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A review of radiation-induced alterations of multi-omic profiles, radiation injury biomarkers, and countermeasures

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Abstract

Increasing utilization of nuclear power enhances the risks associated with industrial accidents, occupational hazards, and the threat of nuclear terrorism. Exposure to ionizing radiation interferes with genomic stability and gene expression resulting in the disruption of normal metabolic processes in cells and organs by inducing complex biological responses. Exposure to high dose radiation causes acute radiation syndrome, which leads to hematopoietic, gastrointestinal, cerebrovascular, and many other organ-specific injuries. Altered genomic variations, gene

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SS, NKM, and NNV performed literature search, compiled the results and wrote the manuscript. LC, TH, RP, REOD, DBB and KWB provided valuable feedback and direction throughout the study that helped improve the content of the manuscript. VKS provided supporting data and critical input to improve the manuscript. CG conceived, coordinated and supervised the study and wrote sections of the manuscript.

expression, metabolite concentrations, and microbiota profiles in blood plasma or tissue samples reflect the whole-body radiation injuries. Hence, multi-omic profiles obtained from high-resolution omics platforms offer a holistic approach for identifying reliable biomarkers to predict the radiation injury of organs and tissues resulting from radiation exposures.

In this review, we performed a literature search to systematically catalog the radiation-induced alterations from multi-omic studies and the radiation countermeasures. We covered the radiation-induced changes in the genomic, transcriptomic, proteomic, metabolomic, lipidomic, and microbiome profiles. Furthermore, we have covered promising multi-omic biomarkers, FDA-approved countermeasure drugs, and other radiation countermeasures that include radioprotectors and radiomitigators. This review presents an overview of radiation-induced alterations of multi-omics profiles and biomarkers, and associated radiation countermeasures.

Keywords

Radiation damage; DNA damage repair; radiomitigators; radioprotectors; multi-omics; radiation biomarkers

Introduction:

Exposure to high dose ionizing radiation (IR) causes complex cellular damage at the molecular level (1). Acute radiation syndrome (ARS) occurs due to total body exposure to high doses of IR or with long term exposure of significant doses to partial body condition. Radiation-induced DNA damage poses both direct and indirect consequences.

Direct consequences result when organic molecules absorb the radiation energy (DNA, proteins, or metabolites), leading to point mutations, DNA strand breaks, DNA crosslinks, chromosomal aberrations, protein modifications, and metabolite alterations (Figure 1). If such alterations are unrepaired, they can cause permanent cellular damage or cell death (2). Indirect biological effects of radiation exposure occur when water molecules in cells are oxidized and/or ionized through radiolysis. The free radicals and peroxides produced by this process interact with the surrounding cellular components causing cellular damage (3). Radiolysis results in the formation of free radicals, such as hydroxyl radical, superoxide radical anion, and hydrogen radicals, and their derivative non-radical species such as hydrogen peroxide, peroxynitrite, and ozone; all of which can lead to DNA damage. The extent of DNA damage caused by free radicals or reactive oxidants includes single-strand breaks, double-strand breaks, amplified damaged sites, base modifications, and adduct formation, which are often more significant than the direct action of radiation (4).

Identification of early radiation response genes by using RNAseq and whole human genome DNA-microarrays have been major approaches to study radiation biology. Currently, there are several approaches for screening biomarkers of IR, which involve measuring blood cell counts, protein concentrations, or gene expression, and cytogenetic approaches in irradiated cells. In addition to tracking DNA lesions and DNA repair proteins, other radiation-induced changes such as genome-wide copy number variants (CNVs) and mutations have also been exploited as radiation biomarkers. CNV changes after radiation exposure are distributed non-randomly across the genome and are also found recurrent in some loci. Genome-wide hotspots that harbor recurrent CNVs have been effectively utilized as biomarkers of radiation exposure (5). Chromosomal microarray analysis (CMA), single nucleotide polymorphism (SNP) arrays, comparative genome hybridization (CGH) arrays, or Next-generation genome sequencing methods were utilized for studying genome-wide CNV changes and quantifying the exposure (6, 7). Similarly, germline mutations in the offspring of individuals exposed to radiation were used as biomarkers for estimating parental radiation exposure and biomonitoring (8).

A detailed account of different exposure sources and resulting damages on DNA, proteins, metabolites, and the microbiome is depicted in Figure 1. This review covers the consequences of radiation on genomic, transcriptomic, metabolomic, proteomic, and microbiome profiles. We performed a literature search to cover radiation-based omics studies to identify biomarkers. Specifically, the keywords such as “gene/miRNA/protein biomarkers in radiation”, “omic-based biomarkers in radiation injuries”, “radiation omics”, and “radiation countermeasures”, “radiation drugs” were used to search the literature. The information on omics-based biomarkers and radiation drugs studied in any injured tissue/organ in human, mouse, nonhuman primates (NHPs), or any other model organism, were saved. In the latter part of the review, we focused on the literature covering the promising radiation countermeasures that include both radioprotectors and radiomitigators. Hundreds of abstracts extracted from keyword searches were manually curated for their suitability and included in the present review.

Radiation-induced genomic alterations:

Experiments in a controlled setting exploring the impact of IR on laboratory animals or cell lines can help understand the extent of radiation damage possible in humans. A genome-wide study on the impact of IR on germline changes in mice noted increased *de novo* CNVs and indels in offspring due to irradiation at 3 Gy (9). This study also identified a significantly higher number of clustered mutations in the progeny of irradiated male mice. A signature of radiation exposure is the association of these mutations with clustered damage sites. These clustered DNA lesions occur within one or two helical turns of DNA, i.e., within a short distance. DNA lesions are mostly seen as an aftermath of radiation exposure. Complex double-stranded and single-stranded DNA breaks and clustered mutations in specific genomic areas are the most damaging as the repair process of these types of changes are challenging. Single-stranded DNA breaks in the clustered damage sites can lead to inefficient base excision repair pathways resulting in persistent lesions during subsequent replication cycles (10, 11). Complex clusters of DNA lesions caused by IR initiate further mutagenesis and genomic instability, which could eventually lead to cell death (12). This property of IR is exploited in medicine to target and kill tumor cells. The increased number of DNA breaks induced by γ-radiation (<2.0 Gy) and the increased replication rate in tumor cells act in synergy to eliminate cancerous cells (13). Cells with a high proliferation rate are prone to radiation-induced DNA damage clusters (14), suggesting that different tissues might respond to different dose, dose rates, and radiation quality.

In vitro studies have also demonstrated the ability of radiation exposure to induce CNVs (5, 15). Experiments conducted on human fibroblast cells detected genome-wide distributions of CNVs associated with radiation exposure (<=3 Gy), with several hotspots corresponding to aphidicolin (APH) and hydroxyurea (HU) induced replication stress (5). This study also reported a higher percentage of duplications than other stressors and that CNVs were detected more than seven days post-exposure. The aftermath of radiation exposure on the germline of male mice identified an eight-fold increase in CNVs in offspring, indicating a transgenerational impact (9). Several other studies using different radiation sources, such as laser-driven electron accelerators or X-rays, identified increasing CNVs in chromosome hotspots (15, 16). It was also observed that radiation-induced tumors in Trp53 mutant mice developed CNV changes in chromosome hotspots associated with specific tumor types (7). For example, radiation-induced mammary tumors exhibited amplification of the MET locus on chromosome 6. Consistent with this observation, radiation-induced gliomas in Trp53/PTEN mutant mice also developed recurrent amplification of the locus containing the RTK and MET gene in chromosome 6 (17), changes that were associated with cancer stem cell maintenance in both of these cancers (18, 19).

High doses of **γ**-radiation on hematopoietic cells induced gene fusions associated with leukemogenesis, including AML1-ETO, BCR-ABL, DEK-CAN, and DEK-ABL, indicated that DNA breakage and misrepair is a significant risk factor for leukemia (20). Low and therapeutic dose radiation on hematopoietic stem and progenitor cells (HSPC) isolated from human umbilical cord blood also led to increased formation of preleukemic fusion genes associated with radiation-induced DNA damage (21). A significant increase in BCR-ABL fusion was reported in this study compared to controls, suggesting that the risk of developing leukemia exists even at low radiation doses.

Exposure to high-intensity radiation is also known to cause excessive skin damage. A study investigating the impact of **γ**-irradiation (53 Gy, dose rate 0.6 Gy/minute) on minipig skins found elevated apoptosis and weakened stem cell replication after irradiation (22). A higher percentage of γH2AX phosphorylation and increased frequency of radiation-induced 53PB1 foci indicated radiation-induced DNA damage. Extensive radiation-induced fibrosis (RIFs) persisted for weeks in a minor fraction of cells (<1%) and reflect the complex DNA damage, including single-strand and double-strand DNA breaks, and base lesions that are refractory to DNA repair mechanisms. A similar observation of persistent RIFs after low-intensity *in vivo* irradiation of human skin was observed 24 h after 4 Gy exposure with significant inter-individual variation in RIF levels that could be associated with differences in DNA repair mechanisms (23).

Recent advancements that aid in studying three-dimensional (3D) DNA organization have helped the research community to understand the effect of radiation stress on genome-wide 3D organizational structure. CCCTC-binding factor (CTCF) and cohesin, involved in chromatin organization, are early responders to DNA damage induced by radiation (24, 25). In this context, incipient role of G protein-coupled receptors (GPCRs) signaling system in DNA damage response has opened up a new direction to controlling the damage due to radiation and subsequently developing target-specific therapeutics (26). A previous study showed that protein G2A (member of GPCR family) responds to DNA damages when induced in lymphocytes (27). Similariliy, the combined role of GPCR relaxin family peptide 3 receptor (RXFP3) and GPCR interacting protein 2 (GIT2) in response to oxidative stress and DNA damage have been identified by Gastel and collegues (28, 29). These studies also concluded that RXFP3-GIT2 system plays a significant role in regulating cellular degrdation associated with DNA damage. Nevertheless, further studies are needed to identify the involvement of GPCRs in radiation-caused DNA damage. There are currently no reports that explore the consequences of γ-radiation on chromatin organization, but one study revealed the ability of 5 Gy X-ray irradiation to induce changes in the genome-wide 3D organization in human fibroblasts and lymphoblastoid cells (30). A strengthening of topologically associating domain (TAD) formation was observed after X-ray exposure, suggesting noticeable 3D genome changes after exposure. TADs, formed through the interaction of CTCF, play a crucial role in bringing genes and regulatory elements in close contact with each other, leading to preserving genome integrity after irradiation. This impact lasted for days and was more pronounced in lymphoblastoid cells than in fibroblasts (30), pointing to differences in radiosensitivity across cell types. This study also linked the structural change to the Ataxia Telangiectasia Mutated (ATM) DNA repair pathway. These reports noted that radiation-induced DNA damage was extensive and included point mutations, DNA breaks, and changes in the genome-wide 3D organization, highlighting the importance of functional DNA repair mechanisms to mitigate against the lasting effects of such radiation-induced genomic insults.

