic changes to molecular pathology. Collectively, these integrated assessments provide a high-resolution profile of exposure-induced dysfunction, bridging molecular mechanisms with organ-level pathology.

Dosimetric and environmental standardization. Precision in CRI modeling requires rigorous dosimetry (116). The definition of chronic varies; thus, reporting the precise dose rate (Gy/h) is as critical as the total accumulated dose (117). Isodose cages ensure that animals receive uniform exposure regardless of movement (118). Furthermore, adherence to ARRIVE guidelines ensures husbandry factors (microbiome, circadian light cycles) are controlled to isolate the radiation variable (119).

5. Multidimensional validation and construct validity of animal models

The utility of a preclinical model relies on its construct validity, the fidelity with which it recapitulates the human pathological landscape (120). Establishing a standardized validation framework is key, as CRI presents a subtle, non-linear progression distinct from the clear endpoints of acute syndrome (121). A robust validation strategy must triangulate data across physiological performance, hematological integrity, histopathological architecture and molecular signatures, providing systems-level corroboration of radiation toxicity (122).

Physiological and behavioral deep phenotyping. Physiological metrics serve as the frontline indicators of systemic stress and sickness behavior, typically preceding clinically detectable organ failure (123). Unlike the rapid weight loss seen in acute syndrome, chronic radiation induces a wasting phenotype akin to cancer cachexia (124). Longitudinal monitoring typically reveals a blunted growth trajectory or gradual BMI decline, driven by hypothalamic inflammation and sustained catabolic signaling (125). Clinical frailty index, an aggregate score of deficits (alopecia, gait anomalies, grip strength), is a superior metric for quantifying radiation-induced accelerated aging compared with body weight alone (126). Changes in feeding behavior reflect the disruption of the gut-brain axis (127).

Table IV. Strategic selection of animal models based on physiological homology and research goal.

Model	Advantages	Limitations	Recommended application
Mouse (C57BL/6)	High availability of transgenic and knockout strains; Th1-dominant immune response	Small size limits localized dosimetry; high metabolic rate	Mechanistic studies (fibrosis), genetic knockout
Mouse (BALB/c)	Th2-dominant; high radiosensitivity to solid tumors	Prone to radiation-induced pleural effusion	Carcinogenesis, solid tumor induction
Rat	Larger blood volume; hemodynamics similar to humans	Fewer transgenic strains compared with mice	Cardiovascular toxicity, renal injury, serial sampling
Minipig	Anatomical/physiological homology (skin, GI tract)	High cost; specialized housing required	Cutaneous radiation injury, translational GI toxicity
Non-human primate	High genetic homology (>98%); complex cognition	Ethical constraints; prohibitive cost; low throughput	Neurobehavioral deficit, FDA animal rule validation

GI, gastrointestinal; NHP, non-human primate; FDA, Food and Drug Administration.

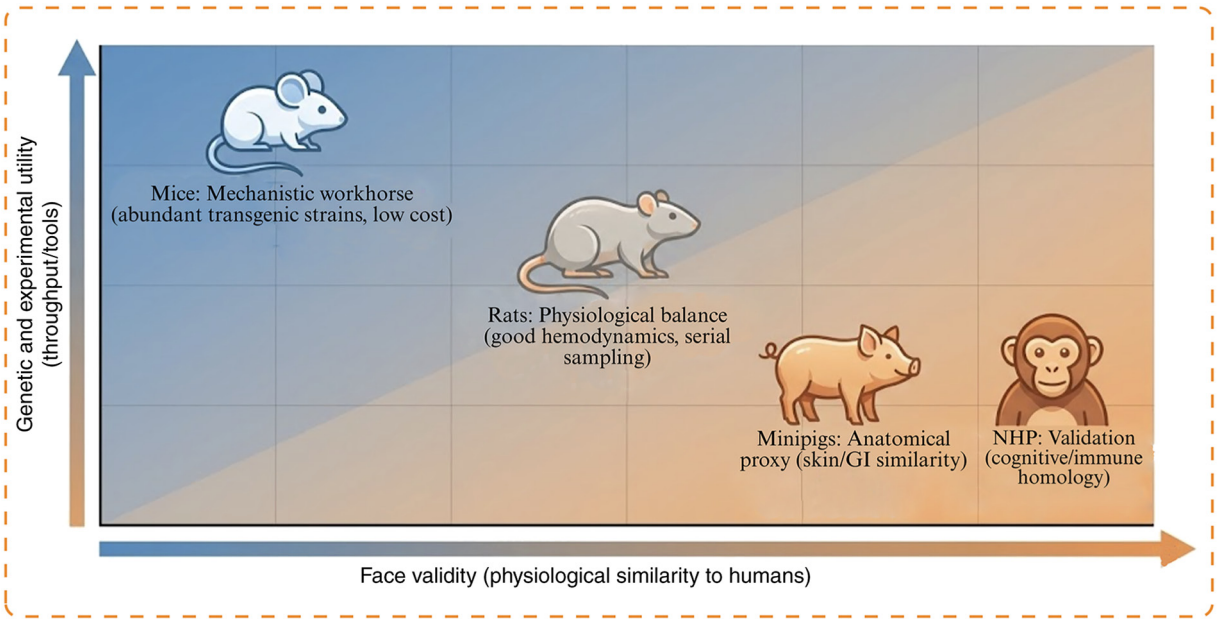

Figure 6. Strategic alignment map for CRI animal model selection: Balancing mechanistic utility with translational relevance. Trade-off between experimental throughput (genetic utility) and physiological similarity to humans (face validity) when selecting animal models for CRI research. Mice offer unparalleled genetic manipulability (transgenic strains) and high-throughput screening capabilities, serving as the primary mechanistic workhorse despite lower physiological homology. Rats provide a balanced platform with larger physiological volumes suitable for surgical interventions and serial sampling, bridging the gap between molecular discovery and clinical relevance. Large animal models (minipigs and NHPs) exhibit high anatomical and immunological similarities that are key for pivotal preclinical validation. Minipigs serve as anatomical proxies for cutaneous and GI injury, while NHPs are the gold standard for assessing complex neuro-cognitive and immune outcomes. CRI, chronic radiation injury; GI, gastrointestinal; NHP, non-human primate.

Radiation-induced mucositis and hypothalamic dysregulation manifest as anorexia and polydipsia (128). A sustained 20-30% decline in caloric intake suggests a transition from transient stress to chronic metabolic dysregulation (129). Quantitative behavioral assays are key for validating CNS injury (130). Automated tracking using open field test and Morris water maze detects decreased locomotor velocity (lethargy), anxiety-like thigmotaxis and cognitive deficits in spatial memory (131). These behavioral phenotypes are associated with hippocampal neuroinflammation and serve as non-invasive biomarkers for successful model induction (132).

Hematological surveillance: Lineage skewing and exhaustion. Peripheral blood analysis provides a dynamic liquid biopsy of the bone marrow microenvironment (133). In CRI models, the validation endpoint is lineage skewing (a persistent imbalance in the production of different hematopoietic cell types that reflects underlying marrow dysfunction and stem cell injury. While acute exposure causes rapid pancytopenia, chronic exposure typically leads to a myeloid-biased output (increased granulocyte/lymphocyte ratio) at the expense of lymphopoiesis, a hallmark of hematopoietic aging (134). Progressive, refractory normocytic anemia (hemoglobin

<100 g/l) and elevated red cell distribution width serve as diagnostic criteria for cumulative marrow failure (135). Flow cytometric profiling must assess functional status (136). Validated models demonstrate an inverted CD4/CD8 ratio and the expansion of regulatory T cells (137,138). Upregulation of exhaustion markers on T cells-specifically programmed cell death protein 1 (PD-1) and T-cell immunoglobulin and mucin domain-containing protein 3, along with decreased natural killer cell cytotoxicity, provide definitive immunophenotypic evidence of chronic radiation stress (138).

Histopathological architecture and artificial intelligence (AI)-assisted quantification. Histopathology remains the gold standard for defining irreversible tissue remodeling (139). However, modern validation requires specific staining and digital quantification beyond standard hematoxylin and eosin staining (140). A pathognomonic feature of CRI is the replacement of hematopoietic cellularity with adipose tissue (141). Validated models demonstrate a quantifiable shift in the marrow adipocyte-to-hematopoietic cell ratio (142-144). A hallmark of late-stage CRI is the excessive deposition of extracellular matrix (143). Validation should utilize Masson's trichrome or Sirius Red staining to visualize collagen (144). Immunohistochemistry for α-smooth muscle actin (identifying myofibroblasts) is key for distinguishing active fibrogenesis from static scarring (145). To enhance reproducibility, studies employ AI-driven image analysis algorithms to score fibrosis area fraction and cellularity, eliminating inter-observer variability inherent in manual scoring (145,146).

Molecular signatures: Omics of injury. Phenotypic observation must be corroborated by molecular mechanisms (147). The persistence of DNA double-strand breaks is the molecular footprint of radiation (148). Immunofluorescence quantification of phosphorylated histone H2AX and p53-binding protein 1 (53BP1) foci-two established biomarkers of DNA double-strand breaks-in circulating lymphocytes serves as a biodosimeter (149). Persistent upregulation of repair genes, such as ATM and X-ray repair cross-complementing protein 1, indicates sustained genomic stress and failed repair kinetics (150). Chronic injury is maintained by the SASP (151). Validated models must demonstrate a specific cytokine signature in plasma: Elevated IL-6, IL-1β and MMPs, coupled with reduced IGF-1 (152). This biochemical profile links molecular senescence to macroscopic fibrosis (153). Emerging validation strategies use cell-free DNA and radiation-responsive miRs (miR-150, miR-34a) as minimally invasive markers of tissue damage, offering a translational bridge to human clinical diagnostics (153,154).

A model is considered validated only when it satisfies this multidimensional matrix: Exhibiting the phenotypic frailty, hematological skewing, histological fibrosis and the molecular SASP signature characteristic of human CRI pathology (Fig. 7; Table V) (155).

6. Translational paradigms: From mechanistic discovery to clinical countermeasure

Animal models of CRI serve as the operational bridge between *in vitro* mechanistic data and human clinical application (156,157). Because efficacy testing of radioprotective agents in humans is ethically precluded, these models are typically the primary source of evidence for regulatory approval under US. Food and Drug Administration (FDA) 'Animal Rule, which allows for the approval of new drugs based on animal efficacy data when human clinical trials are ethically or logistically unfeasible (Table VI) (157).

Unraveling molecular networks and epigenetic landscapes. Animal models of chronic radiation injury allow the mapping of complex signal transduction networks that drive chronic pathology (158,159). Chronic LDR exposure triggers a senescence-like arrest distinct from acute apoptosis (159). Models have been pivotal in identifying the p53-p21 axis as the gatekeeper of this arrest and the subsequent activation of NF-κB, which drives the SASP (160,161). This demonstrates how irradiated cells survive but remain metabolically active, propagating inflammation to bystander tissue (161). epigenetic scars (persistent, long-term alterations in the epigenome (such as stable changes in DNA methylation patterns) that continue to drive abnormal gene expression long after the initial radiation exposure has ceased (162,163). High-throughput bisulfite sequencing in chronically exposed rodents has identified persistent hypermethylation of tumor suppressor promoters ($p16^{INK4a}$) and global hypomethylation of retrotransposons (163). Integrative multi-omics (transcriptomics + metabolomics) has mapped the dysregulation of the tricarboxylic acid cycle and fatty acid oxidation, providing a systems-level view of radiation-induced metabolic rewiring (164).

