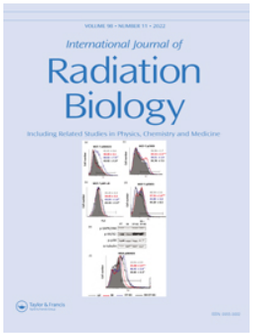

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Application of radiation omics in the development of adverse outcome pathway networks: an example of radiation-induced cardiovascular disease

Omid Azimzadeh[a], Simone Moertl[a], Raghda Ramadan[b], Bjorn Baselet[b], Evagelia C. Laiakis[c,d], Soji Sebastian[e], Danielle Beaton[e], Jaana M. Hartikainen[f], Jan Christian Kaiser[g], Afshin Beheshti[h,i], Sisko Salomaa[j], Vinita Chauhan[k], and Nobuyuki Hamada[l]

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ABSTRACT

Background: Epidemiological studies have indicated that exposure of the heart to doses of ionizing radiation as low as 0.5 Gy increases the risk of cardiac morbidity and mortality with a latency period of decades. The damaging effects of radiation to myocardial and endothelial structures and functions have been confirmed radiobiologically at high dose, but much less are known at low dose. Integration of radiation biology and epidemiology data is a recommended approach to improve the radiation risk assessment process. The adverse outcome pathway (AOP) framework offers a comprehensive tool to compile and translate mechanistic information into pathological endpoints which may be relevant for risk assessment at the different levels of a biological system. Omics technologies enable the generation of large volumes of biological data at various levels of complexity, from molecular pathways to functional organisms. Given the quality and quantity of available data across levels of biology, omics data can be attractive sources of information for use within the AOP framework. It is anticipated that radiation omics studies could improve our understanding of the molecular mechanisms behind the adverse effects of radiation on the cardiovascular system. In this review, we explored the available omics studies on radiation-induced cardiovascular disease (CVD) and their applicability to the proposed AOP for CVD.

Results: The results of 80 omics studies published on radiation-induced CVD over the past 20 years have been discussed in the context of the AOP of CVD proposed by Chauhan et al. Most of the available omics data on radiation-induced CVD are from proteomics, transcriptomics, and metabolomics, whereas few datasets were available from epigenomics and multi-omics. The omics data presented here show great promise in providing information for several key events (KEs) of the proposed AOP of CVD, particularly oxidative stress, alterations of energy metabolism, extracellular matrix (ECM), and vascular remodeling.

Conclusions: The omics data presented here shows promise to inform the various levels of the proposed AOP of CVD. However, the data highlight the urgent need of designing omics studies to address the knowledge gap concerning different radiation scenarios, time after exposure, and experimental models. This review presents the evidence to build a qualitative omics-informed AOP and provides views on the potential benefits and challenges in using omics data to assess risk-related outcomes.

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Introduction

Experimental evidence for the cardiovascular impacts of ionizing irradiation has been described since the late 1890s in poikilotherm species and the early 1920s in homeotherm species (Desjardins 1937). The circulatory system has long been considered to be relatively radioresistant, such that higher doses (e.g. therapeutic radiation exposure with 40–80 Gy in 1.8–2 Gy daily fractions) are required to cause

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damage, in particular degenerative changes (ICRP 1984). However, since the late 1990s, there has been mounting epidemiological evidence for increased risk of diseases of the circulatory system (DCS) at dose and dose rates much lower than previously thought (Kreuzer et al. 2015; Little et al. 2021; Tapio et al. 2021). The International Commission on Radiological Protection (ICRP), in 2011, recommends the nominal threshold of 0.5 Gy to the heart for cardiovascular disease (CVD) and to the brain for cerebrovascular disease (CeVD) (Stewart et al. 2012), independent of rate of dose delivery, i.e. assuming no dose rate effect. In 2021, the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) established an expert group to prepare a report on the scientific basis of radiogenic DCS, and ICRP established Task Group 119 to prepare a report on the implications of such radiogenic DCS in the radiation protection system.