Transcriptomic changes induced by radiation:

Messenger RNA (mRNA)-expression:

Genome-wide expression analysis of the peripheral blood (PB) in different mammalian systems has shown radiation-induced alterations at different exposure intensities. Experiments in partial-body irradiated at 0.5 Gy, 2 Gy and 10 Gy mice identified PB expression signatures that differentiated radiation damage with 79–100% accuracy (31). Additional studies on global gene expression profiles in the blood of male C57BL/6 mice identified a 74-gene signature associated with moderate to low radiation doses (at 0.5, 2, 5, and 8 Gy). More than one-third of these genes were regulated by TP53, suggesting that TP53 plays a vital role in radiation responses (32). The most marked response was in genes associated with natural killer (NK) cell functions, reflecting a relative loss of NK cells from the population. T- and B-cell mediated immunity genes were also significantly influenced by 48 h after γ-ray irradiation (0, 0.5, 2, 5, 8 Gy). Downregulation of NK-cytotoxicity-associated genes was observed, including NKG7, GNLY, and GZMA (33). Several of these genes were further validated in independent studies, including human PB, indicating that these genes could be further explored as reliable radiation biomarkers (34, 35) (Table 1). Other reports that analyzed the global expression profile of irradiated mice have identified trends in gene expression. An increasing number of genes were differentially expressed within days after irradiation with 2, 3, and 5 Gy, and gene expression increased with increasing radiation doses (21). Specifically, the expression of SLC25A51 and CCNA2 showed an initial suppression followed by recovery of the transcript levels by seven days after exposure to mice with doses less than 10 Gy (21). Another study focused on differential expression of genes in mice after irradiation at 4 and 8 Gy found many upregulated genes including CDKN1A, MDM2, BBC3, and CCNG1, and downregulated genes including TCF4 and MYC. The same study also identified genes, DDB2, PCNA, GADD45A, SESN1, RRM2B, KCNN4, IFI30, and PTPRO, which are downregulated in mice but uprgulated in human (36). The differnence in gene expression were also observed in wild-type C57BL/6 (8 Gy) and DNA double-strand break repair-deficient Atm−/− (4 Gy) and Prkdcscid (3 Gy) mutants of C57BL/6, concluding that regulators including TP53 and NFκB are activated by radiation exposure only in wild type mice (37). The study further identified that mutant strains show inflammatory responses after radiation exposure. The source of the radiation can be a key factor for the transcriptomic changes, as discussed by Broustas et al., 2017, based on the experiments where 7,285 and 5,045 genes were differentially expressed in irradiated blood of mice at 0.25 or 1 Gy of neutron or 1 or 4 Gy x-ray radiation, respectively (38). Similarly, effects of age on transcriptomics profile have been observed after irradiating (4 Gy x-rays) young (2 months) and old (21 months) male mice for 24h. The microarray-based gene expression analysis suggested that young mice were more active against radiation by upregulating pathways related to apoptosis and phagocytosis. The pathways associated with fibroblast growth factor signaling were underrepresented in old mice, while hematologic malignancies related pathways were enriched (39).

In a *ex vivo* irradiated (0.56 Gy, 2.23 Gy and 4.45 Gy, acute dose rate = 1.03 Gy/min, low dose-rate = 3.1 mGy/min) human whole blood, 454 genes were differentially expressed 24h after exposure to all doses, while 598 genes were differentially expressed after acute exposure. These genes were mainly enriched in functions related to immune response, B-cell mediated immunity, cell-to-cell signaling, and natural killer cell activation (40). Similarly, in the whole-thorax irradiated (single dose of 10 Gy) NHP, 1,187 mRNA transcripts were significantly dysregulated 30 days after exposure. The differentially regulated genes mostly belonged to functions related to immune responses (41). The transcriptomics effect of radiation dose (2.5 Gy and 0.1 Gy of low-LET protons) were also observed in a human three dimensional tissue model EPI-200 at 4, 16 and 24 h after exposure. The study found that high dose reduced terminal differentiation and structural integrity, while low dose were mainly associated with recovery and tissue repair (42). A systematic review included 27 previous radiation-based studies and identified 27 potential genes that have significant correlation with radiation dose. Top five discriminatory genes, TNFSF4, FDXR, MYC, ZMAT3, and GADD45A were idenfied when compared between doses < 2 Gy and ≥ 2 Gy (43). The roles of several other long ncRNAs in radiation responses have been discussed in previous studies (44–46); however not covered in present review.

Experiments in NHPs, such as baboons, can model radiation-induced changes comparable to humans. Baboons that developed the clinically relevant disease, hematologic acute radiation syndrome (HARS, classified based on severity ranging from H1–3), had a persistent change in peripheral gene expression within 1 or 2 days post-irradiation to 2.5 or 5 Gy γ-radiation (57). Of these, three genes (WNT3, POU2AF1, and ZZZ3) showed a persistent change in gene expression over time. Several genes associated with immune-related functions that impact T-cell migration (CCR7, CD117) and T-cell responses (VSIG4), antimicrobial function (RNASE3), promotion of Interleukin-12 (IL-12) response signal transducer and activator of transcription 4 protein (STAT4), stimulation of B- and T-cells (SH2D1A), and initiation of apoptosis in pathogen-infected cells (GZMH) and cytolysis (PRF1, NCR3, and KLRF1) were associated with the radiation-induced response (58). Another study in the same mammalian system identified radiation-induced overexpression of genes involved in cell cycle regulation (CDCA7L), modification of the T-cell and B-cell immune responses (GBP2, GLUL, HERC5, and PPP3CC), erythropoiesis (GBP2), and cell migration of cancer and hematopoietic cells (HERC5, HMHA1) (59) when irradiated with 2.5 or 5 Gy. A recent study using NHPs showed that IL-3 signaling, ephrin receptor signaling, ErbB signaling, nitric oxide signaling in the cardiovascular system, Wnt/β-catenin signaling, and inflammasome pathways were associated with positive survival outcomes in NHPs after acute exposure to 6.5 Gy γ-radiation (96).

Experiments to study the effect of radiation (γ-rays of 0.1 Gy) on gene expression in a human myeloid tumor cell line (ML-1) identified genes that responded in a dose-dependent manner (72, 73). Among the set of genes identified in these studies (CDKN1A, GADD45, MDM2, ATF3, and BAX), CDKN1A, GADD45A, and MDM2 were also overexpressed with low-dose γ-radiation. Of the transcriptionally active genes identified after radiation exposure, induction of CDKN1A and GADD45A was proportional to exposure intensity. Another study that explored the transcriptional changes in human peripheral blood lymphocytes (PBL) also identified CDNK1A and GADD45A as radiation-induced genes after exposure to 2 Gy using X-ray (74). This study also identified a linear dose-dependent response in the expression of DDB2, CDKN1A, and XPC. Human PB signatures are of interest because radiation exposure biomarkers can distinguish between the irradiated and non-irradiated samples with 100% accuracy (54).

Exposure to high doses of γ-radiation (5, 10 and 20 Gy) in human lymphoblastoid TK6 cells elevated mRNA levels of GPX, GADD45, P21, and PCNA, moderately repressed XRCC1 expression, and strongly down-regulated the expression of KU80 (78). A similar observation was noted when non-immortalized T-cells were exposed to low to moderate γ-radiation doses (between 0.15–12 Gy), with transcriptional induction of several genes, including CDKN1A, GADD45A, TNFSF4, KIF20A, PSRC1, and CDCA3 (86). Another *in silico* network analysis identified eight ARS-associated genes (BRD4, NFKBIA, CDKN1A, TFPI, MMP9, CBR1, ZAP70, IDH3B) and confirmed through literature mining (69, 70). In these experiments, commonly studied genes such as CDKN1A and GADD45 in mice, NHPs, and human cell lines showed promise to be effectively utilized as radiation biomarkers.