Preclinical development of MCMs. The primary industrial application of animal models of chronic radiation injury is the rigorous screening of MCMs, distinguishing between prophylactic agents (pre-exposure) and mitigators (post-exposure) (165). In the screening phase, models quantify the dose reduction factor of candidate agents (166). Effective agents must demonstrate significant preservation of the HSC pool and a reduction in marrow adiposity (167). Research has moved beyond free radical scavengers to targeted therapy (168). Models are validating senolytics (navitoclax, quercetin) that selectively eliminate senescent cells to rejuvenate tissue (168,169). Furthermore, pharmacodynamic studies optimize dosing to mitigate DEARE, ensuring that agents do not interfere with DNA repair in a manner that promotes secondary carcinogenesis (Table VII) (57,170).

Integrated protection: Lifestyle and metabolic interventions. Beyond pharmaceuticals, models are key for testing holistic strategies suitable for long-term occupational exposure (171). Comparative studies demonstrate that dietary polyphenols and probiotics remodel the gut microbiome, which is often dysbiotic after radiation (171,172). This gut-bone marrow axis modulation enhances Nrf2-ARE signaling, the master regulator of antioxidant defense, thereby decreasing systemic oxidative stress (malondialdehyde levels) (173). Controlled exercise studies reveal that mechanical loading upregulates AMPK signaling, promoting mitochondrial biogenesis (174,175). This counteracts radiation-induced sarcopenia and fatigue, offering a non-pharmacological strategy for astronauts or nuclear workers (175).

Risk assessment: Adverse outcome pathways (AOPs) and the exposome. Animal models provide the empirical data

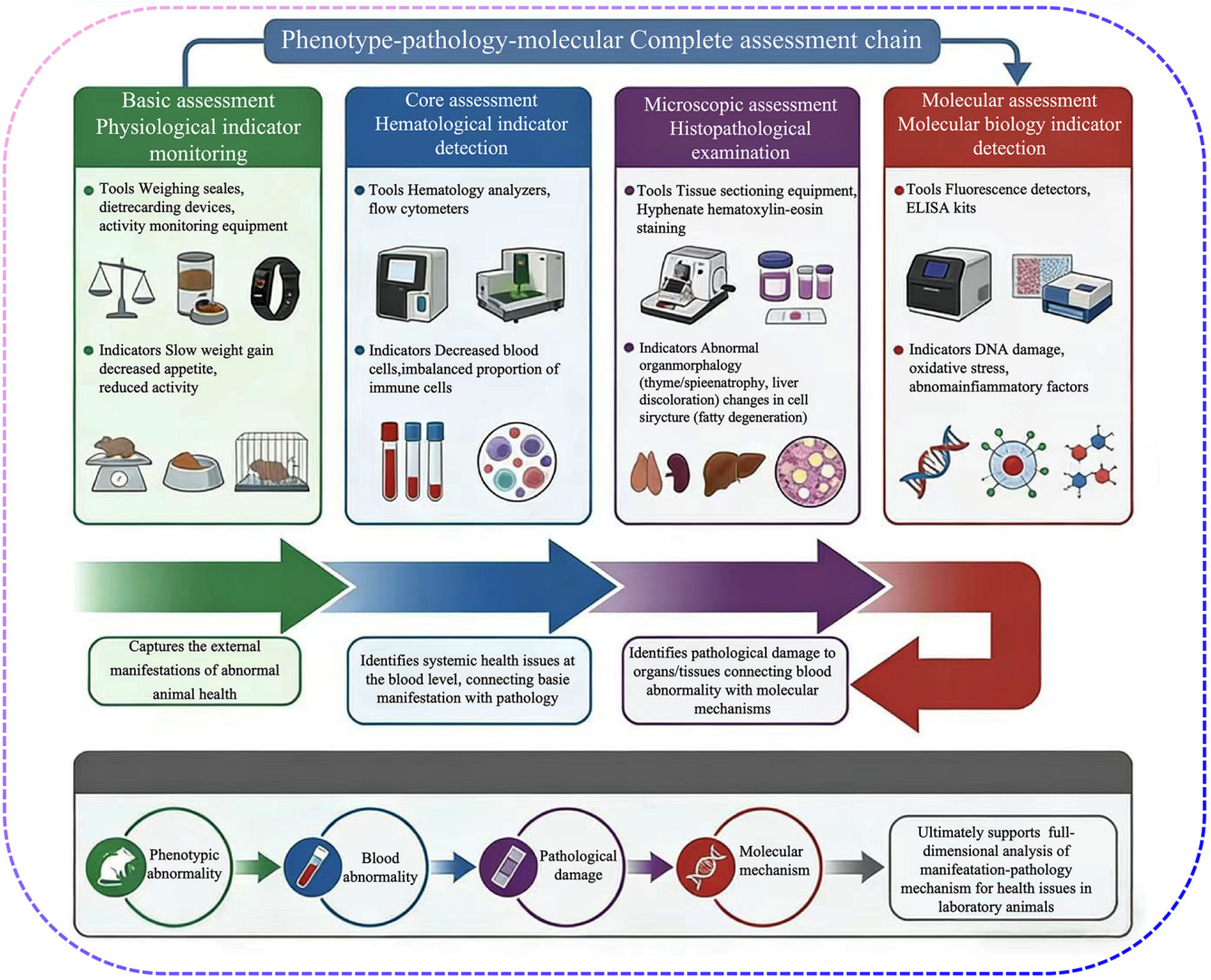

Figure 7. Multidimensional, closed-loop framework for establishing construct validity in chronic radiation injury models. Physiological assessment captures early systemic manifestations of radiation stress through longitudinal monitoring of the frailty index (body weight, activity levels, feeding behavior), distinguishing chronic wasting from acute transient toxicity. Hematological surveillance provides a dynamic readout of bone marrow integrity. Analysis focuses on lineage skewing (myeloid bias) and immunosenescence (T cell exhaustion) via flow cytometry, rather than simple pancytopenia. Histopathological architecture defines irreversible tissue remodeling at the microscopic level, characterized by organ atrophy, marrow adipogenesis and fibrotic degeneration quantified by digital pathology. Molecular interrogation establishes the mechanistic root of injury. This includes the detection of genomic instability (phosphorylated histone H2AX), oxidative stress and the systemic senescence-associated secretory phenotype signature (elevated IL-6, TGF-β) that drives the pathology. Macroscopic phenotypic abnormalities can be traced back to underlying molecular dysfunction. This closed-loop assessment confirms that the model recapitulates the progressive, non-linear pathology of human chronic radiation exposure.

necessary to construct AOPs, which link a molecular initiating event (such as DNA oxidation) to an adverse outcome (such as fibrosis). By exposing large cohorts to low-dose rates, researchers test the validity of the LNT model vs. hormesis (adaptive response) (176,177). This data is critical for setting occupational limits (such as for interventional cardiologists) (178). Real-world risk involves combined stressors (179). Advanced models simulate the exposome by co-exposing animals to radiation in the presence of heavy metals (such as uranium mining) or microgravity (spaceflight) (178,179). These studies reveal synergistic toxicities that single-stressor models miss, refining ecological risk assessments (179,180).

Translational perspective: Toward precision radioprotection. The future of CRI animal models lies in precision radioprotection (181). By using diversity outbred mice that reflect human genetic heterogeneity, researchers can identify genetic polymorphisms (in ATM or TGF-β) that confer individual radiosensitivity (182). Furthermore, the integration of spatial transcriptomics allows the mapping of radiation injury at single-cell resolution *in situ*, identifying rare, radio-resistant SC subpopulations that drive tissue regeneration or fibrosis (183,184). These refined models may facilitate the development of personalized radiation health passports, guiding individual risk management based on genetic and metabolic profiles (183-185).

7. Future outlook: Precision radiobiology

CR modeling is on the precipice of a technological revolution (186). Animal models are key for bridging the translational gap between laboratory-based basic research and clinical

Table V. Multidimensional validation matrix for establishing CRI models.

A, Physiological		
Validation parameter	Assessment method/metric	Expected pathological shift (CRI phenotype)
Frailty and metabolism	FI score	Increased FI score; wasting phenotype (cachexia)
Neurobehavioral	Open-field/water maze	Decreased locomotor velocity; spatial memory deficit
B, Hematological		
Validation parameter	Assessment method/metric	Expected pathological shift (CRI phenotype)
Lineage integrity	CBC and flow cytometry	Myeloid skewing (increased granulocytes, decreased lymphocytes); anemia
Immunosenescence	T cell exhaustion markers (PD-1 and Tim-3)	CD4/CD8 inversion; PD-1^{+} and Tim-3^{+} upregulation
C, Histological		
Validation parameter	Assessment method/metric	Expected pathological shift (CRI phenotype)
Tissue architecture	Masson's trichrome/Sirius Red	Increased collagen volume fraction (fibrosis)
Marrow niche	Adipocyte count (H&E)	Fatty marrow replacement of cellularity
D, Molecular		
Validation parameter	Assessment method/metric	Expected pathological shift (CRI phenotype)
Genomic instability	γ-H2AX/53BP1 foci	Persistent foci in circulating lymphocytes (repair failure)
SASP signature	ELISA/multiplex immunoassay	Elevated IL-6, IL-1β, MMPs; decreased IGF-1

FI, frailty index; CBC, complete blood count; H&E, hematoxylin and eosin; SASP, senescence-associated secretory phenotype; IGF-1, insulin-like growth factor 1; 53BP1, p53-binding protein 1; CRI, chronic radiation injury; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3.

Table VI. Alignment of CRI animal models with FDA animal rule criteria.

FDA criterion	Requirement for CRI models	Challenges in modeling
Mechanism of toxicity	Pathophysiology of the radiation injury in the animal model must be well-understood and sufficiently overlap with the human disease mechanism.	Differentiating between specific direct radiation toxicity and natural aging-associated decline in long-duration studies requires robust age-matched controls
Effect prediction	Effect of the countermeasure in the animal species must be demonstrated to predict the response in humans	Species-specific differences in immune surveillance and DNA repair kinetics (mice repair DNA faster than humans) complicate direct translation of efficacy
Dose selection	Study must provide sufficient pharmacokinetic and pharmacodynamic data to select an effective dose for humans	Establishing a human equivalent dose for chronic LDR exposure is difficult due to the variability of human exposure scenarios (spaceflight vs. occupational).
GLP	Studies must be conducted under rigorous GLP conditions to ensure data integrity and quality assurance	Long-duration studies (1-2 years) face high risk of attrition (animal death from non-radiation causes), which can compromise statistical power and GLP compliance

CRI, chronic radiation injury; FDA, Food and Drug Administration; LDR, low-dose-rate; GLP, good laboratory practice.

Table VII. Translational frontiers: Therapeutic targets and biomarkers for precision radioprotection.