In the context of radiation protection, especially for stochastic effects (i.e. cancer and heritable effects) of low linear energy transfer radiation, the dose <0.1 Gy is defined as low dose, 0.1–1 Gy as moderate dose, 1–5 Gy as high dose, and >5 Gy as very high dose. For dose rate, <0.005 Gy/h is defined as low dose rate, 0.005–0.1 Gy/h as moderate dose rate, and >0.1 Gy/h as high dose rate (Rühm et al. 2015; Little et al. 2021, 2022b). The epidemiological studies performed on exposed populations such as Japanese atomic bomb survivors serve as the basis of linear-non-threshold (LNT) model applied in radiation risk assessment of cancer for more than half a century. Such approach facilitates linear extrapolation of data from high and medium doses to low dose radiation. However, there are considerable uncertainties in assessing the risk-related outcomes at low doses or low dose rates (Preston 2017; Shore et al. 2018). Several national and international organizations of radiation protection have recommended integrating the data of radiation biology and epidemiology to improve the radiation risk assessment process (Hamada and Fujimichi 2014; NCRP 2020; Chauhan, Beaton, et al. 2022; NASEM 2022). The integration of experimental and epidemiological data has been introduced by several radiation biologically based dose-response (BBDR) models to estimate cancer risk (Preston 2015, 2017; Rühm et al. 2017; Preston et al. 2021). Among non-cancer endpoints of radiation exposure, disease of the circulatory system, including CVD, is the main domain for which radiation experimental data (e.g. on potential biomarkers) are becoming increasingly available and could be incorporated into epidemiological studies. However, compared to carcinogenesis, only a few mechanistic risk models have been developed for radiation-induced CVD. These early models were mainly concerned with the impact of cholesterol metabolism on atherosclerosis but have not been fitted to radiation epidemiological cohorts (Cobbold et al. 2002; Little et al. 2009; Mc Auley 2022). The recently developed BBDR model for late CVD risk after radiotherapy (RT) applied to breast cancer patients aims to address this issue using integration of experimental and clinical data (Simonetto, Kaiser, et al. 2022).

The AOP approach has been developed in the chemical toxicology field to assemble current knowledge on key events (KEs) that underlie disease progression (Villeneuve et al. 2014) and has been identified as being instrumental for the successful implementation of mechanistic data into research and regulatory framework (Ankley et al. 2010). An AOP is an analytical construct that begins with a molecular initiating event (MIE). It describes the sequential chain of KEs and causally linked key event relationships (KERs) at different levels of biological organization as it leads to an adverse outcome (AO) of interest to regulatory decision-making (Ankley et al. 2010).

In 2012, the Organization for Economic Co-operation and Development (OECD) launched a formal framework to provide the structure for building high-quality AOPs (OECD 2018). The framework allows the assembly of knowledge across scientific disciplines using evidence streams defined by the modified Bradford-Hill (B-H) criteria (Becker et al. 2015). This informs the weight of evidence of an AOP, derived from information on biological plausibility, empirical evidence, the essentiality of KEs and any documented uncertainties. As fluid documents, AOPs can continually evolve as new data or methods become available.

Because KEs are conceptually defined by interactions of different genes, proteins, or metabolites, omics data have the potential to contribute to the development and evaluation of AOP. The advances in high-throughput molecular analysis have completely reformed our understanding of biological processes. Mainstream omics are powerful analytical tools for the study of various biomolecules in a biological system at a given time and status (Vailati-Riboni et al. 2017). The DNA, epigenetic modifications, RNA, proteins, lipids, extracellular signaling molecules, and metabolites are the target molecules for genomics, epigenomics, transcriptomics, proteomics, lipidomics, secretomics, and metabolomics, respectively. The application of omics is rapidly emerging in different research areas and clinical investigations.