MicroRNA (miRNA) expression: Serum microRNA (miRNA) signatures indicate the long-term impact of total-body irradiation (TBI, 6.5 Gy and 8 Gy) in mice when measured within 24 h of exposure (97). These miRNA signatures distinguished mice exposed to radiation from unirradiated animals, which correlated with the impact of irradiation on hematopoietic stem cells (HSCs). Several studies in mice have explored the miRNA signatures associated with radiation exposure. An analysis identified long term elevation of miR-21 in the brain when hippocampal cells and brain tissue from mice were irradiated at 0.5 Gy using X ray at different times for 1 year (98), and upregulation of miR-145 and miR-663 in AHH-1 cells and HPBLs, when irradiated at 4 Gy using γ-ray for 4 h or 24 h (99). Radiation-induced miRNA profiles were also found to be time- and dose-dependent. Serum miRNAs (miR-27a-3p, miR-187–3p, miR-30a-3p, and miR-30c-5p) were detectable within 24 h after radiation exposure in mice. Of these miRNAs, the expression of miR-30a-3p and miR-30c-5p were able to differentiate between radiation doses (6.5 Gy vs 8 Gy) after a week of post-exposure (97). The microRNAs were also correlated with injuries to human bone marrow cells bassed on serum profiling of mice exposed to sublethal (6.5 Gy) and lethal (8 Gy) doses of radiation (97). In a different study, 600 miRNAs from serum of irradiated (at 1 to 12 Gy) mice were compared in a dose dependent manner at time points of 24 and 48 hr (100). Similarly, serum miRNA signatures containing miR-130a-3p, miR-150-5p, miR-142-5p, miR-706, and miR-342-3p can be used to identify low-dose (2 Gy) radiation cohorts exposed to radiation within 24 h (97). The dose reconstruction algorithms that were developed based on serum miR-150-5p depletion normalized with miR-23a-3p in mouse models can approximate the absorbed dose at various time points during the recovery phase (101). Leukemia specimens from patients treated with fractionated radiation showed depletion of miR-150-5p in blood (101). Changes in plasma miRNAs such as miR-34a-5p, miR-100-5p, and miR-150-5p were associated with pro-inflammatory NF-κB-mediated functions as studied in heart and lung damaged C3H mouse after irradiation. In the same study, expression of miRNAs, miR-34b-3p, miR-96-5p, and miR-802-5p, were significantly altered in C57Bl/6 mice after exposing their heart and lung at 13.99 Gy (102). In a separate study using rats, miRNAs, miR-144-5p, miR-144-3p, miR-142-5p and miR-19a-3p, were differentially regulated in the blood after lung-specific injuries caused by a single dose of radiation at 15 Gy (dose rate of 1.43 Gy/min) radiation (103). miRNA miR-150 found in blood and lung also showed significant downregulation after thoracic irradiation in female WAG/RijCmcr rats (103). Similarly, thoracic exposure of NHPs to radiation causing injuries in lung and heart have shown differences in the expression profile of blood miRNAs, miR-199a-3p and miR-25-3p, after a single exposure to whole-thorax and lung irradiation (WTLI) at 9.8 or 10.7 Gy (104). In C3H mice afte whole thorax irradiation at dose 13.92 Gy, differentially expressed miRNAs miR-34a-5p, miR-100-5p, and miR-150-5p were identified associated with survival (102). These studies have improved our ability to consider circulatory miRNAs as organ-specific markers upon IR damage.

Similarly, microarray analysis identified seven miRNA signatures altered by irradiation at 5.8, 6.5, or 7.2 Gy (dose rate of 0.6 Gy/min) in NHPs (105). Conserved serum miRNA signatures have the potential to serve as predictive biomarkers for radiation injury in humans, NHPs, and mice. A combination of three miRNAs (miR-133b, miR-215, and miR-375) was found to identify radiated versus unexposed NHPs, accurately. Two microRNAs, miR-199a-3p and miR-25-3p, from blood of whole-thorax lung irradiated NHPs at 10.7 Gy were differentially expressed and associated with survival (104). Similarily in another study, microRNAs associated with neutropenia were identified in NHPs after TBI (at 2–6.5 Gy) and whole thorax lung irradiation (at 9.8 or 10.7 Gy) (106). Radiation-induced mortality could also be predicted by a five-miRNA (miR-133b, miR-215, miR-375,miR-126, and miR-30a) composite signature in macaques (105). The same study identified a set of two miRNAs (miR-30a and miR-126), which together can be used as a survival indicator (107).

Global miRNA expression changes measured in the PB of baboons within the days after irradiation at 2.5 or 5 Gy (dose rate- 0.08 Gy/min for 5 Gy TBI and 5 Gy 50% partial body irradiation, and 0.32 Gy/min for other) identified miR-425-5p expression that distinguished different HARS groups (108). Six miRNA species (miR-133, miR-124, miR-29c, miR-378, miR-574-3p, and rno-miR-7) were identified as promising candidates that can distinguish HARS groups with and without pancytopenia (59). Many miRNA species were already known to be linked with radiosensitivity (e.g., miR-22, miR-29c, miR-195, miR-212) or chemotherapy resistance (e.g., miR-331-5p). In particular, miR-212 involved in radiosensitivity and immune modulation was upregulated 48 to 77-fold over an extended period (60). Another study that compared radiation-induced global gene expression profiles in baboons when exposed to total-body radiation at 2.5 or 5 Gy (dose rate- 0.08 Gy/min for 5 Gy TBI and 5 Gy 50% partial-body irradiation, and 0.32 Gy/min for other), identified a significant downregulation of miR-342-3p, which allowed an almost complete separation of HARS categories (109). These miRNAs can be further explored as reliable radiation-biomarkers for accurate screening and evaluation of radiation exposure in humans.

A systematic review and meta-analysis study showed that seven miRNAs that include miR-150, miR-29a, miR-29b, miR-30c, miR-200b, miR-320a, and miR-30a showed significant correlation with given dose of radiation across different species that mainly include human, mouse, rat and NHPs (110, 111). These studies support the hypothesis that miRNAs from body fluids can be used as biomarkers for detecting organ-specific injuries caused by high dose radiation exposures. Studies in humanized mice engrafted with human CD34$^+$ HSCs showed that the expression profile of a serum miRNA signature containing miR-27a-3p, miR-187-3p, miR-30a-3p, and miR-30c-5p was altered in response to irradiation at 6.5 Gy and 8 Gy. This indicates that radiation-induced miRNA signatures may be conserved between mice and humans and can serve as viable biomarkers of radiation injury in humans, however, further studies are needed to validate their utility as biomarkers (97).

An extensive list of important mRNAs, miRNAs, and their tested effects in different animal models is provided in Table 1 and Table 2, respectively. The summary of miRNA and gene-based biomarkers studied in different animal models is illustrated in Figure 2A. Note that the overlap among the gene or miRNA biomarkers across the species is little to none warranting the need to further investigate and validate their utility as effective radiation biomarkers.

Radiation effects on mammalian microbiota: Microorganisms are essential to host cell maintenance in health and disease; therefore, the human gut microbiota has attracted increasing attention in recent years. The gastrointestinal (GI) tract hosts the largest and most diverse microbiome in the human body, where the microbiome plays a vital role in several metabolic processes that are essential for human health. ARS occurs after TBI, and death is frequently attributed to poor hematopoietic recovery and/or death of epithelial cells lining the GI tract. The GI tract is the fastest-renewing adult tissue, making it highly sensitive to radiation (125). It also harbors a diverse microbial community comprising 10 to 100 trillion microorganisms, raising the possibility that the gut microbiota is highly prone to radiation-induced damage (126–130). Although some studies have shown associations between gut microbiota and radiation-induced damage (130–132), possible mechanisms are poorly understood.

Most cancer patients undergoing pelvic irradiation experience side effects such as fatigue and diarrhea; however, the impact of radiation on the microorganisms colonizing the GI tract's mucosal surfaces is unexplored. Severe diarrhea may also complicate radiotherapy as there is no current clinical or experimental information on the role of gut microbiota in this pathogenesis. A study focusing on the fecal microbiota of patients receiving pelvic radiotherapy and suffering from acute post-radiotherapy diarrhea revealed changes in microbial diversity. In healthy volunteers and patients without diarrhea, microbial diversity was stable throughout the study. However, patients exhibiting diarrhea showed a progressive modification in their microbial diversity. Patients who developed diarrhea harbored bacterial phyla, *Actinobacteria*, and some Firmicutes, which were either not detected or least abundant in patients who did not develop diarrhea. On the other hand, patients who developed diarrhea had a reduced abundance of some Clostridia species, which are members of the phylum *Firmicutes* (131).

Irradiation-induced changes in the bacterial compositions of the large and small intestines at the genus level are one of the hallmarks of radiation injury. For instance, irradiation with a single dose of 8 Gy increased several genera, including *Alistipes, Lactobacillus,* and *Akkermansia* in the large intestine and *Corynebacterium* and *Turicibacter* in the small intestine. Compared with the corresponding unexposed control group, the abundance of the genera *Prevotella* was lower in the irradiated large intestine, while levels of *Alistipes* were lower in the irradiated small intestine (132).

The gut microbiota may contribute to radiation-induced pathogenesis, and it differs between patients with and without radiation enteropathy. Reports also indicated that microbial diversity decreased over time in patients with rising radiation enteropathy. A consistent association between bacterial diversity and late radiation enteropathy was observed, and higher counts of *Clostridium IV*, *Roseburia*, and *Phascolarctobacterium* were significantly associated with radiation enteropathy (133).

A study that analyzed 'elite survivors' in a population of mice that recovered from exposure to total-body radiation at high-dose (8.0 to 9.2 Gy) had overrepresented members of the bacterial taxa, *Lachnospiraceae* and *Enterococcaceae*. These microorganisms were associated with post-irradiation restoration of hematopoiesis and GI repair. These bacteria were also found to be more abundant in leukemia patients undergoing radiotherapy, who also displayed milder GI dysfunction (134). A different study in the radiation enteritis (RE) mice model, considering a single dose of 18 Gy X-ray irradiation at a rate of 5 Gy/min, identified an abundance of bacteria representing 12 genera from *Alloprevotella, Alistipes, Akkermansia, Bacteroides, Dubosiella, Eggerthellaceae, Enterococcus, Escherichia-Shigella, Lactobacillus, Lachnospiraceae, Muribaculaceae,* and *Rikenellaceae* after radiation exposure (135). These studies highlight the importance of GI microbiota in radiation-induced pathogenesis and potentially pave the way for novel treatment protocols involving alterations of human gut microbiota.

In a recent study, the bacterial 16S rRNA amplicon sequencing and untargeted metabolomics were accomplished to investigate the effects of BIO 300, a promising radiation countermeasure under advanced development, on the gut microbiome and metabolome of

CD2F1 male mice exposed to ^{60}Co gamma-radiation (9.2 Gy, 0.6 Gy/min, $LD_{70/30}$ dose). Irradiation changed the ratio of *Firmicutes/Bacteroidetes* and also decreased the relative abundance of *Lactobacillus* in BIO 300-treated as well as control mice after irradiation (136). The ratio returned to pre-irradiated levels in BIO 300-treated animals by day 14 post-irradiation. Concurrently, there was corrective shifts in metabolic pathways that were altered after radiation exposure. In brief, these results demonstrated that irradiation resulted in a relative depletion of commensals like *Lactobacillus* leading to an inflammatory metabolic phenotype in untreated control mice while the BIO 300-treated mice demonstrated alleviation of this condition by restoring normal gut microbiota.