Pathological driver	Molecular target	Candidate diagnostic biomarker	Intervention
Senescence (SASP)	$p16^{INK4a}$, $p21^{Cip1}$, NF-κB	Plasma IL-6, TNF-α, GDF-15	Senolytics (navitoclax, quercetin) to clear senescent cells
Oxidative stress	Nrf2/ARE pathway, mitochondria	Urinary 8-oxo-dG, lipid peroxides (MDA)	Mito-protectants; microbiome modulation (probiotics)
Fibrotic remodeling	TGF-β1/Smad signaling	Circulating pro-collagen peptides, miR-21	Anti-fibrotics; epigenetic modifiers (HDAC inhibitors)
HSC exhaustion	c-Kit, CXCL12	Circulating $CD34^+$ count, miR-150	Niche rejuvenation; extracellular vesicle therapy
Genomic instability	DNA repair (ATM, PARP)	Cell-free DNA concentration	Precision radioprotection guided by genetic screening (DO mice)

SASP, senescence-associated secretory phenotype; GDF-15, growth differentiation factor 15; MDA, malondialdehyde; HDAC, histone deacetylase; HSC, hematopoietic stem cell; DO, diversity outbred; miR, microRNA; ATM, Ataxia-Telangiectasia Mutated kinase.

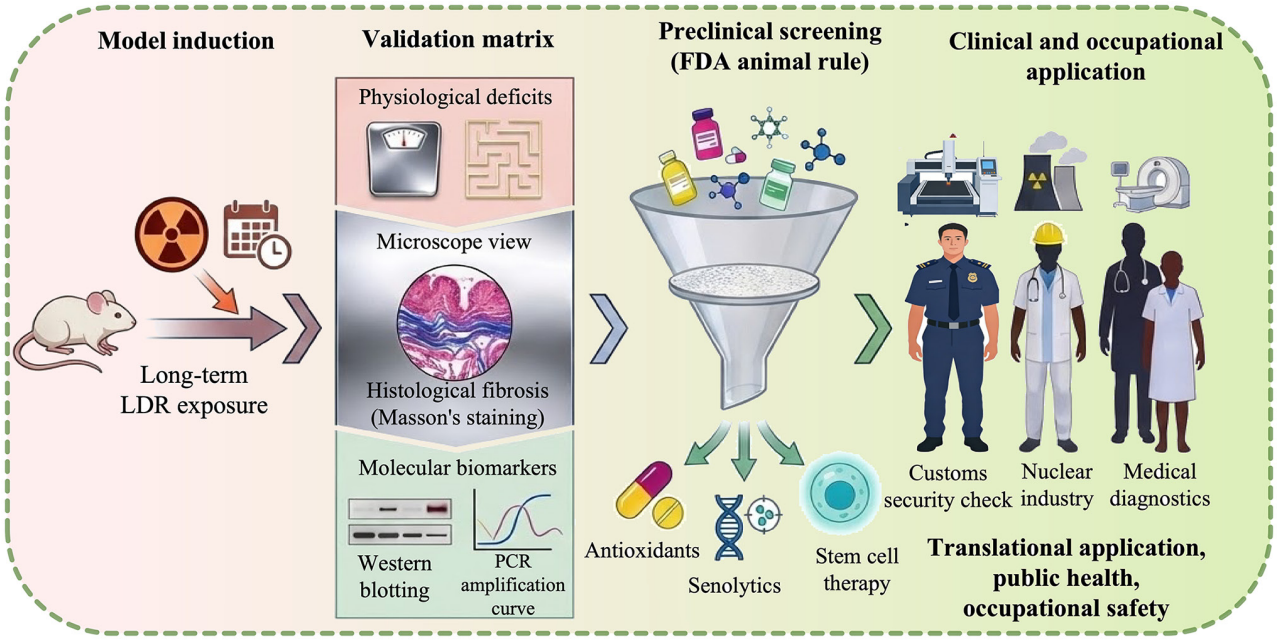

Figure 8. Translational roadmap: Bridging preclinical modeling and precision radioprotection. Validated animal models (minipigs, humanized mice) serve as the operational core for screening medical countermeasures. These high-fidelity systems provide efficacy data required by the FDA animal rule, bypassing the ethical constraints of human testing. Integration of spatial transcriptomics and artificial intelligence-driven deep phenotyping enhances the sensitivity of these models, allowing detection of subtle pathologies and the mapping of mechanism-based targets (such as senolytics). By leveraging digital twins (*in silico* models constructed from large multi-omics datasets), researchers can simulate long-term outcomes and design personalized radiation health passports for diverse risk groups, ranging from nuclear workers to deep-space astronauts. FDA, Food and Drug Administration; LDR, low-dose-rate.

implementation, where many promising candidates fail due to unforeseen toxicities or lack of efficacy, yet the traditional black box approach, exposing animals and waiting for phenotypic outcomes, is being superseded by systems biology and engineering (187). The future lies in the convergence of high-fidelity *in vivo* modeling with high-resolution omics and AI, offering opportunities to rewrite the paradigms of radiation protection and therapy (Fig. 8) (188).

From bulk analysis to spatiotemporal resolution. Future mechanistic inquiry will transcend bulk tissue analysis to identify the spatiotemporal dynamics of injury (189). By integrating single-cell RNA sequencing with spatial transcriptomics, researchers may move beyond merely identifying which cells are damaged to understanding where they are located relative to the niche (190). This will map the neighborhood effects (how a senescent stromal cell spatially corrupts adjacent stem cells via SASP) (191). Advanced genetic fate-mapping will unveil the clonal trajectories of surviving cells, distinguishing between regenerative and pre-leukemic clones (192). This high-resolution mapping may identify specific molecular switch points (such as epigenetic loci) that determine whether a tissue undergoes repair or irreversible fibrosis (193).

Next-generation therapeutics: Senolytics and cell-free regenerative medicine. The therapeutic landscape is shifting from symptom management to disease modification (194). A notable frontier is the targeting of senescent cells (195). Future models will rigorously validate senolytics (drugs that induce apoptosis in senescent cells) and senomorphics (agents that suppress SASP without killing the cell) (196). The goal is to restore the irradiated microenvironment to a pre-exposure state (197). While SC therapy holds promise, the future may lie in extracellular vesicles (EVs) and exosomes (198). Derived from mesenchymal SCs, these cell-free cargoes carry regenerative miRs and proteins with lower immunogenicity and tumorigenic risk than live cells (199). Models optimize engineered EVs loaded with specific radioprotective cargos (mitochondria or mRNA) for targeted delivery (199,200). Clustered regularly interspaced short palindromic repeats-associated protein 9 and base editing *in vivo* will evolve toward correcting radiation-induced mutations in somatic tissue or epigenetically silencing pro-fibrotic genes (TGF-β) via modifiable promotors (201).

AI: Dosimetry and digital twins. AI may transform experimental design and risk assessment (202). Machine learning algorithms may replace manual observation, detecting subtle neurobehavioral deficits (gait asymmetry, micro-tremors) invisible to the human eye, increasing the sensitivity of chronic injury models (203). By integrating large omics datasets from animal studies, researchers aim to create digital twins of radiation injury (204). These *in silico* models can simulate decades of chronic exposure in seconds, predicting long-term outcomes and screening millions of drug candidates virtually before an animal is treated (205). This may accelerate MCM discovery.

Humanized avatars and microphysiological systems (MPSs). Hybrid systems may overcome the interspecies gap (206). The use of immunodeficient mice reconstituted with human hematopoietic and immune systems (MISTRG mice) may become standard for assessing human-specific immune responses to chronic radiation (207). Integration of MPSs (organs-on-chips) with animal validation may enable transition from high-throughput *in vitro* mechanistic screening to definitive *in vivo* validation (208). MPS screen for human-specific toxicity mechanisms, while the animal model confirms systemic safety (209). This aligns with the replacement, reduction and refinement principle while maximizing translational relevance for diverse populations, from astronauts to nuclear workers (210).

While the present review provides a methodological framework for CRI modeling, limitations must be acknowledged. First, due to the logistical, ethical and financial constraints of conducting life-span studies in large animal models (such as non-human primates), the majority of the mechanistic data, particularly regarding SASP and inflammaging, is derived from murine models. Extrapolating these rodent-derived mechanisms to humans requires extreme caution, given the species-specific differences in telomere dynamics, metabolic rate and immune surveillance. Second, experimental models traditionally isolate radiation as a single stressor to maintain controlled variables. However, real-world human exposure (spaceflight or nuclear accidents) typically involves complex exposome interactions, such as concomitant exposure to heavy metals, psychological stress or microgravity, which may alter the CRI trajectory. Finally, spatial multi-omics and AI-driven digital twins are currently in their early developmental or conceptual phases and require empirical validation before widespread translational application.

In conclusion, CR animal models are transitioning from descriptive pathology to predictive precision medicine (211). This may facilitate development of robust, personalized defenses against adverse health effects of ionizing radiation (212).

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Authors' contributions

ZX, XiaodongL, ChunhuiY, LW, JM, QLiu, CL, QLi, YH, JW, ChengzhuoY, FS, ChaoY, MW, BY, YL, QH, LZ, XuemeiL and XiaobingL wrote the manuscript and constructed figures. XuemeiL and XiaobingL edited the manuscript and supervised