The first application of omics in radiation biology was published more than two decades ago, but omics profiling is yet young in radiation research (Azimzadeh, Gomolka, et al. 2021; Subedi et al. 2022). With the omics studies in radiation biology, the researchers can address several issues related to the biological effects of radiation exposure, radiation biomarkers, the individual difference in radiation response, and risk assessment (Pernot et al. 2012; Amundson 2021; Hladik et al. 2022; Subedi et al. 2022).

Omics data can contribute to a deeper understanding of molecular events associated with AOPs. The chemical and ecological fields have recently directed efforts toward integrating omics data within AOPs to refine and strengthen their predictive utility. The results from different omics studies have already been used in the development of AOP in chemical risk assessment in toxicology (Ankley et al. 2010; Villeneuve et al. 2014; Brockmeier et al. 2017). However, the applicability of omics data for regulatory purposes remains debatable, mainly due to the lack of standardized approaches for conducting and interpreting omics experiments on the one hand, and the gap between quantitative omics results and measurable phenotypic endpoints on the other hand (Sauer et al. 2017).

An optimal example for the application of omics data in the chemical toxicology field is benchmark dose (BMD) modeling to identify a point of departure at which a defined change from the control occurs that signifies a relevant phenotypic change (Filipsson et al. 2003). Studies have demonstrated transcriptional BMD values to be highly correlated with toxic doses of chemicals derived using traditional animal models. More recently, the approach has been applied to radiation datasets and has shown promise in identifying the point of departures of molecular pathway with reproducibility across datasets generated at different institutions (Chauhan et al. 2016; Chauhan, Rowan-Carroll, et al. 2019). Such an approach would be valuable to integrate within the KERs of an AOP and could be explored through case studies.

The AOP framework has increasingly gained attention from the radiation community as a means to advance the mechanistic understanding of the health effects of exposure to ionizing radiation at low dose and low dose rates (Chauhan, Said, et al. 2019; Chauhan, Hamada, et al. 2021; Chauhan, Wilkins, et al. 2021; Hamada et al. 2021; Preston et al. 2021; Chauhan, Hamada, et al. 2022; Hamada et al. 2022, in press). The overarching objective of such an approach is to identify the sequence of critical KEs leading to an AO and to identify robust bioindicators for the adverse pathological events. Subsequently, the biological dose-response data provided by bioindicators should be combined with epidemiological data in BBDR models to improve risk assessment.

In this context, a recent workshop on AOPs, organized by the Multidisciplinary European Low Dose Initiative (MELODI) and the European Radioecology Alliance associations (ALLIANCE), was held virtually on 12–16 April 2021. A working group was formed of experts in the field of CVD from both regulatory and research institutions, discussed the development of an AOP network for radiation-induced CVD (Chauhan, Hamada, et al. 2021). The group members deliberated on various exposure scenarios, potential toxicity mechanisms, the MIE, KEs, and their potential relationships. Based on these initial expert discussions, the group proposed an AOP for CVD (Chauhan, Hamada, et al. 2021). The AOP network is preliminary and describes biologically plausible mechanisms for cardiac toxicity at multiple levels of organization from molecular, cellular, and tissue to organ levels. It comprises three main branches: endothelial dysfunction, metabolic and extracellular matrix (ECM) remodeling leading to vascular, myocardial pathology, and fibrosis. The potential cellular interplay in irradiated cardiac tissue was also considered by proposing some bidirectional relationships between KEs (Chauhan, Hamada, et al. 2021). The next steps involve a documented assessment of the literature to support causal linkages of the KERs.

Here, we provide a summary of omics data that may inform the proposed radiation-induced CVD AOP. In particular, we describe the characteristics of omics profiles available in radiation research, including transcriptome, proteome, secretome, epigenome, metabolome and those from multi-omics analyses. We discuss the potential and deficiencies of omics data that can be used in the development of AOP for radiation-induced cardiovascular effects. The review also points to scientific and analytical domains of radiation research where sufficient omics data are not yet generated and interpreted.