Alterations to the gut microbiome of NHPs exposed to high doses of radiation detected several bacterial species. Post-irradiation, significant increases in the relative abundance of *Treponema* and *Helicobacter* genera were observed in rhesus macaques when exposed to 6.8 Gy of radiation (137). In another study, relative abundances of *Prevotella*, *Lactobacillus*, *Clostridium XIVa*, *Oscillibacter,* and *Treponema* were found to be highly correlated with radiation intensity. *Prevotella*, *Oscillibacter,* and *Treponema* were closely associated with the overall survival, while *Streptococcus* was associated with death in macaques (138). The Firmicutes/Bacteriodetes ratio, a factor related to the disruption of metabolic homeostasis, declined from 1.2 to below one post-radiation exposure at 7.4 Gy. *Actinobacillus*, *Bacteroides*, *Prevotella*, and *Veillonella* genera were significantly increased by more than 2-fold, and *Acinetobacter* and *Aerococcus* genera were diminished by greater than 10-fold post-irradiation (139).

Other omic profiles altered by radiation:

Altered lipid profiles:

Concerns over a potential exposure of IR in large populations have emphasized the need for rapid and reliable biodosimetry methods to determine the absorbed dose and required triage. Indirect consequences of radiation exposure include the generation of reactive oxygen species (ROS) through water hydrolysis, enhanced NADPH oxidase activity, compromised mitochondrial function leading to damaged cellular lipids. Since lipidomics is a powerful technique for large-scale identification and quantification of lipids, rapid identification of altered lipid molecules are promising biomarkers for biodosimetry.

Experiments conducted in mice and NHP models to characterize lipidomic profiles that respond to radiation exposure have helped identify important radiation biomarkers. A study that analyzed global lipid profiling from mouse serum identified significant molecular alterations following γ-radiation exposure. A Low-abundance of oxygenated, polyunsaturated fatty acids (PUFAs) was observed after irradiation at 8 Gy of γ rays (dose rate- 1.67 Gy/min). Exposure to γ-radiation induced a significant increase in the serum levels of phosphatidylcholines (PCs) and arachidonic acid, while levels of diacyl PCs carrying PUFAs were decreased (140).

Radiation exposure in NHPs caused significant perturbations in lipid metabolism, affecting all major lipid species, including free fatty acids, glycerolipids, glycerophospholipids, and esterified sterols. In particular, a significant increase in the levels of PUFA-containing lipids and polyunsaturated triglycerides in the serum of NHPs exposed to 10 Gy radiation was identified. These TGs contained primarily arachidonic acid and docosahexaenoic acid acyl moieties (141). Temporal changes in the serum lipidome from hours to days after radiation exposure in NHPs have also been reported. Marked lipidomic changes occurred within 24 h post-irradiation with 6.5 Gy, along with increased levels of cytokine, free fatty acids, monoacylglycerides, and C-reactive protein. Simultaneous decreases in di- and tri-acylglycerides, sphingomyelins, lysophosphatidylcholines, and esterified sterols were also observed in this study (142). Decreased sphingomyelins and increased levels of lysophosphatidylcholines may be important markers for biodosimetry within days following irradiation. The biphasic and dynamic alterations linked to radiation exposure in the serum lipidome emphasized the importance of determining the long-term temporal response of these promising radiation biomarkers (142).

Global lipidomic analysis using ultra-high performance liquid chromatography-mass spectrometry (UHPLC-MS) performed on intestinal tissue specimens from acute RE at 18 Gy X-irradiation at a dose rate of 5 Gy/min revealed distinct lipid metabolite fingerprints. Several lipids were significantly altered by the occurrence of peroxidation in the acute or chronic RE group compared with the control, which included glucosylceramide, phosphatidylethanolamine, lysophosphatidylcholine, lysophosphoglycerol, lysophosphatidyl-inositol, phosphatidylcholinephosphatidylglycerol, phosphatidylinositol, and sphingosine (135). Metabolism of sphingolipids is a very complex process that involves the catabolism of several lipids by enzymes such as glucosylceramide synthase and sphingosine kinase 1 (143). Though current technologies can perform lipid profiling for various exposure conditions, data interpretation becomes very difficult because of their complex biological roles; hence, lipid profiling is not widely used for biomarker identification in radiation studies.

Altered metabolic profiles:

The rapid identification of radiation-induced metabolomic markers in biological samples, such as urine, blood, tissue, and saliva, have also been investigated for developing countermeasures to a radiological or nuclear public health emergency (144). Radiation metabolomics has primarily focused on the mass spectrometry (MS) analysis of samples from radiation-exposed animals to monitor an altered biological response. In this manner, metabolic studies are valuable for understanding the systems-level biological impact of radiation exposure. Moreover, radiosensitive biodosimetry methods were developed to accurately measure exposure levels and understand the impact of radiation exposure on tissues and organs. Metabolomic studies helped to understand changes in metabolite levels in normal and irradiated organs in mice, NHPs, and humans. For example, Gao *et al.* measured 31 low molecular weight metabolites such as lactamide, 1,2,4-benzenetriol, taurine, and piperine to assess the metabolic changes in rat lungs when exposed to single dose of 10 or 20 Gy radiation (145). Similarly, age-dependent correlation was observed for N(1)-acetylspermidine and 2’-deoxyuridine, but a poor correlation for elevated xanthine and N(1)-acetylspermidine in older irradiated mice when exposed to 3 Gy γ-radiation (146). These findings suggested that aging might be associated with higher levels of oxidative stress and a decline in DNA damage-repair efficiency while also implying a specific role for polyamine metabolism. Other studies have identified a time- and dose-dependent response in the GI metabolites to 4–8 Gy of IR in mice (147) or in the urinary metabolites, β-thymidine and N-hexanoylglycine, in mice when exposed to doses of 0, 3 and 8 Gy (2.57 Gy/min) for 24 h (148). Altered metabolic profiles of tissues, including bone marrow, ileum, liver, muscle, and lung, were also observed within 12 h of radiation exposure (6 Gy, dose rate 0.92 Gy/min), which are associated with DNA methylation, energy metabolism, and amino acid metabolism (149). Li and colleagues analyzed T-cells from irradiated mice when exposed to 0.1, 0.5, or 3 Gy TBI at a dose rate of 1.7 Gy/min, and concluded that radiation effects were correlated with a decrease in key metabolic pathways such as glycolysis and energy metabolism (150).

A sex-specific study confirmed that thirteen dose-responsive metabolic biomarkers that include L-carnitine, xanthine, L-acetylcarnitine, and xanthosine were increased in male NHPs when exposed to 2, 4, 6, 7 and 10 Gy for 7 days (151). A follow-up study demonstrated that several derivatives of carnitine and acylcarnitines were also significantly altered in NHPs after exposure to γ-radiation (152). Numerous LC-MS-based studies have been used to measure radiation-induced metabolic markers pertaining to energy metabolism, DNA damage, organ injuries, and inflammation (153–155). Metabolic profiles have also been evaluated for their use in the therapeutic intervention of post-radiation exposure. There is a recent report for conducting a study in irradiated NHP to evaluate metabolic changes in plasma and plasma-derived exosomes. NHP were exposed to gamma-radiation and blood samples were collected at various time points in relation to 5.8 Gy or 6.5 Gy TBI. Exosomes were isolated and analyzed for untargeted metabolomic and lipidomic profiling. Plasma profiling demonstrated markers of dyslipidemia, inflammation and oxidative stress post-irradiation. Based on the differences in metabolite composition between plasma and exosomes, it was suggested that exosomal profiling may augment the identification of low abundance biomarkers that would otherwise be obscured in plasma (156). In another study with 7.2 Gy TBI NHP serum, authors reported temporal fluctuations of metabolites within 96 h post-irradiation and higher fold changes of altered metabolites at 7.2 Gy compared to 6.5 Gy at 24 h post-irradiation. These findings highlight the importance of biofluid collection timepoint for successful interpretation of serum metabolic profiles (157, 158). The profound elevation of long-chain acylcarnitines in irradiated NHPs across multiple tissue types underscored the role of this class of metabolites as a generic indicator of radiation-induced tissue injury (159).

Metabolomics studies have also been applied to biodosimetry-based analyses (160, 161). For example, in human cell line studies, depleted metabolites such as glutathione, adenosine monophosphate (AMP), and nicotinamide adenine dinucleotide (NAD) were linked to oxidative stress and DNA repair pathways 1 h after radiation exposure to IR doses of 0.5 to 8.0 Gy (162).

Low-dose irradiated human keratinocytes also exhibited a disruption in energy metabolism when exposed to 0.03, 0.1 and 2 Gy of X-ray for 3, 24 and 48 h (163). An integrated study involving transcriptomics and metabolomics of irradiated human bronchial epithelial (HBE) cells measured 326 differentially expressed genes and 147 altered metabolites 24 h after 4 Gy exposure. These omics results suggested that post-irradiation cellular metabolism may be regulated by p53 (164). There is also a report for metabolomic and lipidomic profiles in multiple tissues (liver, kidney, jejunum, heart, lung, and spleen) of NHP exposed to 7.2 Gy γ-TBI. There were robust metabolic changes in the kidney and liver and modest changes in other tissues. Overall, metabolomics has identified numerous potential biomarkers that may be useful for analyzing, diagnosing, or treating ARS or other symptoms of radiation exposure.

Altered proteomic profiles:

Like metabolomics profiling, proteomics analyses can also be exploited to measure the detrimental effects of radiation exposure. Radiation might alter regulatory networks or cause proteomic modifications such as decarboxylation, disulfide bonds, or aggregation (165) and subsequently affect the steady-state levels of specific proteins. Several studies have analyzed different tissues to measure changes in protein abundance resulting from radiation exposure. For example, 19 differentially expressed proteins associated with biological functions such as the DNA damage response, stress response, and cytoskeleton system were observed in the intestines of irradiated mice (exposure to 9 Gy for 24 h and 72 h) when analyzed using two-dimensional gel electrophoresis (166). A single dose exposure study on the liver proteome of mice (from 0.02 to 1 Gy) showed a remarkable downregulation of glycolysis and pyruvate dehydrogenase availability. A subsequent long-term outcome was an increase in liver inflammation (167). Another study focused on the spleen proteome of tocotrienol (GT3) treated mice 24 h prior to 7 Gy TBI, which showed a difference in the expression of several proteins, including the upregulation of Wnt signaling pathways (168). This study also identified significant alterations in the levels of metabolic enzymes such as aldehyde dehydrogenase and propionyl coenzyme A, guanylate cyclase, and glycine amidinotransferase, which suggested possible changes in the carbon and amino acid metabolism due to radiation. Other differentially expressed proteins suggested that cell signaling proteins attenuated radiation-induced injuries.