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Abbas SF, Abdulkadim H, Al-Hashemi HA and Hadi NR: Assessment of cardioprotective effect of necrostatin-1 stable in a mice model of acute doxorubicin-induced cardiotoxicity. Wiad Lek 76: 1600-1607, 2023.
2. Ahmad A, Mallela SK, Ansari S, Alnukhali M, Ali M, Merscher S, Pollack A, Zeidan YH, Fornoni A and Marples B: Radiation-induced nephrotoxicity: Role of sphingomyelin phosphodiesterase acid-like 3b. Int J Radiat Oncol Biol Phys 121: 1271-1281, 2025.
3. Ahmad A, Shi J, Ansari S, Afaghani J, Molina J, Pollack A, Merscher S, Zeidan YH, Fornoni A and Marples B: Noninvasive assessment of radiation-induced renal injury in mice. Int J Radiat Biol 97: 664-674, 2021.
4. Ahmad A, Shi J, Ansari S, Merscher S, Pollack A, Zeidan Y, Fornoni A and Marples B: Radiation nephropathy: Mechanisms of injury and recovery in a murine model. Radiother Oncol 187: 109813, 2023.
5. Akter R, Rahman MA, Rafi MKJ, Siddique TA, Bithy FY, Akter S, Nisa FY, Khan MAN and Sultana F: The protective effect of lasia spinosa (Linn.) dissipates chemical-induced cardiotoxicity in an animal model. Cardiovasc Toxicol 23: 32-45, 2023.
6. Al-Rubaiey S, Senger C, Bukatz J, Krantchev K, Janas A, Eitner C, Nieminen-Kelhä M, Brandenburg S, Zips D, Vajkoczy P and Acker G: Determinants of cerebral radionecrosis in animal models: A systematic review. Radiother Oncol 199: 110444, 2024.
7. Ancel L, Grison S, Gabillot O, Gueguen J, Svilar L, Guen BL, Gruel G, Benderitter M, Martin JC, Souidi M, *et al*: Metabolomics identifies plasma biomarkers of localized radiation injury. Sci Rep 15: 2166, 2025.
8. Ancel L, Gueguen J, Thoër G, Marçais J, Chemloul A, Le Guen B, Benderitter M, Tamarat R, Souidi M, Benadjaoud MA and Flamant S: Presymptomatic microRNA-based biomarker signatures for the prognosis of localized radiation injury in mice. PLoS One 20: e0329737, 2025.
9. Aqeel M, Medhora M, Gore E, Borkenhagen J, Klawikowski S, Eastwood D, Banerjee A and Jacobs ER: Evaluation of radiation-induced pleural effusions after radiotherapy to support development of animal models of radiation pneumonitis. Health Phys 121: 434-443, 2021.
10. Athanasiadi I, Perez WD, Plantenga JM, Jones-Hall Y and Perez-Torres CJ: Feasibility of a mini-pig model of radiation-induced brain injury to one cerebral hemisphere. Radiat Oncol 16: 30, 2021.
11. Azmoonfar R, Mirzaei F, Najafi M, Varkeshi M, Ghazikhanlousani K, Momeni S and Saber K: Radiation-induced testicular damage in mice: Protective effects of apigenin revealed by histopathological evaluation. Curr Radiopharm 17: 238-246, 2024.
12. Beach T, Authier S, Javitz HS, Wong K, Bakke J, Gahagen J, Bunin DI and Chang PY: Total body irradiation models in NHPs-consideration of animal sex and provision of supportive care to advance model development. Int J Radiat Biol 97: 126-130, 2021.
13. Beach T, Bakke J, McDonald JT, Riccio E, Javitz HS, Nishita D, Kapur S, Bunin DI and Chang PY: Delayed effects of radiation exposure in a C57L/J mouse model of partial body irradiation with ~2.5% bone marrow shielding. Front Public Health 12: 1349552, 2024.
14. Behnke V, Wolf A, Hector M and Langmann T: C3aR1-deletion delays retinal degeneration in a white-light damage mouse model. Invest Ophthalmol Vis Sci 66: 15, 2025.
15. Kamiya K, Ozasa K, Akiba S, Niwa O, Kodama K, Takamura N, Zaharieva EK, Kimura Y and Wakeford R: Long-term effects of radiation exposure on health. Lancet 386: 469-478, 2015.
16. Lin RT, Boonhat H, Lin YY, Klebe S and Takahashi K: Health effects of occupational and environmental exposures to nuclear power plants: A meta-analysis and meta-regression. Curr Environ Health Rep 11: 329-339, 2024.
17. Britten RA, Fesshaye AS, Tidmore A, Tamgue EN and Alvarado-Arriaga PA: Different spectrum of space radiation induced cognitive impairments in radiation-naïve and adapted rats. Life Sci Space Res (Amst) 43: 68-74, 2024.
18. Bolduc DL, Cary LH, Kiang JG, Kurada L, Kumar VP, Edma SA, Olson MG, Vergara VB, Bistline DD, Reese M, *et al*: Natural-history characterization of a murine partial-body irradiation model system: Establishment of a multiple-parameter based GI-ARS severity-scoring system. Radiat Res 201: 406-417, 2024.
19. Camargo CP, Zavala JPM, Serafim GP, Carvalho HA, Santos BL, Nunes VA, Uno M, Alves MJF, Furuya TK and Gemperli R: Effects of adipocyte-derived stem cells treatment for moderate radiodermatitis: Animal model. Int J Radiat Biol 101: 827-834, 2025.
20. Cao H, Yue L, Shao J, Kong F, Liu S, Huai H, He Z, Mao Z, Yang Y, Tan Y and Wang H: Small extracellular vesicles derived from umbilical cord mesenchymal stem cells alleviate radiation-induced cardiac organoid injury. Stem Cell Res Ther 15: 493, 2024.
21. Chan LSA, Gu LC and Wells RA: The effects of secondary iron overload and iron chelation on a radiation-induced acute myeloid leukemia mouse model. BMC Cancer 21: 509, 2021.
22. Chen X, Chen L, Tan J, Zhang L, Xia J, Cheng B and Zhang W: Rspo1-LGR4 axis in BMSCs protects bone against radiation-induced injury through the mTOR-dependent autophagy pathway. J Cell Physiol 236: 4273-4289, 2021.
23. Chen Y, Cheng Z, Ma L and Shi CM: Analysis of the number, type, and functional heterogeneity of senescent cells in the radiation-induced skin wounds in mice. Zhonghua Shao Shang Yu Chuang Mian Xiu Fu Za Zhi 41: 577-586, 2025 (In Chinese).
24. Cyran M, Stawarz K, Chambily L, Kusza K and Siemionow M: Assessment of hematopoietic response to total body irradiation in a rat experimental model. Ann Plast Surg 93: 100-106, 2024.
25. Dai J, Gao Y, Wang J, Zhang S and Liu P: Effects of ionizing radiation on intestinal bile acid metabolism: Mechanism of the radioprotective effect of glycoursodeoxycholic acid. Sichuan Da Xue Xue Bao Yi Xue Ban 55: 1195-1201, 2024 (In Chinese).
26. Dar HH, Epperly MW, Tyurin VA, Amoscato AA, Anthonymuthu TS, Souryavong AB, Kapralov AA, Shurin GV, Samovich SN, St Croix CM, *et al*: P. aeruginosa augments irradiation injury via 15-lipoxygenase-catalyzed generation of 15-HpETE-PE and induction of theft-ferroptosis. JCI Insight 7: e156013, 2022.
27. Dasgupta Q, Jiang A, Wen AM, Mannix RJ, Man Y, Hall S, Javorsky E and Ingber DE: A human lung alveolus-on-a-chip model of acute radiation-induced lung injury. Nat Commun 14: 6506, 2023.
28. Dawoud M, Attallah KM, Ibrahim IT, Karam HM and Ibrahim AA: MitoQ and its hyaluronic acid-based nanopreparation mitigating gamma radiation-induced intestinal injury in mice: Alleviation of oxidative stress and apoptosis. Naunyn Schmiedebergs Arch Pharmacol 397: 5193-5205, 2024.
29. Dhingra N, Gupta V, Tyagi A, Agrawala PK and Gupta V: Trichostatin A ameliorated combined radiation and skin wound injury-induced mortality and hematopoietic suppression in a rat model. Int J Radiat Biol 101: 952-972, 2025.
30. Diaz MF, Horton PD, Dumbali SP, Kumar A, Livingston M, Skibber MA, Mohammadalipour A, Gill BS, Zhang S, Cox CS Jr and Wenzel PL: Bone marrow stromal cell therapy improves survival after radiation injury but does not restore endogenous hematopoiesis. Sci Rep 10: 22211, 2020.
31. Dos Santos M, Demarquay C, Ermeneux L, Aberkane F, Bléry P, Weiss P, Milliat F and Mathieu N: Refining the mandibular osteoradionecrosis rat model by in vivo longitudinal μCT analysis. Sci Rep 11: 22241, 2021.
32. Down JD, Cornwall-Brady MR, Huang W, Hurwitz M, Floyd SR and Yilmaz OH: Selecting the most relevant mouse strains for evaluating radiation-induced multiple tissue injury after leg-shielded partial-body gamma irradiation. Radiat Res 202: 510-522, 2024.