Search criteria

All searches were performed in NCBI PubMed (https://pubmed.ncbi.nlm.nih.gov/advanced/) (accessed 25 April 2022). A combination of keywords, including the name of the omics platform, cardiovascular, and radiation, was searched in title/abstract of studies published from 2000 to 2022 as follows:

For genomics: *('genome*'[Title/Abstract] OR ('GWAS'[Title/Abstract] AND 'cardiovascular'[Title/Abstract] AND ('radiation'[Title/Abstract])*

For Epigenetics: *('epigenom*'[Title/Abstract] OR 'dna methylation'[Title/Abstract]) AND 'cardiovascular'[Title/Abstract] AND 'radiation'[Title/Abstract])*

For transcriptomics: *('transcriptom*'[Title/Abstract] OR 'microarray'[Title/Abstract] OR 'rna seq'[Title/Abstract]) AND 'cardiovascular'[Title/Abstract] AND 'radiation'[Title/Abstract]*

For miRNA array: *('miRNA*'[Title/Abstract] AND 'cardiovascular'[Title/Abstract] AND ('radiation'[Title/Abstract])*

For Proteomics: *('proteom*'[Title/Abstract] AND 'cardiovascular'[Title/Abstract] AND ('radiation'[Title/Abstract])*

For Secretome: *('secretom*'[Title/Abstract] OR 'exosome*'[Title/Abstract] OR 'extracellular vesicle' [Title/Abstrcact]) AND 'cardiovascular'[Title/Abstract] AND 'radiation'[Title/Abstract]*

For metabolomics and lipidomics: *('metabolom*'[Title/Abstract] OR 'lipidom*'[Title/Abstract]) AND 'cardiovascular'[Title/Abstract] AND 'radiation'[Title/Abstract]*

To cover a full range of data, no exclusion criteria were applied for experimental models, radiation exposure scenarios (e.g. dose, dose rate, and radiation quality), and time after exposure. This is consistent with guidelines for AOP development, whereby all studies irrespective of dose range were included, similar to an earlier commentary (Chauhan, Hamada, et al. 2021).

Results of the literature search

The PubMed search using the searching matrices applied in the title/abstract returned 108 articles. These articles were subjected to full-text review by authors to ascertain if they had original omics analyses. Among these, 41 articles (2 epigenomic, 11 transcriptomic, 2 miRNA, 23 proteomic, 1 secretomic, and 2 metabolomic analyses) qualified for inclusion. As the automatic PubMed search does not necessarily identify all relevant existing articles (Little et al. 2021, 2022a, 2022b; Subedi et al. 2022), additional articles and reviews (3 epigenomics, 7 transcriptomics, 7 miRNA, 7 proteomics, 13 metabolomics, and 8 secretomics) were manually selected by authors and included in the final list. Finally, 80 articles were discussed in the context of AOP CVD proposed by Chauhan, Hamada, et al. (2021). Proteomics (27 studies),

transcriptomics (16 studies), and metabolomics (15 studies) accounted for a large part (>70%) of all omics data included here. Only a few profiles were available for epigenomics (3 studies), miRNA (7 studies), and secretomics (6 studies) analyses of the cardiovascular system after irradiation. The articles for multi-omics (5 studies), and systems biology (1 study) were also manually included indicating significant research and knowledge gaps in these areas.

Genomics

Genomics is the analysis of an individual's whole DNA, such as gene variants and single nucleotide polymorphisms (SNPs). The evolving large amount of data on human genetic information provides insights into susceptibilities and has the potential to be incorporated into risk assessments (Mortensen et al. 2018).