Previous studies characterized the radiation-induced proteome changes in different body fluids such as urine and blood plasma (169) from NHPs, when exposed to 6.7 Gy and 7.4 Gy doses of radiation (169, 170). Some of the differentially expressed proteins based on dose and time points in both the samples from the same animal included ferritin (F6ZV45), angiotensinogen preproprotein (G7MFR4), putative uncharacterized proteins (G7NQN4 and G7MJ28), angiotensin-converting enzyme isoform 1 (H9FJ99), and other uncharacterized proteins (F6TLR3, F7DHQ1, and F7GRY2). Further, the resulting urine proteome profile identified many proteins associated with cell adhesion, disease progression, and key metabolic pathways (170). Proteomic changes in the serum of high-dose irradiated NHPs after administrating BIO 300, a synthetic genistein nanosuspension, identified upregulated proteins, e.g., tubulin α chain (B3KT06), cDNA FLJ57036 (B4E3P1), CP protein (A5PL27), glutathione peroxidase (V9HWN8), carbonic anhydrase I (V9HWE3), glutathione S-transferase pi 1 (V9HWE9), which helped understand the metabolic changes associated with drug effects (171).

Several previous studies also focused on understanding the proteome changes in human tissues such as endothelial cells (exposure to <2.5 Gy of γ-radiation) (172, 173), peripheral lymphocytes (exposure to 1, 2, and 4 Gy γ-radiation) (174), skin fibroblast cell lines (exposure to 10 Gy γ-radiation) (175). Proteomics-based studies have also suggested that tumor-derived factors are upregulated by radiation exposure and may serve as potential therapeutic targets during radiation treatment (176). The changes in the proteomic profiles due to radiation exposure is associated with biological phenotype such as inflammation, toxicity, immune response and retinoic acid signaling in human (177, 178). Some studies have noted that protein expression changes were associated with radiotherapy and tumor resistance in different organs such as the breast, lungs, and brain (176, 179–182). A study that treated breast cancer cell lines with a single dose of 10 Gy of γ-radiation showed the top differentially regulated proteins such as C-type mannose receptor 2, arginino-succinate synthase 1, gelsolin, peroxiredoxin 5, and cathepsin D (183), while the lung cells in the same study showed cofilin-1, HSPB1, annexin A4, and vimentin as the top upregulated proteins (184). Overall, these reports have demonstrated the potential of proteins as reliable biomarkers for high-dose radiation exposure.

Radiation countermeasures: radioprotectors and radiomitigators

As discussed above, exposure to high or low doses of radiation can affect human health in many ways, primarily resulting in ARS, cutaneous radiation syndrome (CRS), neurovascular syndrome, or even death. These health effects are caused by radiation-induced damage such as genomic alterations or direct DNA damage, destruction of blood-forming stem cells, and damaging the immune system and other metabolic functions.

Current drug discovery efforts are focused on developing radioprotectors and radiomitigators for their use during pre- and post-radiation exposure treatments, respectively. To date, several agents have been tested as potential radioprotectors and/or radiomitigators to counter ARS. The manifestation of ARS is related to disorders of the GI, neurovascular, hematopoietic, and cutaneous systems (185).

Radiomitigators

Under this category, the thrombomodulin (Thbd)-activated protein C (aPC) pathway has been shown to stimulate blood cell production and help attenuate radiation injuries in mice (dose rates- 1.37 Gy/min and 0.52 Gy/min for two separate mouse models) (186). In general, aPC has an association with several cellular activities such as anti-coagulation, anti-inflammation in blood, and other cytoprotective properties such as endothelial barrier protection, protection against vascular leakage, inflammation, apoptosis, and inflammasome activation (187). The drug TP508 (rusalatide acetate, Chrysalin) also mitigates the effects of radiation by activating radioresistant stem cells in the intestines and colonic regions of mice when treated 24 h after lethal radiation exposure of 9 Gy (188). In another study, TP508 was found to stimulate cellular events linked with the repair of bone, skin, and muscle tissues in rats (189). Among the FDA-approved radiomitigators, Neupogen and Neulasta are the most efficient for treating radiation damage and neutropenia (190, 191). These drugs help improve granulocyte colony-stimulating factor (G-CSF) pharmacokinetics and subsequently empower the immune response against radiation injuries (192). Another FDA-approved drug, Leukine (Sargramostim), has also shown potential radiomitigatitve effects to treat neutropenia in radiation-exposed patients (193–196). Apart from G-CSF, NPLATE (Romiplostim) is the first FDA-approved thrombopoietin receptor agonist used as radiomitigator to treat low platelet counts due to acute radiation exposure as studied in (197). In a recent study, Singh and colleagues analyzed metabolic and lipidomic profiles in the serum of NHPs (exposed to 7.2 Gy of γ-radiation) after treatment of a candidate drug, Ex-Rad (ON01210), which showed significant alterations in biochemical pathways towards the recovery of radiation-injured organs (198). Several other studies and reviews were focused on repurposing of drugs as radiomitigators (199–203).

Radioprotectors

Unlike radiomitigators, radioprotectors are administered before radiation exposure and investigated for their counter effects against ARS in different models, including mice and NHPs. BIO 300 is one example of a promising candidate that causes alterations in the metabolic profile, which further helped identify potential biomarkers associated with lung and other radiation-induced tissue injuries in the mice model when exposed to a single dose of 11.0 or 12.5 Gy whole thorax lung irradiation (204–206). In NHPs, serum-based global lipidomics and metabolomic changes were observed after treatment with BIO 300, which were again used to understand the regulation of different pathways associated with the radiation-caused injuries. Specifically, significant alterations in the levels of important metabolites such as tyrosine, glycerophosphoserine, glycerophosphocholine, and phenylalanine were observed (207). A similar study with proteomics concluded that BIO 300 causes elevation of actin by minimizing its nitration in NHP model (171).

Similarly, amifostine (WR-2721), as a radioprotecting candidate, showed significant positive impacts against ARS in humans. Metabolomics and lipidomics analyses of control and amifostine-treated mice, when exposed to whole-body at 9.6 Gy radiation, revealed that radiation exposure caused the dysregulation of 1,614 metabolites in bone marrow, jejunum, and lung samples. Further analysis concluded that bone marrow exhibited a heightened response to the protective outcomes of amifostine, while jejunum and lung had a modest response (208). In another study, reduced levels of metabolites such as hypoxanthine, glutamic acid, and L-valine due to radiation exposure was mitigated, while, some elevated metabolites like PS (18:0/20:4) and L-arginine were corrected after treatment by amifostine in mice, which were exposed to 9.6 Gy γ-radiation (209). Similarly, MS and NMR studies of serum of mice (exposed to 14 Gy γ-radiation) and NHPs (exposed to 5.8 Gy or 7.2 Gy γ-radiation, dose rate- 0.6 Gy/min) showed dysregulation of twenty-three pathways after exposure to γ-radiation. These altered metabolic pathways mainly included lipid biosynthesis, glycolysis, and nucleotide metabolism (210). This study further observed reversed metabolic signatures of ARS progression through pretreatment of Amifostine, showing the potential of the drug as a radioprotector; however, side effects such as nausea and vomiting are still a major concern. Amifostine has been tried to treat ARS but showed toxic side effects, however later approved by FDA for xerostomia (211–213).

Antioxidants, especially the group of vitamin E compounds, have been widely studied as radioprotectors (214, 215). For example, α-tocopherol enhanced the survival of mice when administered 24 h before γ-irradiation (dose rate of 0.6 Gy/min) (215). Similarly, GT3 has also been investigated as radioprotective agent. This agent exerted metabolic changes in NHPs, which were linked with increasing levels of antioxidants, suggesting a protective benefit to countermeasure radiation-induced injuries (216). Global metabolomic changes were analyzed in another study using irradiated NHP treated with GT3. Analysis of serum samples identified several altered metabolites after irradiation, including compounds involved in fatty acid beta-oxidation, purine catabolism, and amino acid metabolism. A machine-learning algorithm, Random Forest, separated control, irradiated GT3-treated, and irradiated vehicle-treated NHPs at 12 h and 24 h. Primary metabolites validated included carnitine/acylcarnitines, amino acids, creatine, and xanthine. Overall, GT3 administration reduced high fluctuations in serum metabolite levels, suggesting an overall beneficial effect on animals exposed to radiation (158). Recently conducted studies with serum and jejunum samples of GT3-treated mice exposed to 11 Gy TBI demonstrated the restoration of irradiation-induced proteomic changes by GT3 (217, 218). Likewise, an injection of selenium-containing compounds, such as sodium selenite or selenomethionine, resulted in the improved survival of mice after radiation exposure.

Agents that serve both as radiomitigators or radioprotectors

Some of the drugs that have been investigated as radioprotectors and radiomitigators to modulate ARS effectively include glucans, 5-androstenediol (5-AED), and meloxicam (219, 220). In animal trials, β-glucan has shown potential both as a radioprotector and a radiomitigator when mice were exposed to the doses of 6, 7, and 8 Gy γ-radiation and doses of 4 Gy (dose rate- 0.15 Gy/min) in two different studies (221, 222). β-glucan combined with other radioprotectors, such as cystamine or WR-2721, showed a positive impact in protecting from radiation damage (223). The administration of β-glucan with WR-2721 and selenium also resulted in favorable outcomes (224). Several other studies revealed similar successes in the use of β-glucan either pre- or post-irradiation to treat radiation toxicity and improve animal survivability (225–228). A pre- or post-irradiation treatment with 5-AED was also effective in modulating the immune response to counter the impact of radiation. 5-AED stimulated myelopoiesis and the recovery from infections in mice (exposed to 3 Gy total-body γ-radiation) and NHPs (TBI 4 Gy γ) (219, 229). Increased G-CSF production in 5-AED treated mice 24–48 h prior to TBI with 7.5 Gy (dose rate- 0.6 Gy/min), synergistically improved the activation of monocytes, granulocytes, and NK cells, along with an increase in the number of innate immune cells (230–232). 5-AED is an open Investigational New Drug (IND) used as a radioprotector or radiomitigator for radiation-related injuries (233).