33. Dreyfuss AD, Goia D, Shoniyozov K, Shewale SV, Velalopoulou A, Mazzoni S, Avgousti H, Metzler SD, Bravo PE, Feigenberg SJ, *et al*: A novel mouse model of radiation-induced cardiac injury reveals biological and radiological biomarkers of cardiac dysfunction with potential clinical relevance. Clin Cancer Res 27: 2266-2276, 2021.
34. Duval KEA, Aulwes E, Zhang R, Rahman M, Ashraf MR, Sloop A, Sunnerberg J, Williams BB, Cao X, Bruza P, *et al*: Comparison of tumor control and skin damage in a mouse model after ultra-high dose rate irradiation and conventional irradiation. Radiat Res 200: 223-231, 2023.
35. Ewing LE, Biju PG, Pathak R, Melnyk S, Hauer-Jensen M and Koturbash I: Methods for induction and assessment of intestinal permeability in rodent models of radiation injury. Methods Cell Biol 168: 235-247, 2022.
36. Fang D, Zhao H, Pei L, Jiang K, Gan Y, Zhai X, Zhang L, Cheng Y, Liu C, Du J and Gao F: Diprovocim protects against the radiation-induced damage via the TLR2 signaling pathway. Mol Med 31: 139, 2025.
37. Farber E, Kwiecien JM, Bojic D, Ngu M, Akohene-Mensah P, Vanhie JJ, Lloyd J, Larkin J and DE Lisio M: Exercise improves cancer-free survival and health span in a model of radiation-induced cancer. Med Sci Sports Exerc 53: 2254-2263, 2021.
38. Farese AM, Drouet M, Herodin F, Bertho JM, Thrall KD, Authier S, Doyle-Eisele M and MacVittie TJ: Acute radiation effects, the H-ARS in the non-human primate: A review and new data for the cynomolgus macaque with reference to the rhesus macaque. Health Phys 121: 304-330, 2021.
39. Farh ME, Kim HJ, Kim SY, Lee JH, Lee H, Cui R, Han S, Kim DW, Park S, Lee YJ, *et al*: Transcriptional changes in radiation-induced lung injury: A comparative analysis of two radiation doses for preclinical research. Int J Mol Sci 25: 3766, 2024.
40. Feng J, Liu X, Xu L, Wang K, He S, Wang X, Huang Y, Wang S, Lei X, Huang L, *et al*: Optimization and characterization of acute radiation-induced esophagitis in mice. Radiat Oncol 20: 147, 2025.
41. Feng Y, Kong J, Sun W, Li Y, Ren F, Sun X, Li M, Liu Y, Sun S and Qin H: NLRP3 regulates macrophage function by M-CSF/M-CSFR signaling in acute radiation-induced lung injury. Mol Immunol 183: 213-224, 2025.
42. Fish BL, Hart B, Gasperetti T, Narayanan J, Gao F, Veley D, Pierce L, Himburg HA, MacVittie T and Medhora M: IPW-5371 mitigates the delayed effects of acute radiation exposure in WAG/RijCmcr rats when started 15 days after PBI with bone marrow sparing. Int J Radiat Biol 99: 1119-1129, 2023.
43. Fish BL, MacVittie TJ, Gao F, Narayanan J, Gasperetti T, Scholler D, Sheinin Y, Himburg HA, Hart B and Medhora M: Rat Models of partial-body irradiation with bone marrow-sparing (Leg-out PBI) Designed for FDA approval of countermeasures for mitigation of acute and delayed injuries by radiation. Health Phys 121: 419-433, 2021.
44. Fu J, Liu X, Zhou Y, Zhao S, Zeng L, Pan Y, Zhang J, Prise KM, Shao C and Xu Y: Development of delayed pulmonary toxicities and transcriptional changes in pre-existing interstitial lung disease mice after partial thoracic irradiation. Radiat Oncol 20: 20, 2025.
45. Fuentes A, Hyde D, Johnson I and Haston CK: Acute radiation-induced hematopoietic depletion does not alter the onset or severity of pneumonitis in mice. Radiat Res 196: 297-305, 2021.
46. Gans I, El Abiad JM, James AW, Levin AS and Morris CD: Administration of TGF-ß inhibitor mitigates radiation-induced fibrosis in a mouse model. Clin Orthop Relat Res 479: 468-474, 2021.
47. Gao J, Li Y, Chen J, Feng W, Bu J, Lu Z and Wang J: Emodin ameliorates acute radiation proctitis in mice by regulating AKT/MAPK/NF-κB/VEGF pathways. Int Immunopharmacol 132: 111945, 2024.
48. Gassert FT, Burkhardt R, Gora T, Pfeiffer D, Fingerle AA, Sauter AP, Schilling D, Rummeny EJ, Schmid TE, Combs SE, *et al*: X-ray dark-field CT for early detection of radiation-induced lung injury in a murine model. Radiology 303: 696-698, 2022.
49. Gibbs A, Gupta P, Mali B, Poirier Y, Gopalakrishnan M, Newman D, Zodda A, Down JD, Serebrenik AA, Kaytor MD and Jacksone IL: A C57L/J mouse model of the delayed effects of acute radiation exposure in the context of evolving multi-organ dysfunction and failure after total-body irradiation with 2.5% bone marrow sparing. Radiat Res 199: 319-335, 2023.
50. Glowacki J, Epperly MW, Bellare A, Wipf P and Greenberger JS: Combined injury: Irradiation with skin or bone wounds in rodent models. J Radiol Prot 41: 10.1088/1361-6498/ac125b, 2021.
51. Gu J, Zhao L, Chen YZ, Guo YX, Sun Y, Guo Q, Duan GX, Li C, Tang ZB, Zhang ZX, *et al*: Preventive effect of sanguinarine on intestinal injury in mice exposed to whole abdominal irradiation. Biomed Pharmacother 146: 112496, 2022.
52. Guan B, Li D and Meng A: Development of radiation countermeasure agents for acute radiation syndromes. Animal Model Exp Med 6: 329-336, 2023.
53. Guan H, Zhang W, Xie D, Nie Y, Chen S, Sun X, Zhao H, Liu X, Wang H, Huang X, *et al*: Cytosolic release of mitochondrial DNA and associated cGAS signaling mediates radiation-induced hematopoietic injury of mice. Int J Mol Sci 24: 4020, 2023.
54. Guan Z, Zhang J, Jiang N, Tian M, Wang H and Liang B: Efficacy of mesenchymal stem cell therapy in rodent models of radiation-induced xerostomia and oral mucositis: A systematic review. Stem Cell Res Ther 14: 82, 2023.
55. Hansel C, Barr S, Schemann AV, Lauber K, Hess J, Unger K, Zitzelsberger H, Jendrossek V and Klein D: Metformin protects against radiation-induced acute effects by limiting senescence of bronchial-epithelial cells. Int J Mol Sci 22: 7064, 2021.
56. Hanson I, Juvkam IS, Zlygosteva O, Søland TM, Galtung HK, Malinen E and Edin NFJ: TGF-β3 increases the severity of radiation-induced oral mucositis and salivary gland fibrosis in a mouse model. Int J Radiat Biol 100: 767-776, 2024.
57. Holmes-Hampton GP, Kumar VP, Valenzia K and Ghosh SP: FSL-1: A synthetic peptide increases survival in a murine model of hematopoietic acute radiation syndrome. Radiat Res 201: 449-459, 2024.
58. Hormozi Moghaddam Z, Mokhtari-Dizaji M, Nilforoshzadeh MA, Bakhshandeh M and Ghaffari Khaligh S: Low-intensity ultrasound combined with allogenic adipose-derived mesenchymal stem cells (AdMSCs) in radiation-induced skin injury treatment. Sci Rep 10: 20006, 2020.
59. Horseman T, Rittase WB, Slaven JE, Bradfield DT, Frank AM, Anderson JA, Hays EC, Ott AC, Thomas AE, Huppmann AR, *et al*: Ferroptosis, inflammation, and microbiome alterations in the intestine in the Göttingen minipig model of hematopoietic-acute radiation syndrome. Int J Mol Sci 25: 4535, 2024.
60. Horseman TS, Parajuli B, Frank AM, Weaver A, Schauer DA, Moran S, Anderson JA, Holmes-Hampton GP and Burmeister DM: Microbiome and inflammasome alterations found during radiation dose finding in a sinclair minipig model of gastrointestinal acute radiation syndrome. Shock 62: 556-564, 2024.
61. Hritzo B, Aghdam SY, Legesse B, Kaur A, Cao M, Boerma M, Chakraborty N, Dimitrov G, Gautam A, Hammamieh R, *et al*: Late health effects of partial body irradiation injury in a minipig model are associated with changes in systemic and cardiac IGF-1 signaling. Int J Mol Sci 22: 3286, 2021.
62. Hritzo B, Legesse B, Ward JM, Kaur A, Aghdam SY, Kenchegowda D, Holmes-Hampton GP and Moroni M: Investigating the multifaceted nature of radiation-induced coagulopathies in a Göttingen minipig model of hematopoietic acute radiation syndrome. Radiat Res 196: 156-174, 2021.
63. Huang B, An L, Su W, Yan T, Zhang H and Yu DJ: Exploring the alterations and function of skin microbiome mediated by ionizing radiation injury. Front Cell Infect Microbiol 12: 1029592, 2022.
64. Huang H, Shi Y, Liu X, Hao L, Zhu J and Lu J: Protective effect of vinegar powder on ^{60}Coγ radiation-injured mice and its potential mechanism. J Nutr 155: 3663-3675, 2025.
65. Huang J, Zhang Y, Jiang F, Zhang Y, Li S, He S, Sun J, Chen D, Pang Q and Wu Y: Bach1 deficiency ameliorates radiation pneumonitis via activating TFAM signaling pathway. Antioxid Redox Signal 43: 75-91, 2025.
66. Hunter KS, Carnell LS, DiCarlo AL, Hoffman CM, Loelius SG and Homer M: Interagency approaches to animal models for acute radiation exposure. Int J Radiat Biol 97 (Suppl 1): S2-S5, 2021.
67. Iddins CJ, DiCarlo AL, Ervin MD, Herrera-Reyes E and Goans RE: Cutaneous and local radiation injuries. J Radiol Prot 42: 10.1088/1361-6498/ac241a, 2022.
68. Jackson IL and Doyle-Eisele M: Animal model considerations for medical countermeasure development for radiation and sulfur mustard exposures: Animal models for radiation and HD exposures. Disaster Med Public Health Prep 18: e81, 2023.
69. Jackson IL, Gurung G, Poirier Y, Gopalakrishnan M, Cohen EP, Donohue TS, Newman D and Vujaskovic Z: A New Zealand white rabbit model of thrombocytopenia and coagulopathy following total body irradiation across the dose range to induce the hematopoietic-subsyndrome of acute radiation syndrome. Int J Radiat Biol 97 (Suppl 1): S19-S31, 2021.
70. Jacobson JR: Sphingolipids as a novel therapeutic target in radiation-induced lung injury. Cell Biochem Biophys 79: 509-516, 2021.