Various risk factors (e.g. high cholesterol and hypertension) and genetic factors (e.g. gene variants) are strongly recognized in CVD research. For example, the heritability of coronary artery disease (CAD) has been estimated at 40%, suggesting a strong genetic contribution to the disease (McPherson and Tybjaerg-Hansen 2016). Genome-wide association studies (GWAS) have identified ~300 risk loci for CAD and myocardial infarction (Chen Z and Schunkert 2021). Moreover, large-scale, genome-wide, and targeted genetic association data have been combined to develop a genomic risk score for CAD (Inouye et al. 2018). To address the question of how the GWAS-identified risk variants function to increase the risk of CAD, Selvarajan et al. presented an integrative genomics approach representing a comprehensive effort in identifying putative causal regulatory regions and target genes that could predispose to clinical manifestation of CAD by affecting liver function (Selvarajan et al. 2021). The contribution of genetic predisposition to radiation sensitivity or radiation resistance in cancer is well accepted; however, the knowledge in the area of radiation-induced non-cancer effects is not very advanced (Foray et al. 2016; Rajaraman et al. 2018). In recent years, some associations between SNPs and long-term normal tissue radiation toxicities in the bowel, esophagus, lung, and skin were identified (Kerns et al. 2020). However, studies on genomics and radiation-induced cardiotoxicity are completely lacking. Neither our own search strategy nor other review work identified suitable studies (Tapio et al. 2021).

Epigenomics

Epigenetic modifications are dynamic modifications of the genome (e.g. DNA methylation and histone modification) that confer heritable changes in gene expression without altering the genome sequence (Dupont et al. 2009). GWAS analyses have identified several CAD and myocardial infarction-associated variants located in the non-coding regions of the genome, emphasizing the role of epigenetics in pathogenesis (Örd et al. 2021). A series of recent systematic reviews highlight epigenetic aspects in gene expression linked to the pathophysiology of CVD and related risk factors such as atherosclerosis, inflammation, hypertension, and diabetes (Muka, Nano, et al. 2016; Gonzalez-Jaramillo et al. 2019; Sallam et al. 2022).

Gene-specific studies suggest a higher frequency of methylation marks in CVD for genes involved in cholesterol transport and for mitochondrial cytochrome c oxidases but not for mitochondrial ATP synthases (Muka, Koromani, et al. 2016; Sallam et al. 2022). Higher frequency of methylations was also associated with myocardial infarction related to one-carbon metabolism while stroke was associated with lower frequency methylation at the TNF-alpha promoter (Muka, Koromani, et al. 2016). Heart diseases were associated with a greater frequency of methylation at the F7 promoter and genomic regions associated with genes for the ATP binding cassettes, estrogen receptor-alpha, inhibitors of metalloproteinases, and phospholipase A2 Group VII (Muka, Koromani, et al. 2016). Functional analysis of the differentially methylated genes (DMGs) revealed an association with various pathophysiological mechanisms of CVD, such as inflammatory responses, lipid metabolism, oxidative stress, and endothelial dysfunction, as well as with signaling pathways, such as JAK/STAT, PI3K, and interleukin (Sallam et al. 2022). The single-cell sequencing in cells derived from human atherosclerotic lesions demonstrated that genetic variants associated with CAD are mainly enriched in vascular endothelial and smooth muscle cell-specific open chromatin (Örd et al. 2021), further highlighting the importance of gene regulation.

Radiation-induced epigenetic alterations, especially changes in DNA methylation on both a global and a gene-specific scale are described in several normal (fibroblasts) and tumor (e.g. colorectal carcinoma) cells and tissues (e.g. thymus and spleen) (Pogribny et al. 2005; Koturbash et al. 2007; Aypar et al. 2011; Goetz et al. 2011; Luzhna et al. 2015; Koturbash et al. 2016; Miousse et al. 2017). Radiation-induced DNA methylation seems to be highly complex and depends on several variables such as radiation quality, dose, dose rate, time of sampling, and the biological model.

Investigation of epigenetics in radiation-induced CVD is relatively new; however, a potential contribution of epigenetic mechanisms in radiation-induced CVD has been recently proposed (Sallam et al. 2022). Among the various types of epigenetic processes, only DNA methylation has been investigated in a few studies on irradiated hearts (Impey et al. 2016; Koturbash et al. 2016; Seawright et al. 2017).