The mechanism of action and efficacy of a variety of such compounds and biomolecules were comprehensively discussed in previous reviews (202, 234, 235). Various highlighted compounds, especially the repurposed ones, that can be used to modulate ARS pre- and post-radiation exposure, which include immunomodulators, are listed in Supplementary Table S1. A short summary of radiation countermeasures studied in different animal models is provided in Figure 2B. Different radiation drugs were categorized into four main classes i.e. immunomodulator, prostaglandin, antioxidant and other biologicals. Interestingly, our literature search showed 12 compounds that have been studied as radioprotectors and radiomitigators [Figure 2B and Table S1].

In the recent past, countermeasures have been used for studying metabolomics in NHP models with different doses of TBI. The metabolomic profile in serum samples of NHPs treated with Ex-Rad after irradiation (7.2 Gy, 0.6 Gy/min, $LD_{70/60}$) has been investigated. Two different dose administration schedules (24 and 36 h post-irradiation as well as 48 and 60 h post-irradiation) were used to investigate the global profiling approach. Alterations in the biochemical pathways relating to inflammation and oxidative stress after irradiation were alleviated in animals that received Ex-Rad treatments (201).

Conclusions

Decades of research into the effects of radiation damage in several model systems, along with the generation, analysis, and interpretation of radiation-altered omics data, have identified several promising candidates as biomarkers. These biomarkers were identified from various data sources, including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiome-based studies. Here, we discussed current progress in the identification of these biomarkers for radiation exposure-associated disease manifestations. Several of these radiation-induced transcriptomic signatures, including GADD45, PCNA, CCNA2, CDKN1A, and MDM2, could be employed as rapid and cost-effective biomarkers to detect the extent of radiation damage. Similarly, lipid biomarkers, such as glucosylceramide, phosphatidylethanolamine, and sphingosine have the potential to be population-based biodosimetry biomarkers, owing to their dynamic and reliable response to radiation damage and the availability of robust analytical assays for detection. There has also been significant progress in identifying proteomic and metabolic markers associated with radiation damage. In this context, radiation-altered proteins such as FDXR, DDB2, and ACTN1, and metabolites such as β-thymidine and N-hexanoylglycine were associated with dysregulated molecular pathways that included glycolysis, DNA methylation, central carbon metabolism, and nucleic acid and amino acid metabolism. Furthermore, these pathway-level alterations and the associated system-level phenotypic changes may provide a rapid assessment of radiation exposure. The use of multiple biomarkers from different data sources would help enhance the prediction accuracy of diagnostic approaches compared to using a single biomarker.

Biomarkers of radiation injuries are extensively used for optimizing and tracking the damage induced by radiotherapy (236, 237). Since differences in tissue sensitivity to radiation exposure are reported, the optimization of an accurate dose for each tissue is essential for the efficacy of radiotherapy with minimal side effects. Also, identifying the extent of exposure associated with unfortunate nuclear accidents, such as the Chernobyl and the Fukushima Daiichi incidents or occupational radiation exposures, requires continuous monitoring using the biomarkers discussed here. To summarize, radiation biomarkers are essential for monitoring both unforeseen radiation accidents as well as the side effects of calibrated exposures such as radiation therapy. Recent advancements in high-throughput biomedical research technologies that generate multi-omics data coupled with the development of efficient data-analytical tools and computational algorithms have the potential to detect novel and reliable biomarkers associated with radiation exposure. Analysis of publicly available data and literature mining of radiation-injury data will also provide new therapeutic targets to help develop appropriate radiation countermeasures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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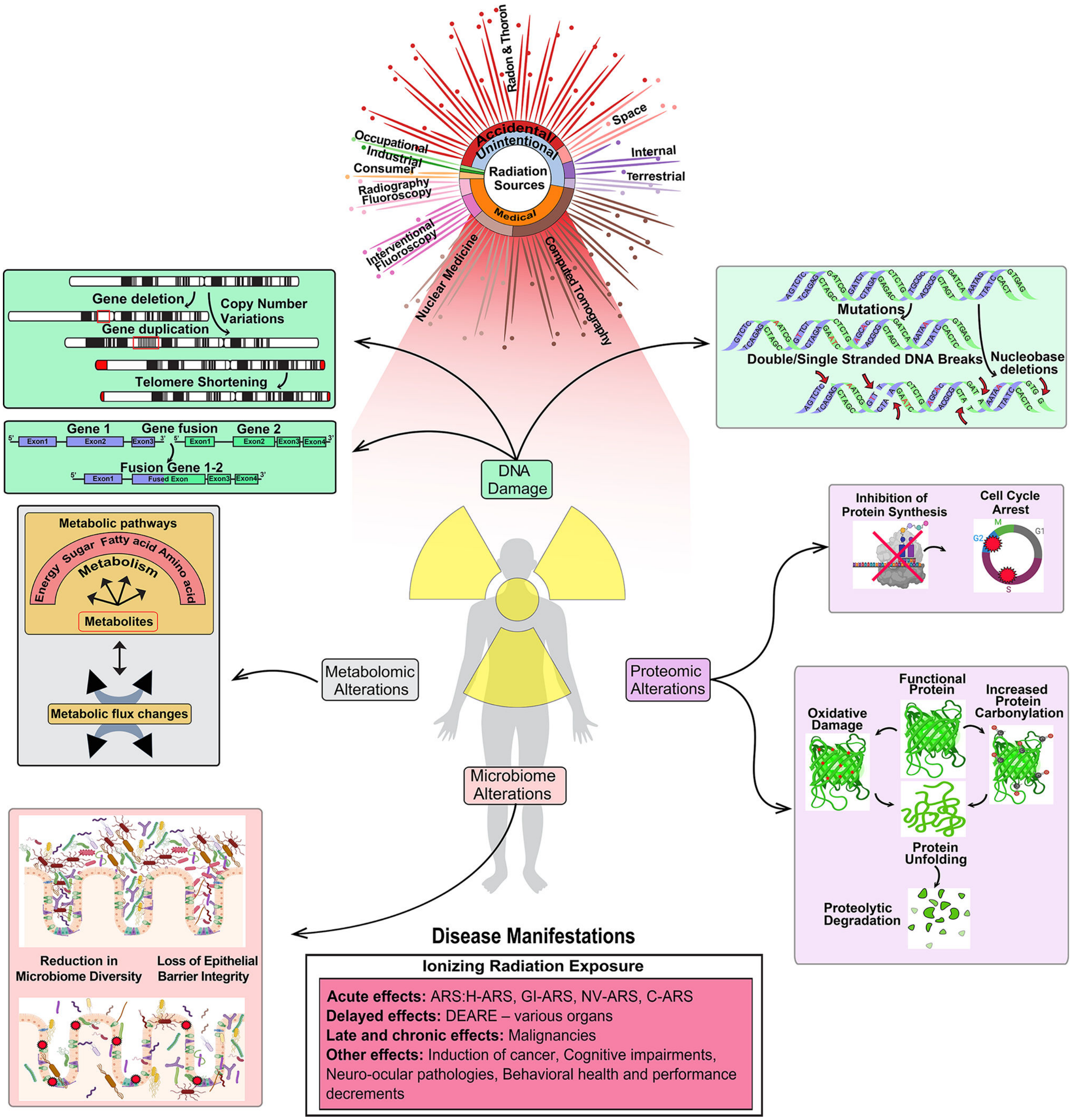
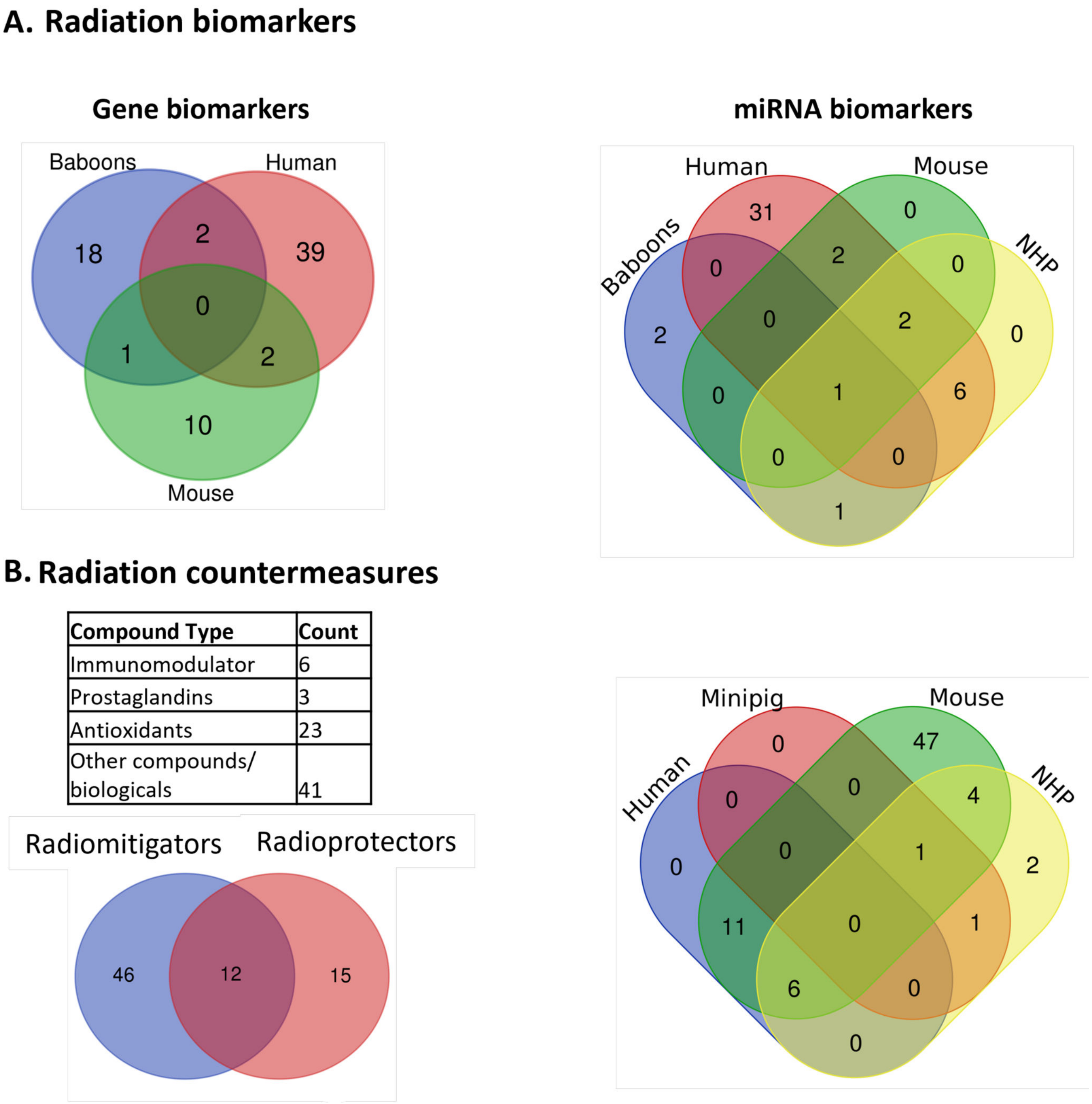