71. Jiajia D, Yiping W, Enyan J, Shouwu Z, Shuai Y, Xiaojian Z, Juan J, Zhen F, Jia Z, Jikai W, *et al*: Maresin-1 alleviates lipid peroxidation-induced ferroptosis after radiation-induced brain injury in mice through the RORα/NRF2 pathway. Exp Neurol 389: 115258, 2025.
72. Jiang H, Wang R, Liu A, Liu J, Wang X, Lin W, Ren C, Liu K, Zhao X and Li Y: RAS-RH up-regulates the level of miR-126 and inhibits the opening of mPTP in a rat model of coronary microvascular disease. Microvasc Res 162: 104856, 2025.
73. Jiao W, Cheng Y, Liu C, Feng J, Lin J and Shen Y: SGLT1 inhibition alleviates radiation-induced intestinal damage through promoting mitochondrial homeostasis. Free Radic Biol Med 224: 831-845, 2024.
74. Kayalı A, Arda DB, Bora ES, Uyanikgil Y, Atasoy Ö and Erbaş O: Oxytocin: A shield against radiation-induced lung injury in rats. Tomography 10: 1342-1353, 2024.
75. Kenchegowda D, Bolduc DL, Kurada L and Blakely WF: Severity scoring systems for radiation-induced GI injury-prioritization for use of GI-ARS medical countermeasures. Int J Radiat Biol 99: 1037-1045, 2023.
76. Kenchegowda D, Seed TM and Singh VK: What are the practical, ethical, and pathobiological considerations in the use of minipigs as an animal model in drug discovery for acute radiation syndrome and delayed effects of acute radiation exposure? Expert Opin Drug Discov 16: 119-124, 2021.
77. Khodamoradi E, Rahmani N, Rashidi K, Najafi M, Shahsavari S and Mohammadi M: Exploring the potential of metformin in mitigating radiation-induced gastrointestinal and hematopoietic system injury in rats after whole-body X-ray radiation: An experimental study. Curr Radiopharm 17: 200-208, 2024.
78. Kim HC, Oh H, You JS and Chung YE: Glycyrrhizin ameliorating sterile inflammation induced by low-dose radiation exposure. Sci Rep 11: 18356, 2021.
79. Kim SY, Park S, Cui R, Lee H, Choi H, Farh ME, Jo HI, Lee JH, Song HJ, Lee YJ, *et al*: NXC736 Attenuates radiation-induced lung fibrosis via regulating NLRP3/IL-1β signaling pathway. Int J Mol Sci 24: 16265, 2023.
80. Klaus R, Niyazi M and Lange-Sperandio B: Radiation-induced kidney toxicity: Molecular and cellular pathogenesis. Radiat Oncol 16: 43, 2021.
81. Kleiman NJ, Edmondson EF, Weil MM, Fallgren CM, King A, Schmidt C and Hall EJ: Radiation cataract in heterogeneous stock mice after γ-ray or HZE ion exposure. Life Sci Space Res (Amst) 40: 97-105, 2024.
82. Kočović DM, Bajuk-Bogdanović D, Pećinar I, Nedeljković BB, Daković M and Andjus PR: Assessment of cellular and molecular changes in the rat brain after gamma radiation and radioprotection by anisomycin. J Radiat Res 62: 793-803, 2021.
83. Krasnoselsky MV, Pushkar OS, Simonova LI and Myroshnychenko MS: The effect of photodynamic therapy and platelet-enriched plasma on the healing of skin radiation ulcers infected by staphylococcus aureus. Probl Radiac Med Radiobiol 25: 338-352, 2020 (In English, Ukrainian).
84. Kumar VP, Holmes-Hampton GP, Biswas S, Stone S, Sharma NK, Hritzo B, Guilfoyle M, Eichenbaum G, Guha C and Ghosh SP: Mitigation of total body irradiation-induced mortality and hematopoietic injury of mice by a thrombopoietin mimetic (JNJ-26366821). Sci Rep 12: 3485, 2022.
85. Kumar VP, Jaiswal S, Wuddie K, Ward JM, Lawrence M and Ghosh SP: Development of a radiation-induced pulmonary fibrosis partial body irradiation model in C57BL/6 mice. Radiat Res 201: 460-470, 2024.
86. Kumar VP, Wuddie K, Tsioplaya A, Weaver A, Holmes-Hampton GP and Ghosh SP: Development of a multi-organ radiation injury model with precise dosimetry with focus on GI-ARS. Radiat Res 201: 19-34, 2024.
87. Kura B, Kalocayova B, Szeiffova Bacova B, Fulop M, Sagatova A, Sykora M, Andelova K, Abuawad Z and Slezak J: The effect of selected drugs on the mitigation of myocardial injury caused by gamma radiation. Can J Physiol Pharmacol 99: 80-88, 2021.
88. Kwak SY, Jang WI, Park S, Cho SS, Lee SB, Kim MJ, Park S, Shim S and Jang H: Metallothionein 2 activation by pravastatin reinforces epithelial integrity and ameliorates radiation-induced enteropathy. EBioMedicine 73: 103641, 2021.
89. L'Abbate S, Chianca M, Fabiani I, Del Franco A, Giannoni A, Vergaro G, Grigoratos C, Kusmic C, Passino C, D'Alessandra Y, *et al*: In vivo murine models of cardiotoxicity due to anticancer drugs: challenges and opportunities for clinical translation. J Cardiovasc Transl Res 15: 1143-1162, 2022.
90. Lai YF, Wang HY and Peng RY: Establishment of injury models in studies of biological effects induced by microwave radiation. Mil Med Res 8: 12, 2021.
91. Laiakis EC, McCart EA, Deziel A, Rittase WB, Bouten RM, Jha J, Wilkins WL, Day RM and Fornace AJ Jr: Effect of 3,3'-diindolylmethane on pulmonary injury following thoracic irradiation in CBA mice. Health Phys 119: 746-757, 2020.
92. Lawrence J, Seelig D, Demos-Davies K, Ferreira C, Ren Y, Wang L, Alam SK, Yang R, Guedes A, Craig A and Hoeppner LH: Radiation dermatitis in the hairless mouse model mimics human radiation dermatitis. Sci Rep 14: 24819, 2024.
93. Lebon C, Malaise D, Rimbert N, Billet M, Ramasamy G, Villaret J, Pouzoulet F, Matet A and Behar-Cohen F: Role of inflammation in a rat model of radiation retinopathy. J Neuroinflammation 21: 162, 2024.
94. Lee CL, Wright AO, Lee JW, Brownstein J, Hasapis S, Satow S, Da Silva Campos L, Williams N, Ma Y, Luo L, *et al*: Sensitization of endothelial cells to ionizing radiation exacerbates delayed radiation myelopathy in mice. Radiat Res 197: 193-198, 2021.
95. Lee J, Jeon BS, Kang S, Son Y, Lim YB, Bae MJ, Jo WS, Lee CG, Shin IS, Moon C, *et al*: Protective effects of tauroursodeoxycholate against radiation-induced intestinal injury in a mouse model. Biochem Biophys Res Commun 724: 150226, 2024.
96. Levy K, Natarajan S, Wang J, Chow S, Eggold JT, Loo PE, Manjappa R, Melemenidis S, Lartey FM, Schüler E, *et al*: Abdominal FLASH irradiation reduces radiation-induced gastrointestinal toxicity for the treatment of ovarian cancer in mice. Sci Rep 10: 21600, 2020.
97. Li L, Nie X, Zhang P, Huang Y, Ma L, Li F, Yi M, Qin W and Yuan X: Dexrazoxane ameliorates radiation-induced heart disease in a rat model. Aging (Albany NY) 13: 3699-3711, 2021.
98. Li L, Zhang S, Ge C, Ji L, Lv Y, Zhao C, Xu L, Zhang J, Song C, Chen J, *et al*: HSCs transdifferentiate primarily to pneumonocytes in radiation-induced lung damage repair. Aging (Albany NY) 13: 8335-8354, 2021.
99. Li N, Zhao W, Li J, Zhang D, Li K, Yang M, Lu X, Du L, Xu C and Liu Q: Autophagy and exosome dynamics in radiation-induced pulmonary fibrosis: The critical role of TRIB3. Respir Res 26: 194, 2025.
100. Li W, Jiang L, Lu X, Liu X and Ling M: Curcumin protects radiation-induced liver damage in rats through the NF-κB signaling pathway. BMC Complement Med Ther 21: 10, 2021.
101. Li W, Lin Y, Luo Y, Wang Y, Lu Y, Li Y and Guo H: Vitamin D receptor protects against radiation-induced intestinal injury in mice via inhibition of intestinal crypt stem/progenitor cell apoptosis. Nutrients 13: 2910, 2021.
102. Li W, Lu L, Liu B and Qin S: Effects of phycocyanin on pulmonary and gut microbiota in a radiation-induced pulmonary fibrosis model. Biomed Pharmacother 132: 110826, 2020.
103. Li X, Liang J, Qu L, Liu S, Qin A, Liu H, Wang T, Li W and Zou W: Exploring the role of ferroptosis in the doxorubicin-induced chronic cardiotoxicity using a murine model. Chem Biol Interact 363: 110008, 2022.
104. Lin Y, Xia P, Cao F, Zhang C, Yang Y, Jiang H, Lin H, Liu H, Liu R, Liu X and Cai J: Protective effects of activated vitamin D receptor on radiation-induced intestinal injury. J Cell Mol Med 27: 246-258, 2023.
105. Lipiec SM, Torres LN, Ryan KL, Walters TJ, Klemcke HG and Xiang L: A combat-relevant model of traumatic hemorrhage in rats for the study of combined radiation injury: A pilot study. Radiat Res 204: 253-258, 2025.
106. Liu D, Dong S, Liu C, Du J, Wang S, Yu H, Li W, Chen Z, Peng R, Jiang Q, *et al*: CRX-527 induced differentiation of HSCs protecting the intestinal epithelium from radiation damage. Front Immunol 13: 927213, 2022.
107. Liu E, Tamplin MR, Rosius J, Tedeschi TR, Gramlich OW, Kardon RH and Grumbach IM: Mouse model of radiation retinopathy reveals vascular and neuronal injury. Exp Eye Res 238: 109729, 2024.
108. Liu G, Chen Y, Dai S, Wu G, Wang F, Chen W, Wu L, Luo P and Shi C: Targeting the NLRP3 in macrophages contributes to senescence cell clearance in radiation-induced skin injury. J Transl Med 23: 196, 2025.
109. Liu P, Fu M, Liu D, Chao T and Zhang J: Mechanisms of radiation-induced brain injury in mice based on bioinformatics analysis. Radiat Res 203: 321-332, 2025.
110. Liu P, Yu D, Sheng W, Geng F, Zhang J and Zhang S: PPARα activation by fenofibrate ameliorates radiation-induced skin injury. J Eur Acad Dermatol Venereol 36: e207-e210, 2022.

111. Liu Z, Liu J, Hu D, Du J, Liu D, Wang X, Zhang J and Hou Y: Activation of neural modeling-related genes in the heart of mice after gamma irradiation. Comput Math Methods Med 2021: 8522417, 2021.
112. Maan K, Tyagi R, Dutta A, Bakhshi R and Rana P: Comparative metabolic profiles of total and partial body radiation exposure in mice using an untargeted metabolomics approach. Metabolomics 16: 124, 2020.
113. Maciag M, Wnorowski A, Bednarz K and Plazinska A: Evaluation of β-adrenergic ligands for development of pharmacological heart failure and transparency models in zebrafish. Toxicol Appl Pharmacol 434: 115812, 2022.
114. MacVittie TJ: Where are the medical countermeasures against the ARS and DEARE? A current topic relative to an animal model research platform, radiation exposure context, the acute and delayed effects of acute exposure, and the FDA animal rule. Int J Radiat Biol 99: 994-1008, 2023.
115. Martello S, Ueda Y, Bylicky MA, Pinney J, Dalo J, Scott KMK, Aryankalayil MJ and Coleman CN: Developing an RNA signature for radiation injury using a human liver-on-a-chip model. Radiat Res 202: 489-502, 2024.
116. Matsuu-Matsuyama M, Shichijo K, Matsuda K, Fujimoto N, Kondo H, Miura S, Kurashige T, Nagayama Y and Nakashima M: Age-dependent effects on radiation-induced carcinogenesis in the rat thyroid. Sci Rep 11: 19096, 2021.
117. Medhora M, Gao F, Gasperetti T, Narayanan J, Himburg H, Jacobs ER, Clough AV, Fish BL and Szabo A: Biomarkers to predict lethal radiation injury to the rat lung. Int J Mol Sci 24: 5627, 2023.
118. Meng C, Fan L, Wang X, Wang Y, Li Y, Pang S, Lv S and Zhang J: Preparation and evaluation of animal models of cardiotoxicity in antineoplastic therapy. Oxid Med Cell Longev 2022: 3820591, 2022.
119. Mohamed HA and Said RS: Coenzyme Q10 attenuates inflammation and fibrosis implicated in radiation enteropathy through suppression of NF-kB/TGF-β/MMP-9 pathways. Int Immunopharmacol 92: 107347, 2021.
120. Mohammadi M, Kiani A, Aghaz F, Arkan E, Rashidi K and Najafi M: Mitigation of radiation-induced acute hematopoietic system and intestine injury by resveratrol-loaded polymeric nanoparticles after whole body irradiation in mice. Curr Radiopharm 18: 182-200, 2025.
121. Mohammed QKQ and Kancha RK: Evaluation of cardiotoxicity of cancer chemotherapeutics using daphnia magna as a preclinical model. Curr Protoc 4: e70035, 2024.
122. Moraes LR, Lima ML, Ribeiro APA, Rocha NN, Gonçalves TCW, Barbosa RJV, Roque KS, Costa Ferreira Santos G, Cruz APD, Veras RG, *et al*: Integrative physiological study of radiation-induced lung injury: Effects on cardiac function and kidney integrity. J Appl Physiol (1985) 139: 1050-1063, 2025.
123. Mujahid A, Alotaibi B, DeMellier C, Gallegos C, Sherwani M, Alexandrian A, Sorace A, Brady A and George R: Characterization of cutaneous radiation syndrome in a mouse model using [18 F]F-fluorodeoxyglucose positron emission tomography. Health Phys 129: 204-213, 2025.
124. Mukherjee T, Elliott S, Manikandan N, Higgins TJ, Zhong Y, Montalvo SK, Saha D, Wansapura J, Avazmohammadi R and Alluri PG: Principal strain analysis for early detection of radiation-induced cardiotoxicity in a mouse model. Int J Radiat Oncol Biol Phys 123: 306-315, 2025.
125. Muller L, Huang W, Jones JW, Farese AM, MacVittie TJ and Kane MA: Complementary lipidomic, proteomic, and mass spectrometry imaging approach to the characterization of the acute effects of radiation in the non-human primate mesenteric lymph node after partial-body irradiation with minimal bone marrow sparing. Health Phys 121: 372-383, 2021.
126. Niu S, Zhang Y, Cong C, Wu Z, Wang Z, Sun M, Yao C and Zhang Y: Comparative study of radiation-induced lung injury model in two strains of mice. Health Phys 122: 579-585, 2022.
127. Otluoglu GD, Yılmaz B, Ekinci G, Bayri Y, Bozkurt SU and Dağçınar A: Pentoxifylline and vitamin E can restrict radiation necrosis via vascular pathways, experimental study in an animal model. World Neurosurg 179: e530-e538, 2023.
128. Ou M, Fan W, Sun F, Li M, Lin M, Yu Y, Liang S, Liao H, Jie W, Cai Y, *et al*: Nasal delivery of antagomir-741 protects against the radiation-induced brain injury in mice. Radiat Res 195: 355-365, 2021.
129. Pannkuk EL, Laiakis EC, Garty GY, Shuryak I, Kumar K, Suman S, Ghandhi SA, Tan Y, Ponnaiya B, Wu X, *et al*: Sex differences in urinary metabolite profiles between survivors and non-survivors of radiation-induced lung injury in the C57L/J murine model. Radiat Res 204: 1-14, 2025.
130. Paredes A, Lindeblad M, Patil R, Neal MD, Hong Y, Smith B, Nanda JP, Mousafeiris V, Moulder J, Bosland MC, *et al*: The New Zealand white rabbit animal model of acute radiation syndrome: hematopoietic and coagulation-based parameters by radiation dose following supportive care. Int J Radiat Biol 97 (Suppl 1): S45-S62, 2021.
131. Park JH, Byun HJ, Kim HJ, Oh SJ, Choi C, Noh JM, Oh D, Lee JH and Lee DY: Effect of photobiomodulation therapy on radiodermatitis in a mouse model: An experimental animal study. Lasers Med Sci 36: 843-853, 2021.
132. Park SW, Shin J, Jeong BK, Byun S, Lee KS and Choi J: The effects of extracorporeal shock wave therapy on cutaneous radiation injury in a mouse model. Plast Reconstr Surg 155: 813-825, 2025.
133. Patterson AM, Sellamuthu R, Plett PA, Sampson CH, Chua HL, Fisher A, Vemula S, Feng H, Katz BP, Tudor G, *et al*: Establishing pediatric mouse models of the hematopoietic acute radiation syndrome and the delayed effects of acute radiation exposure. Radiat Res 195: 307-323, 2021.
134. Pawliczek D, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Graw J and Dalke C: Ionising radiation causes vision impairment in neonatal B6C3F1 mice. Exp Eye Res 204: 108432, 2021.
135. Pezeshki PS, Mahboubi A, Mohammadi Ganjaroudi N, Ghalehtaki R, Majidi Zolbin M, Salarvand S, Jolany Vangah S, Mehrjoo A and Kajbafzadeh AM: Human umbilical cord mesenchymal stem cells-derived extracellular vesicles as a therapeutic approach to ameliorate bladder injury in animal models of radiation cystitis. Stem Cell Res Ther 16: 387, 2025.
136. Plett PA, Pelus LM and Orschell CM: Establishing a murine model of the hematopoietic acute radiation syndrome. Methods Mol Biol 2567: 251-262, 2023.
137. Qiu Y, Xie X and Lin L: circFOXO3 protects cardiomyocytes against radiation-induced cardiotoxicity. Mol Med Rep 23: 177, 2021.
138. Qu M, Xiong L, Lyu Y, Zhang X, Shen J, Guan J, Chai P, Lin Z, Nie B, Li C, *et al*: Establishment of intestinal organoid cultures modeling injury-associated epithelial regeneration. Cell Res 31: 259-271, 2021.
139. Rao X, Zhou D, Deng H, Chen Y, Wang J, Zhou X, Jie X, Xu Y, Wu Z, Wang G, *et al*: Activation of NLRP3 inflammasome in lung epithelial cells triggers radiation-induced lung injury. Respir Res 24: 25, 2023.
140. Rittase WB, McCart EA, Muir JM, Bouten RM, Slaven JE, Mungunsukh O, Bylicky MA, Wilkins WL, Lee SH, Gudmundsson KO, *et al*: Effects of captopril against radiation injuries in the Göttingen minipig model of hematopoietic-acute radiation syndrome. PLoS One 16: e0256208, 2021.
141. Rittase WB, Slaven JE, Suzuki YJ, Muir JM, Lee SH, Rusnak M, Brehm GV, Bradfield DT, Symes AJ and Day RM: Iron deposition and ferroptosis in the spleen in a murine model of acute radiation syndrome. Int J Mol Sci 23: 11029, 2022.
142. Ruaro A, Taboni S, Chan HHL, Mondello T, Lindsay P, Komal T, Alessandrini L, Sbaraglia M, Bellan E, Maroldi R, *et al*: Development of a preclinical double model of mandibular irradiated bone and osteoradionecrosis in New Zealand rabbits. Head Neck 47: 625-634, 2025.
143. Safarbalou A, Ebrahimi F, Talebpour Amiri F and Hosseinimehr SJ: The potential radioprotective effect of piperine against radiation-induced lung injury in mice: Histopathological and biochemical evaluations. Curr Pharm Des 30: 2179-2186, 2024.
144. Saul-McBeth J, Dillon J, Lee A, Launder D, Kratch JM, Abutaha E, Williamson AA, Schroering AG, Michalski G, Biswas P, *et al*: Tissue damage in radiation-induced oral mucositis is mitigated by IL-17 receptor signaling. Front Immunol 12: 687627, 2021.
145. Schültke E, Bayat S, Bartzsch S, Bräuer-Krisch E, Djonov V, Fiedler S, Fernandez-Palomo C, Jaekel F, Pellicioli P, Trappetti V and Hildebrandt G: A mouse model for microbeam radiation therapy of the lung. Int J Radiat Oncol Biol Phys 110: 521-525, 2021.
146. Seo KJ, Alam MR, Abdul-Ghafar J, Kim SW, Kim HK, Choi HH, Sin SH, Lee HK and Chae HS: Tranilast treatment prevents chronic radiation-induced colitis in rats by inhibiting mast cell infiltration. Pharmacology 110: 77-86, 2025.