Koturbash et al. analyzed changes in cardiac DNA methylation patterns in C57BL/6J male mice exposed to space radiation: protons (0.1 Gy), and iron ions (0.5 Gy). The authors described hypomethylation of retrotransposon LINE-1 at 7 and 90 d after heavy iron irradiation. This event is associated with alterations in the one-carbon metabolism pathway particularly the metabolism of methionine that contributes to the synthesis of S-adenosylmethionine (SAM), the main donor of methyl groups for DNA methylation (Koturbash et al. 2016). Seawright et al. analyzed the methylation potential of cardiac tissue in female, C57BL/6J mice at 7 d, 1, 4, and 9 months after exposure to low-dose-rate

γ-irradiation (4 cGy at 0.01 cGy/h). The analysis showed the reduction in the SAM: S-adenosylhomocysteine (SAH) ratios at 7 d and 1 month after exposure suggesting impaired DNA methylation (Seawright et al. 2017). Impey et al. showed persistent changes in the DNA methylation pattern of the left ventricle of 6-month-old C57BL/6J male mice, 22 weeks after total body irradiation (TBI) with 1 Gy of protons. The gene ontology analysis of these DNA regions indicated changes in the signaling pathways enriched for genes contributing to the heart development and differentiation (Impey et al. 2016). Yao et al. have recently analyzed the changes in cardiac DNA methylation and RNA expression profiles in a rat model of radiation-induced fibrosis (Yao et al. 2022). The study showed a negative regulation between methylation changes and RNA expression levels of 44 genes in the heart at 6 months after local exposure to 18 Gy suggesting a possible molecular mechanism involved in radiation-induced heart fibrosis.

It is important to note that the CVD pathways that are described in the context of methylation changes (Sallam et al. 2022) are well known in the pathogenesis of irradiated hearts (Baselet et al. 2019; Ramadan, Claessens, et al. 2021; Tapio et al. 2021). This encourages further investigation of DNA methylation as a possible contributor to radiation-induced CVD.

Transcriptomics

The transcriptome is defined as the complete collection of RNA transcripts that are produced in a cell- and circumstance-specific manner by the genome. Transcriptomics is the study of this collection using various high-throughput methods, such as microarray analysis and RNA sequencing (Wang Z et al. 2009). The comparison of transcriptomes allows the identification of genes that are differentially expressed in distinct cell populations and/or conditions.

In the field of radiation-induced CVD, 16 transcriptomic studies have thus far been published from 2005 to 2022. A summary of these studies is presented in Table 1.

Transcriptomic studies on irradiated endothelial cells demonstrate an acute activation of the typical DNA damage response associated with cell cycle repression, decreased cell proliferation, induction of oxidative stress signaling, and an increased inflammatory state (Baselet, Belmans, et al. 2017; Baselet et al. 2019). While it is still to be understood what causes this pro-inflammatory reaction in endothelial cells after radiation exposure, a plausible explanation would be the release of damage-associated molecular patterns (DAMPs) by stressed and dying endothelial cells (Sun et al. 2013). In the collected transcriptomic studies, only one article identified pathways linked to apoptosis after exposure to 20 Gy of X-rays (Wu Q et al. 2020). Increased pro-inflammatory response of endothelial cells is linked to radiation-induced chronic oxidative stress, which has been shown to affect the endothelial function by activating redox-sensitive transcription factors, such as NF-κB, AP-1, and Nrf2 (Marui et al. 1993; Gaboury et al. 1994; Rahman et al. 1999; Griendling et al. 2000; Awad et al. 2013). In good agreement with these findings, alterations in expression levels of the genes related to inflammatory pathways including MAPK, TGF beta, and NF-kB-related signaling were identified in the listed transcriptomic studies (Boerma et al. 2005; Halle et al. 2010b; Seemann et al. 2013; Coleman et al. 2015; Subramanian et al. 2017). In the end, this inflammatory cascade could lead to the activation of leukocyte adhesion and migration to cardiovascular tissue (Gupta and Gangenahalli 2019). Inflammation also plays a key role in the development and progression of atherosclerosis (Libby 2002). A comparison of the transcriptome of arterial biopsies from irradiated patients with control subjects revealed alterations in a group of genes involved in the NF-kB-related pathway, suggesting persistent inflammation years after irradiation (60.4 Gy (range 50–68 Gy) (Halle et al. 2010a).