Ionizing Radiation Exposure

Acute effects: ARS:H-ARS, GI-ARS, NV-ARS, C-ARS
Delayed effects: DEARE – various organs
Late and chronic effects: Malignancies
Other effects: Induction of cancer, Cognitive impairments, Neuro-ocular pathologies, Behavioral health and performance decrements

Figure 1:

Overview of the sources of radiation exposure and their impact on human biology. The damaging effects of irradiation on DNA, proteins, metabolites/lipidomes, microbiome, and the resulting health consequence in humans are depicted. Significant sources of natural and medical IR are mentioned here. Exposure to radiation induces DNA damage, leading to chromosomal aberrations, gene fusions, DNA breaks, and mutations. Proteomic alterations can lead to inhibition of protein synthesis, changes in protein folding and degradation. Radiation exposure also affects gut health through impairment of gut epithelial barrier integrity, villus shortening, and causes reduction in microbiome diversity. Irradiation also leads to a lowered activity in key metabolic pathways including glycolysis and energy metabolism. Exposure to high dose IR causes acute, delayed, late, and chronic health effects. Only the major health consequence from both high and low dose radiation exposure is represented in this figure.



A. Radiation biomarkers

Gene biomarkers

miRNA biomarkers

B. Radiation countermeasures

Compound Type	Count
Immunomodulator	6
Prostaglandins	3
Antioxidants	23
Other compounds/ biologicals	41

Figure 2:

A) Summary of genes and miRNAs biomarkers studied in different animal models. The genes or miRNAs studied in different animal models such as baboons, human, mouse, and NHP were compared. B) Statistics of radiation countermeasures, their classification, and experimental studies in different animal models. The drugs studied in animal models e.g. NHP, human, mouse/rat, and minipig were compared to identify unique and common ones in each model.

Table 1:

List of potential mRNA biomarkers in radiation-caused injury in different animal models.

Gene	Full name	Effect	Study model	References
GDF15	Growth Differentiation Factor 15	Cell-cycle arrest	Mouse	(47)
CKAP2	Cytoskeleton-associated protein	Cell-cycle arrest	Mouse	(47)
PTPN1	Protein Tyrosine Phosphatase Non-receptor Type 1	Survival improvement in mice	Mouse	(48)
RALB	RAS like proto-oncogene	Shows radio resistiveness to different tumor types	Mouse	(49)
CKB	Creatine Kinase B	Prognostic biomarker for dose dependent radiation exposure	Mouse	(50)
CCNA2	Cyclin A2	G1/S and G2/M cell cycle regulators	Mouse	(51, 52)
SLC25A51	Solute Carrier Family 25 Member 51	Mitochondrial NAD+ transporter	Mouse	(21, 52)
ACE	Angiotensin-converting enzyme	Inhibition of ACE is associated with hematopoietic recovery following radiation	Mouse	(53)
DDA3	Differential Display And Activated By P53	Supressing cell growth	Mouse	(54, 55)
MPL	MPL Proto-Oncogene, Thrombopoietin Receptor	Associated with survival in radiation-exposed mice	Mouse	(56)
GZMH	Granzyme H	NK-cytotoxicity	Baboons	(57, 58)
NCR3	Natural Cytotoxicity Triggering Receptor 3	NK-cytolysis	Baboons	(57, 58)
PRF1	Perforin 1	Membrane pore in cytolysis	Baboons	(57, 58)
KLRF1	Killer cell lectin-like receptor F1	NK-cytolysis	Baboons	(57, 58)
GBP2	Guanylate Binding Protein 2	Oxidative killing and antiviral activity	Baboons	(59)
GLUL	Glutamate-Ammonia Ligase	Synthesis of glutamine	Baboons	(59)
CCR7	C-C Motif Chemokine Receptor 7	Migration of memory T-cells	Baboons	(57)
CD117	KIT Proto-Oncogene, Receptor Tyrosine Kinase	Regulation of cell survival and proliferation	Baboons	(57)
RNASE3	Ribonuclease A Family Member 3	Antimicrobial function	Baboons	(57)
VSIG4	V-Set And Immunoglobulin Domain Containing 4	Negative regulator of T-cell proliferation	Baboons	(57)
ARG2	Arginase 2	Regulation availability of L-arginine to nitric oxid synthase	Baboons	(60)
CD177	CD177 Molecule	Promote neutrophil activation	Baboons	(60)
WLS	Wnt Ligand Secretion Mediator	Regulates Wnt proteins sorting	Baboons	(60)
PPP3CC	Protein Phosphatase 3 Catalytic Subunit Gamma	T-cell and B cell immune response	Baboons	(59)
SH2D1A	SH2 Domain Containing 1A	Stimulation of B- and T-cells	Baboons	(57, 58)
ARHGAP45	Rho GTPase Activating Protein 45	Migrating cancer and hematopoietic cells	Baboons	(59)
HERC5	HECT Domain And RCC1-Like Domain-Containing Protein 5	T-cell and B-cell immune response, migrating cancer and hematopoietic cells	Baboons	(59)
CDCA7L	Cell Division Cycle Associated 7 Like	Cell cycle regulation	Baboons	(59)
NKG7	Natural Killer Cell Granule Protein 7	Natural killer (NK)-cytotoxicity	Human	(33, 61)

Gene	Full name	Effect	Study model	References
FDXR	Ferredoxin Reductase	Radiation dose estimator	Human	(62–64)
ERBB2	Erb-B2 Receptor Tyrosine Kinase 2	Reducing apoptosis by activating NFκB-related signaling	Human	(65, 66)
FOXM1	Forkhead box protein M1	Inhibition of FOXM1 elevate radiation sensitivity	Human	(66)
TP53	Tumor protein p53	Transcription factors modulating genes which are involved in regulation of irradiated cell cycle	Human	(32, 66)
GNLY	Granulysin	NK-cytotoxicity	Human	(33, 61)
GZMA	Granzyme A	NK-cytotoxicity	Human	(33, 61)
CBR1	Carbonyl Reductase 1	Radioprotective in radiotherapy on head and neck squamous cell carcinoma, radiosensitivity predictor in oesophageal cancer	Human	(67–70)
IGF1R	Insulin-Like Growth Factor 1 Receptor	Increased radio resistance in chemotherapy if IGF1R is overexpressed	Human	(71)
ATF3	Activating transcription factor 3	Regulate expression of other genes human myeloid tumor cell line	Human	(72, 73)
DDB2	Damage Specific DNA Binding Protein 2	Dose-dependent response	Human	(64, 74, 75)
XPC	XPC Complex Subunit, DNA Damage Recognition And Repair Factor	Dose-dependent response	Human	(74, 75)
GADD45A	Growth Arrest And DNA Damage Inducible Alpha	Radiation induced gene expression in human peripheral blood lymphocytes	Human	(72, 74)
FDXR and DDB2 Combined with WNT3 and POU2AF1	FDXR- Ferredoxin Reductase; DDB2- Damage Specific DNA Binding Protein 2; WNT3- Wnt Family Member 3; POU2AF1- POU Class 2 Homeobox Associating Factor 1	Up-regulation of FDXR and DDB2 Combined with down-regulation of WNT3 and POU2AF1: predictive biomarkers via T- and B-lymphocytes regulation	Human	(76, 77)
GPX	Glutathione Peroxidase 1	Elevated expression in human lymphoblastoid TK6 cells for high doses γ-radiation injuries	Human	(78)
P21	Protein 21	Elevated expression in human lymphoblastoid TK6 cells for high doses γ-radiation injuries, upregulation at protein level in irradiated apoptotic PBMCs	Human	(78–80)
BAD	BCL2 Associated Agonist Of Cell Death	Upregulation at protein level in irradiated apoptotic PBMCs	Human	(79, 80)
XIAP	X-Linked Inhibitor Of Apoptosis	Upregulation at protein level in irradiated apoptotic PBMCs	Human	(79, 80)
BAX	BCL2 Associated X, Apoptosis Regulator	Upregulation at protein level in irradiated apoptotic PBMCs	Human	(79, 80)
NNMT	Nicotinamide N-Methyltransferase	Prevention of Mesenchymal Cancer stem cells in case of radiation-caused injuries	Human	(81)
TFPI	Tissue Factor Pathway Inhibitor	Inhibition of TFPI supress hemophilia, coagulopathy due to radiation exposure decreases clotting ability	Human	(82, 83)
MMP9	Matrix metalloproteinase-9	Involve in degradation of extracellular matrix proteins and activates cytokines for tissue remodelling	Human	(69, 70)