147. Sharma AK, Kalonia A, Kumar R, Kirti, Shaw P, Yashvarddhan MH, Vibhuti A and Shukla SK: Alleviation of radiation combined skin injury in rat model by topical application of ascorbate formulation. Int J Radiat Biol 100: 689-708, 2024.
148. Shi XY, Zhu YQ, Liang CJ, Chen T, Shi Z and Wang W: Single-cell transcriptomic analysis of radiation-induced lung injury in rat. Biomol Biomed 24: 1331-1349, 2024.
149. Siemionow M, Cyran M, Stawarz K, Chambily L and Kusza K: Transplantation of donor-recipient chimeric cells restores peripheral blood cell populations and increases survival after total body irradiation-induced injury in a rat experimental model. Arch Immunol Ther Exp (Warsz) 72, 2024.
150. Singh VK, Fatanmi OO, Wise SY, Carpenter AD, Janocha B and Seed TM: Novel biomarkers for acute radiation injury and countermeasures using large and small animal models and multi-omics approach. Radiat Prot Dosimetry 199: 1526-1532, 2023.
151. Singh VK and Seed TM: New opportunities and current challenges using animal models for the discovery of novel countermeasures for acute radiation syndrome. Expert Opin Drug Discov 20: 1045-1060, 2025.
152. Singh VK, Srivastava M and Seed TM: Protein biomarkers for radiation injury and testing of medical countermeasure efficacy: Promises, pitfalls, and future directions. Expert Rev Proteomics 20: 221-246, 2023.
153. Slautin V, Ivanov V, Bugakov A, Chernysheva A, Gavrilov I, Maklakova I, Bazarnyi V, Grebnev D and Kovtun O: Preconditioning with rapamycin improves therapeutic potential of placenta-derived mesenchymal stem cells in mouse model of hematopoietic acute radiation syndrome. Int J Mol Sci 26: 4804, 2025.
154. Stabinska J, Piccolo J, Chhabra A, Liatsou I, Gabrielson K, Li Z, Mohanta Z, Sedaghat F, Hobbs RF, Sgouros G and McMahon MT: MRI detects tubulointerstitial changes in mouse models of radiation-induced nephropathy. Magn Reson Med 94: 251-261, 2025.
155. Stouten S, Verduyn Lunel S, Finnon R, Badie C and Dekkers F: Modeling low-dose radiation-induced acute myeloid leukemia in male CBA/H mice. Radiat Environ Biophys 60: 49-60, 2021.
156. Wang Q, Wang Y, Du L, Xu C, Liu Q and Fan S: The effects of melatonin administration on intestinal injury caused by abdominal irradiation from mice. Int J Mol Sci 22: 9715, 2021.
157. Wang Q, Wang Y, Du L, Xu C, Liu Y, Liu Q and Fan S: Quantitative proteomic analysis of the effects of melatonin treatment for mice suffered from small intestinal damage induced by γ-ray radiation. Int J Radiat Biol 97: 1206-1216, 2021.
158. Wang X, Yuan R, Miao L, Li X, Guo Y and Tian H: Protective mechanism of a novel aminothiol compound on radiation-induced intestinal injury. Int J Radiat Biol 99: 259-269, 2023.
159. Wang Y, Cheng Y, Zhang P, Huang D, Zhai X, Feng Z, Fang D, Liu C, Du J and Cai J: FG-4592 protected haematopoietic system from ionising radiation in mice. Immunology 172: 614-626, 2024.
160. Wang Y, Wang X, Liu Z, Li Y, Lu H, Mo D and Wang D: Establishment of an osteoradionecrosis model and its mechanism via single ionizing radiation exposure. Int Dent J 75: 1672-1682, 2025.
161. Wang YM, Xin T, Deng H, Chen J, Tang SL, Liu LS and Chen XL: Keratin/chitosan film promotes wound healing in rats with combined radiation-wound injury. J Mater Sci Mater Med 36: 15, 2025.
162. Wu S, Tian C, Tu Z, Guo J, Xu F, Qin W, Chang H, Wang Z, Hu T, Sun X, *et al*: Protective effect of total flavonoids of Engelhardia roxburghiana Wall. leaves against radiation-induced intestinal injury in mice and its mechanism. J Ethnopharmacol 311: 116428, 2023.
163. Wu T and Orschell CM: The delayed effects of acute radiation exposure (DEARE): Characteristics, mechanisms, animal models, and promising medical countermeasures. Int J Radiat Biol 99: 1066-1079, 2023.
164. Xia C, Shao L, Ma L, Gao Y, Xin Y, Chen K and Dong L: Captopril alleviates radiation-induced pulmonary fibrosis by suppressing PAI-1 expression and cytoskeleton-dependent epithelial-to-mesenchymal transition. Eur J Pharmacol 1005: 178045, 2025.
165. Xiao M, Li X, Wang L, Lin B, Zhai M, Hull L, Zizzo A, Cui W and Kiang JG: Skin wound following irradiation aggravates radiation-induced brain injury in a mouse model. Int J Mol Sci 24: 10701, 2023.
166. Xie LW, Lu HY, Tang LF, Tang FL, Zhu RQ, Wang DF, Cai S, Tian Y and Li M: Probiotic consortia protect the intestine against radiation injury by improving intestinal epithelial homeostasis. Int J Radiat Oncol Biol Phys 120: 189-204, 2024.
167. Xu J, Yang X, Pu K, Zhang Q, Wei Q, Ma X and He Z: Cynaroside alleviates radiation-induced intestinal injury by inhibiting dynamin 2. Int Immunopharmacol 162: 115167, 2025.
168. Yang B, Wei R and Dai J: Deep learning applications in motion management for radiotherapy. Intell Oncol 1: 244-255, 2025.
169. Xu T, Chakraborty S, Wei D, Tran M, Rhea R, Wei B, Nguyen P, Gagea M, Xie X, Wu L, *et al*: Evaluation of the protective effect of Compound Kushen Injection against radiation-induced lung injury in mice. Mol Med Rep 31: 88, 2025.
170. Xu W, Gao L, Zou W, Tang X, Nian W, Zheng W, Huang R and Wang P: Compound kushen injection improves radiation enteritis via cannabinoid receptor 1 in rats. BMC Complement Med Ther 25: 70, 2025.
171. Xu Y, Tu W, Sun D, Chen X, Ge Y, Yao S, Li B, Zhang Z and Liu Y: Nrf2 alleviates radiation-induced rectal injury by inhibiting of necroptosis. Biochem Biophys Res Commun 554: 49-55, 2021.
172. Yan T, Yang P, Bai H, Song B, Liu Y, Wang J, Zhang Y, Tu W, Yu D and Zhang S: Single-cell RNA-Seq analysis of molecular changes during radiation-induced skin injury: the involvement of Nur77. Theranostics 14: 5809-5825, 2024.
173. Zeng Q, Cheng J, Wu H, Liang W and Cui Y: The dynamic cellular and molecular features during the development of radiation proctitis revealed by transcriptomic profiling in mice. BMC Genomics 23: 431, 2022.
174. Zhai S, Xu H, Xue J, Gan L, Gao F and Hu L: Resveratrol reduces radiation-induced liver damage and fibrosis, and may be related to inhibiting cellular aging and reducing inflammation. Innate Immun 31: 17534259251352623, 2025.
175. Zhang J, Li K, Zhang Q, Zhu Z, Huang G and Tian H: Polycysteine as a new type of radio-protector ameliorated tissue injury through inhibiting ferroptosis in mice. Cell Death Dis 12: 195, 2021.
176. Zhang K, Ren L and Zhai Y: Effect and mechanism of Nintedanib on acute and chronic radiation-induced lung injury in mice. PLoS One 20: e0324339, 2025.
177. Zhang LL, Xu JY, Xing Y, Wu P, Jin YW, Wei W, Zhao L, Yang J, Chen GC and Qin LQ: Lactobacillus rhamnosus GG alleviates radiation-induced intestinal injury by modulating intestinal immunity and remodeling gut microbiota. Microbiol Res 286: 127821, 2024.
178. Zhang M, Lan H, Jiang M, Yang M, Chen H, Peng S, Wang X, Zhang Y, Huang X, Li L, *et al*: NLRP3 inflammasome mediates pyroptosis of alveolar macrophages to induce radiation lung injury. J Hazard Mater 484: 136740, 2025.
179. Zhang R, Xie K, Lian Y, Hong S and Zhu Y: Dexmedetomidine ameliorates X-ray-induced myocardial injury via alleviating cardiomyocyte apoptosis and autophagy. BMC Cardiovasc Disord 24: 323, 2024.
180. Zhang T, He R, Ding X, Zhao M, Wang C, Zhu S, Liao Y, Wang D, Wang H, Guo J, *et al*: Fullerenols mitigate radiation-induced myocardial injury. Adv Healthc Mater 12: e2300819, 2023.
181. Ni J, Guo T, Zhou Y, Jiang S, Zhang L and Zhu Z: The role of cGAS-STING pathway in the development of radiation-induced lung injury. J Cancer Res Clin Oncol 151: 48, 2025.
182. Zhao Z, He D, Wang J, Xiao Y, Gong L, Tang C, Peng H, Qiu X, Liu R, Zhang T and Li J: Swertiamarin relieves radiation-induced intestinal injury by limiting DNA damage. Mol Cell Biochem 480: 2277-2290, 2025.
183. Zhi Y, Chen H, Huang Y, Li L, Chen Z, Huang H, Ke F, Guo Y and Chen C: Novel NLRP3 inhibitors mitigate acute radiation-induced lung injury by suppressing pyroptosis in alveolar epithelial cells. Toxicol Appl Pharmacol 502: 117458, 2025.
184. Zhu R, Li M, Wang D, Liu C, Xie L, Yang Y, Gu X, Zhao K, Tian Y and Cai S: USP15 regulates radiation-induced DNA damage and intestinal injury through K48-linked deubiquitination and stabilisation of ATM. Mol Med 30: 205, 2024.
185. Zhu S, Liang J, Zhu F, Zhang X, Xu M, Zhao K, Zeng L and Xu K: The effects of myeloablative or non-myeloablative total body irradiations on intestinal tract in mice. Biosci Rep 41: BSR20202993, 2021.
186. Strandberg J, Louie A, Lee S, Hahn M, Srinivasan P, George A, De La Cruz A, Zhang L, Hernandez Borrero L, Huntington KE, *et al*: TRAIL agonists rescue mice from radiation-induced lung, skin, or esophageal injury. J Clin Invest 135: e173649, 2025.