Senescent endothelial cells are an emerging contributor to the pathogenesis of atherosclerosis (Wang Y et al. 2016) and are present in human atherosclerotic plaques (Minamino et al. 2002). As early as 14 d after exposure to a single dose of 2 Gy X-rays, premature endothelial senescence was identified (Baselet, Belmans, et al. 2017). Different pathways contribute to radiation-induced senescence, such as persistent activation of p53 signaling after 8.5 Gy (Boerma et al. 2005) or 2 Gy (Baselet, Azimzadeh, et al. 2017), which is usually associated with persistent DNA damage (Rufini et al. 2013). Furthermore, chronic inflammation, observed acutely after radiation exposure, can in theory also be a cause of cellular senescence (Freund et al. 2010; Kojima et al. 2013). In this context, chronic inflammation may cause cellular senescence by inducing the expression of p53 and related family members p21, p16, and p14 by persistent NF-κB activation and oxidative stress (Ren et al. 2009), which has also been identified by the listed transcriptomic studies. However, this cannot explain the induction of senescence at low X-ray doses, at which endothelial activation was not observed (Baselet, Belmans, et al. 2017). Identification of radiation-induced endothelial senescence at doses above 0.5 Gy agreed with other findings. Chronic low-dose-rate γ radiation (4.1 mGy/h) led to premature senescence in HUVECs by the induction of the p53/p21 pathway (Yentrapalli, Azimzadeh, Barjaktarovic, et al. 2013). Further analysis revealed PI3K/Akt/mTOR pathway inactivation, which may directly induce premature senescence by increasing the expression of p21 (Yentrapalli, Azimzadeh, Sriharshan, et al. 2013). At the gene expression level in these cells, the IGFBP5-related pathways were affected after irradiation (1.4 and 4.1 mGy/h), which is known to inhibit cell proliferation through a p53-dependent mechanism (Kim et al. 2007; Rombouts et al. 2014). Similarly, the downregulation of the genes related to PI3K/Akt/mTOR/eNOS and alteration of several senescence-associated genes was observed in the transcriptome profile of the endothelial cells isolated from mouse heart 16 weeks after local exposure of the heart to 16 Gy (Azimzadeh et al. 2015).

Exposure of the Est2-immortalized human coronary artery endothelial cells (HCAECs), to a dose of 10 Gy of X-rays has been shown to induce premature aging by epigenetic activation of CD44 expression (Lowe and Raj 2014).

Table 1. List of the transcriptomic studies on radiation-induced CVD.