Gene	Full name	Effect	Study model	References
ANXA2	Annexin A2	Regulate nuclear factor κB nuclear translocation to prevent radiation-induced apoptosis	Human	(84, 85)
TNFSF4	TNF Superfamily Member 4	Lymphocyte activation	Human	(86)
KIF20A	Kinesin Family Member 20A	Provide radio-resistance	Human	(86)
PSRC1	Proline/serine-rich coiled-coil protein 1	Regulation of mitotic spindle dynamics	Human	(86)
CDCA3	Cell division cycle-associated 3	Modulation of cell cycle progression	Human	(86)
NFKBIA	NF-Kappa-B Inhibitor Alpha	Decreasing growth in cancer lineages and increase in apoptosis by Blocking NF-kB	Human	(69, 70)
AURKA	Aurora Kinase A	Increase in radiosensitivity due to inhibition of AURKA	Human	(87, 88)
ANXA1	Annexin A1	Improving prognosis in radiation-caused lung injuries	Human	(89)
ZAP70	Zeta Chain of T-Cell Receptor Associated Protein Kinase 70	Deficiency is associated with loss of T-cells	Human	(69, 70, 90)
GADD45	Growth arrest and DNA damage-inducible protein GADD45 alpha	Inhibits entry of cells into S phase	Human	(72, 73, 75, 86)
PCNA	Proliferating Cell Nuclear Antigen	Control of eukaryotic DNA replication, elevated expression in human lymphoblastoid TK6 cells for high doses γ-radiation injuries	Human	(33, 36, 78)
BRD4	Bromodomain-Containing Protein 4	BRD4 inhibition improve cancer cell survival following irradiation	Human	(69, 70, 91)
MCL1	MCL1 Apoptosis Regulator	Protects against apoptosis caused by radiation exposure	Human	(92)
MDM2	E3 ubiquitin-protein ligase Mdm2	Ubiquitination of p53/TP53	Human	(72–74)
MYD88	Innate Immune Signal Transduction Adaptor	Prevent fibrosis and long term damage due to radiation exposure	Human	(93)
XRCC1	X-ray repair cross-complementing protein 1	DNA repair	Human	(78)
IDH3B	Isocitrate Dehydrogenase (NAD(+) 3 Beta	IDH3B helps in generating NADH which is a radioprotective for mouse intestine	Human	(69, 70, 94)
STAT4	Signal Transducer And Activator Of Transcription 4	Promotion of IL-12 response	Baboons, Mouse	(57, 95)
WNT3	Wnt Family Member 3	Canonical Wnt signalling pathway	Baboons, Human	(57, 64)
POU2AF1	POU domain class 2-associating factor 1	Response of B-cells to antigens	Baboons, Human	(57, 64, 76, 77)
CDKN1A	Cyclin-dependent kinase inhibitor 1	Inhibition of cellular proliferation in response to DNA damage, radiation-induced gene expression in human peripheral blood lymphocytes, dose-dependent response, cell-cycle arrest	Mouse, Human	(47, 69, 70, 72, 74, 75, 86)
LGALS1	Lectin Galactoside-Binding Soluble	Induction of cell death	Mouse, Human	(54)

Table 2:

List of potential miRNA biomarkers of radiation-caused injuries in different animal models.

miRNA	Full name	Effect	Study model	References
miR-124	MicroRNA 124	Modulator of immunity and inflammation, associated with anti-inflammatory responses post-TBI	Baboons	(59, 112)
miR-212	MicroRNA 212	Radiosensitivity and immune modulation	Baboobs	(88, 109)
miR-322-3p	MicroRNA 322 3p	Distinguisher between high dose (6.5 Gy) and low-dose (2 Gy) sublethal groups	Human	(97)
miR-34b-3p	MicroRNA 34b 3p	Distinguisher between high dose (6.5 Gy) and low-dose (2 Gy) sublethal groups	Human	(97, 102)
miR-27a-3p	MicroRNA 27a-3p	Proliferation and growth signaling pathways	Human	(97)
miR-136-5p	MicroRNA 136 5p	Distinguisher between high dose (6.5 Gy) and low-dose (2 Gy) sublethal groups	Human	(97)
miR-17-3p, miR-17-5p	MicroRNA 17 3p/5p	Distinguisher between high dose (6.5 Gy) and low-dose (2 Gy) sublethal groups, cardiovascular atrophy caused by lethal dose of radiation, differentially expressed and associated with TGF-beta in early phase after TBI	Human	(97, 113, 114)
miR-187-3p	MicroRNA 187-3p	IL-10–mediated suppression of TNF-α	Human	(97)
miR-21	MicroRNA 21	Long term elevation in the brain after radiation exposure, radiation caused bystander effect, epithelium-to-mesenchymal transition, associated with anti-inflammatory responses post-TBI	Human	(98, 112, 115–117)
miR-145	MicroRNA 145	Dose dependent upregulation in AHH-1 cells and HPBLs irradiated ex vivo	Human	(99)
miR-145-5p	MicroRNA 145 5p	Associated with anti-inflammatory responses post-TBI	Human	(112)
miR-663	MicroRNA 663	Dose dependent upregulation in AHH-1 cells and HPBLs irradiated ex vivo	Human	(99)
miR-223-3p	MicroRNA 223 3p	Associated with anti-inflammatory responses post-TBI	Human	(112)
miR-181a-5p	MicroRNA 181a 5p	Associated with anti-inflammatory responses post-TBI	Human	(112)
miR-1307	MicroRNA 1307	Significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99)
miR-3197	MicroRNA 3197	Significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99)
miR-4267	MicroRNA 4267	Significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99)
miR-5096	MicroRNA 5096	Significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99)
miR-7641	MicroRNA 7641	Significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99)
miR-150	MicroRNA 150	Circulatory miRNAs correlated with dose of radiation, radiation-induced bystander effect, involved in adaptive response caused by radiation	Human	(97, 101, 103, 110, 118)
miR-1246	MicroRNA 1246	Targeting Lig4 and inducing bystander DNA damage, significantly upregulated by 4 Gy γ-rays and associated biological functions	Human	(99, 119)
miR-122-5p	MicroRNA 122 5p	Radiation-induced bystander effect, incolved in adaptive response caused by radiation	Human	(118)
miR-122b-3p	MicroRNA 122b 3p	Radiation-induced bystander effect, incolved in adaptive response caused by radiation	Human	(118)
mir-155-5p	MicroRNA 155b 5p	Elevated expression after TBI, and association with anti- and pro-inflammatory functions	Human	(120)

miRNA	Full name	Effect	Study model	References
mir-378	MicroRNA 378	Cardiovascular atrophy caused by lethal dose of radiation	Human	(59, 113)
miR-16-5p	MicroRNA 16 5p	Cardiovascular atrophy caused by lethal dose of radiation	Human	(113)
miR-140-3p	MicroRNA 140 3p	Cardiovascular atrophy caused by lethal dose of radiation	Human	(113)
miR-19b-3p	MicroRNA 19b 3p	Cardiovascular atrophy caused by lethal dose of radiation	Human	(113)
miR-199a-3p	MicroRNA 199a 3p	Cardiovascular atrophy caused by lethal dose of radiation	Human	(104, 113)
miR-125-5p	MicroRNA 125 5p	Pro-inflammatory biomarker candiate post-TBI	Human	(121)
miR-23a-3p	MicroRNA 23a 3p	Pro-inflammatory biomarker candiate post-TBI	Human	(101, 121)
miR-34a-5p	MicroRNA 34a 5p	Pro-inflammatory NF-κB-mediated functions, circulatory biomarker for lung specific injury	Human	(102)
miR-133a/b	MicroRNA 133 a/b	Muscle development, Targeting radiation-associated gene IGF1R, biomarker for irradiated vs unirradiated NHPs	Baboons, NHP	(59, 105, 110)
miR-375	MicroRNA 375	Radioprotective efficacy of GT3, regulate pyruvate dehydrogenase kinase, isozyme 1 (Pdk1) and myotrophin (Mtpn) to control production of beta cells and insulin, biomarker for irradiated vs unirradiated NHPs	Human, mouse	(105, 110, 122)
miR-7-5p	MicroRNA 7 5p	Targeting EGFR and Bcl2 and inducing autophagy	Human, mouse	(123, 124)
miR-215	MicroRNA 215	Targeting radiation-associated gene IGF1R, biomarker for irradiated vs unirradiated NHPs	Human, NHP	(105, 110)
miR-126, miR-126a-5p	MicroRNA 126	Radioprotective efficacy of GT3, survival indicators, radiation-induced bystander effect, involved in adaptive response caused by radiation, radiation caused fatality indicator in NHPs, distinguisher between high dose (6.5 Gy) and low-dose (2 Gy) sublethal groups, cardiovascular atrophy caused by lethal dose of radiation	Human, NHP	(97, 105, 110, 113, 118)
miR-30a-3p, miR-30	MicroRNA 30a-3p	Inhibit cancer cell proliferation, Targeting radiation-associated gene IGF1R, radioprotective efficacy of GT3, survival indicators, circulatory miRNAs correlated with dose of radiation, radiation caused fatality indicator in NHPs, biomarker for lethal (8 Gy) and sublethal (6.5 Gy) groups	Human, NHP	(97, 105, 110)
miR-30c-5p, miR-30c	MicroRNA 30c-5p	Regulates proliferation, apoptosis, and differentiation, circulatory miRNAs correlated with dose of radiation, biomarker for lethal (8 Gy) and sublethal (6.5 Gy) groups, cardiovascular atrophy caused by lethal dose of radiation	Human, NHP	(97, 110, 113)
miR-29a/b/c	MicroRNA 29 a/b/c	Circulatory miRNAs correlated with dose of radiation, distinguisher of HARS groups with and without pancytopenia	Baboons, human, mouse, and NHP	(59, 110)
miR-200	MicroRNA 200	Circulatory miRNAs correlated with dose of radiation	Human, mouse, and NHP	(110)
miR-320	MicroRNA 320	Circulatory miRNAs correlated with dose of radiation	Human, mouse, and NHP	(110)