187. Su L, Dong Y, Guan B, Wang Y, Lu Y, Wang X, Li W, Huo Q, Meng A and Li D: GSDME knockout alleviates hematopoietic stem cell irradiation injury and aggravates myeloid-biased differentiation. Front Cell Dev Biol 13: 1544320, 2025.
188. Su L, Dong Y, Wang Y, Wang Y, Guan B, Lu Y, Wu J, Wang X, Li D, Meng A and Fan F: Potential role of senescent macrophages in radiation-induced pulmonary fibrosis. Cell Death Dis 12: 527, 2021.
189. Sun M, Zhao B, Wang C, Ma S, Shen Z, Xi J, Zhou J, Jia Y and Yue W: RNA-Seq reveals Th17 cell differentiation pathway as a mechanism of radiation-induced brain injury. J Vis Exp, 2025.
190. Suzuki K, Imaoka T, Tomita M, Sasatani M, Doi K, Tanaka S, Kai M, Yamada Y and Kakinuma S: Molecular and cellular basis of the dose-rate-dependent adverse effects of radiation exposure in animal models. Part I: Mammary gland and digestive tract. J Radiat Res 64: 210-227, 2023.
191. Suzuki K, Tsuruoka C, Morioka T, Seo H, Ogawa M, Kambe R, Imaoka T, Kakinuma S and Takahashi A: Combined effects of radiation and simulated microgravity on intestinal tumorigenesis in C3B6F1 $Apc^{Min/+}$ mice. Life Sci Space Res (Amst) 41: 202-209, 2024.
192. Takami M, Hara T, Okimoto T, Suga M, Fukuzawa K, Kiuchi K, Suehiro H, Akita T, Takemoto M, Nakamura T, *et al*: Electrophysiological and pathological impact of medium-dose external carbon ion and proton beam radiation on the left ventricle in an animal model. J Am Heart Assoc 10: e019687, 2021.
193. Tang LF, Tang FL, Zhou H, Li ZK, Pi CQ, He Y and Li M: Bacillus coagulans BC99 protects ionizing radiation-induced intestinal injury and modulates gut microbiota and metabolites in mice. Mol Nutr Food Res 69: e70057, 2025.
194. Tekin YB, Tumkaya L, Mercantepe T, Topal ZS, Samanci TC, Yilmaz HK, Rakici S and Topcu A: Evaluation of the protective effect of coenzyme Q10 against x-ray irradiation-induced ovarian injury. J Obstet Gynaecol Res 50: 1242-1249, 2024.
195. Thandar M, Zhang L, Yang X, Chi P and Li Y: Proteomics analysis revealed the therapeutic role of adipose-derived mesenchymal stem cells on radiation-induced colorectal fibrosis in rats. Biomed Pharmacother 182: 117763, 2025.
196. Thrall KD, Mahendra S, Lovaglio J and Jackson MK: The impact of supportive care on survival in large animal models of total body irradiation. Int J Radiat Biol 97 (Suppl 1): S88-S99, 2021.
197. Tranquilan-Aranilla C, Barba BJ, Relleve L, Estacio MA and Abad L: Hemostatic efficacy evaluation of radiation-crosslinked carboxymethyl cellulose granules and kappa-carrageenan/polyethylene oxide/polyethylene glycol dressing in rat bleeding models. J Biomater Appl 35: 1143-1152, 2021.
198. Tsogbadrakh B, Lee M, Jung JA, Choi YK, Lee YJ and Seo JH: A novel mouse model of image-guided radiation-induced acute kidney injury using SARRP. Biochem Biophys Res Commun 745: 151264, 2025.
199. Tu S, Huang Y, Tian H, Xu L, Wang X, Huang L, Lei X, Xu Z and Liu D: Berberine enhances the function of intestinal stem cells in healthy and radiation-injured mice. Int Immunopharmacol 136: 112278, 2024.
200. Tu W, Tang S, Yan T, Feng Y, Mo W, Song B, Wang J, Cheng S, Geng F, Shi Y, *et al*: Integrative multi-omic analysis of radiation-induced skin injury reveals the alteration of fatty acid metabolism in early response of ionizing radiation. J Dermatol Sci 108: 178-186, 2022.
201. Tzelnick S, Mizrachi A, Barkan N, Shivatzki S, Yosefof E, Hikri E, Attias J and Hilly O: The protective effect of aspirin-induced temporary threshold shift in an animal model of cisplatin-related ototoxicity. J Cancer Res Clin Oncol 149: 2009-2016, 2023.
202. Udho EB, Huebner SM, Albrecht DM, Matkowskyj KA, Clipson L, Hedican CA, Koth R, Snow SM, Eberhardt EL, Miller D, *et al*: Tumor aggressiveness is independent of radiation quality in murine hepatocellular carcinoma and mammary tumor models. Int J Radiat Biol 97: 1140-1151, 2021.
203. Ueda Y, Omiya S, Pinney J, Bylicky MA and Aryankalayil MJ: Liver quad culture chip as a model for radiation injury research. Sci Rep 15: 12414, 2025.
204. Vitali R, Palone F, De Stefano I, Fiorente C, Novelli F, Pasquali E, Fratini E, Tanori M, Leonardi S, Tanno B, *et al*: Characterization of early and late damage in a mouse model of pelvic radiation disease. Int J Mol Sci 24: 8800, 2023.
205. Walls GM, Ghita M, Herron B, Edgar KS, Kuburas R, Watson CJ, Grieve DJ, Cole AJ, Jain S and Butterworth KT: A multimodality assessment of the protective capacity of statin therapy in a mouse model of radiation cardiotoxicity. Radiother Oncol 190: 110004, 2024.
206. Walls GM, O'Kane R, Ghita M, Kuburas R, McGarry CK, Cole AJ, Jain S and Butterworth KT: Murine models of radiation cardiotoxicity: A systematic review and recommendations for future studies. Radiother Oncol 173: 19-31, 2022.
207. Wang C, Wu Y, Liu C, Li Y, Mi S, Yang X, Liu T, Tian Y, Zhang Y, Hu P, *et al*: Nervonic acid alleviates radiation-induced early phase lung inflammation by targeting macrophages activation in mice. Front Immunol 15: 1405020, 2024.
208. Wang J, Wang T, Zhu L, Wang J, Gao Q, Guo L, Lv G, Zhang W, Zhang Z, Yang C, *et al*: The emerging role of IL-22 as a potential radiosensitivity biomarker for radiation-induced intestinal injury. Int Immunopharmacol 155: 114573, 2025.
209. Wang L, Lin B, Zhai M, Hull L, Cui W and Xiao M: Endothelial dysfunction and impaired wound healing following radiation combined skin wound injury. Int J Mol Sci 25: 12498, 2024.
210. Wang L, Wang A, Fu Q, Shi Z, Chen X, Wang Y, Xu W, Wang T, Zhang S and Hu S: Ferroptosis plays an important role in promoting ionizing radiation-induced intestinal injuries. Biochem Biophys Res Commun 595: 7-13, 2022.
211. Wang L, Zhai M, Lin B, Cui W, Hull L, Li X, Anderson MN, Smith JT, Umali MV, Jiang S, *et al*: PEG-G-CSF and L-citrulline combination therapy for mitigating skin wound combined radiation injury in a mouse model. Radiat Res 196: 113-127, 2021.
212. Wang Q, Duan J, Hong J, Ding K, Tai F, Zhu J, Fu H, Zheng X and Ge C: Toll-like receptor agonist CBLB502 protects against radiation-induced intestinal injury in mice. In Vivo 38: 1636-1648, 2024.