Experimental model	Radiation Dose	Radiation quality	Time after irradiation	Analytical platform	Main observations	Reference
Neonatal rat cardiac myocytes and cardiac fibroblasts	8.5 Gy	X-rays	1 d	Microarray analysis	Gene expression responses are cell type-specific Genes involved in oxidative stress, p53 signaling, MAPK, cholesterol biosynthesis, fibrosis, and cytoskeleton	Boerma et al. (2005)
Human arterial biopsies	60.4 Gy (range 50–68 Gy)	Radiotherapy (γ-rays)	30 weeks (range 4–500 weeks)	Microarray analysis Gene enrichment analysis	Overexpression of 13 inflammatory genes related to NF-kB Activation	Halle et al. (2010a)
C57BL/6 mice, 8–12 weeks old, male	Local, to the heart 16 Gy	X-rays, 0.94 Gy/min	4, 20, and 40 weeks	Illumina Bead Array	Increased fibrosis-related genes, TGF-b1, ALK 5, and PDGF (40 weeks) Increased gene expression related to inflammatory and immunological related disease	Seemann et al. (2013)
Zebrafish embryo (26 hpf)	TBI 1, 2, 5, 10 Gy	Cobalt-60	94 h	Microarray analysis	Gene enrichment associated with cardiovascular development, function, and disease	Freeman et al. (2014)
Human umbilical vein endothelial cells (HUVECs)	4 Gy	^{137}Cs 1.4 and 4.1 mGy/h	1, 3, and 6 weeks	Microarray analysis Gene set enrichment analysis	Early stress response Inflammation-related expression profile IGFBP5 related signaling	Rombouts et al. (2014)
C57BL/6 mice, 10-week-old, male	Local, to the heart 8, 16 Gy	X-rays	16 weeks	Targeted transcriptomics	Alterations in PI3K signaling-related genes Altered gene expression involved in endothelial senescence	Azimzadeh et al. (2015)
C57Bl/6NT mice, 8–9 month old, male	TBI 0.15 and 0.9 Gy	Iron ions Protons	1, 3, 7, 14, and 28 d	Microarray analysis	Cell cycle, oxidative responses Transcriptional regulation functional groups involving ERK1/2, p38 MAPK, NFATc4, GATA4, STAT3, and NF-kB	Coleman et al. (2015)
HUVECs	2.5 Gy	X-rays, 5 Gy/min	6, 12, and 24 h	Microarray analysis	Downregulation of the cell cycle regulation genes Increased in inflammatory response genes, Type 1 interferon response Identification of interferon response factor 7 gene network	Furusawa et al. (2016)
C57BL/6J mice, 8-week old, male	16 Gy	X-rays	40 weeks	Illumina Expression Bead Chips Mouse Whole Genome	Overexpression of genes involved in TGF beta and MAPK signaling, down regulation of genes of PPAR alpha signaling	Subramanian et al. (2017)
Human telomerase-immortalized coronary artery endothelial cells	0.05, 0.1, 0.5, and 2 Gy	X-rays, 0.5 Gy/min	24 h 7 and 14 d	Microarray analysis Functional enrichment Analysis Transcription factor binding site Enrichment analysis	Dose- and time-dependent changes in gene expression linked to cell cycle progression and inflammation	Baselet, Belmans, et al. (2017)
Human telomerase-immortalized coronary artery endothelial cells	2 Gy	X-rays, Fe ions 1.5 Gy/min	24 h, 7 d	Transcriptomics and proteomics	Induction of endothelial inflammation and adhesiveness	Baselet, Azimzadeh, et al. (2017)
Human telomerase-immortalized coronary artery endothelial cells	10 Gy	X-rays	14 d	Targeted transcriptomics	Activation of Type I-interferon-mediated signaling	Philipp et al. (2017)

Transgenic hiPSC-derived cardiomyocytes	5 Gy	X-rays, 1 Gy/min	2 d	RNA sequencing Large-scale gene function analysis	Gene expression linked to cell cycle processes, Genes implicated in cardiac calcium homeostasis, oxidative stress response, and etiology of cardiomyopathy	Becker BV et al. (2018)
Primary endothelial cells derived from adult human bone marrow (hBMECs)	6 Gy	^{60}Co	24 h	Microarray analysis Gene ontology and enrichment analysis Protein–protein interaction (PPI)	Increased in adhesion pathways (leukocyte adhesion and migration) Alterations in adhesion pathways (cell-substrate adhesion and cell spreading) when combined with amifostine	Gupta and Gangenahalli (2019)
Rat brain microvascular endothelial cell (BMEC)	20 Gy	X-rays, 2.5 Gy/min	24 h	Next-generation sequencing functional pathway enrichment	Cell cycle Apoptosis Vascular permeability Extracellular junctions Ca^{2+} signaling, PI3K/Akt signaling Methionine degradation	Wu K et al. (2019)
CB6F1/Hsd mice, 3–4-month old, female	TBI 3–26, 4–32, and 40–160 cGy	^{137}Cs ^{14}Si ^{22}Ti	16 months	Microarray analysis with self-organizing map machine and Gene enrichment analyses	Expressed gene clusters identified for three radiation types	Garikipati et al. (2021)

The target transcriptomics analysis on these cells, 14 d after irradiation (10 Gy), indicated significant changes in the set of genes related to the interferon-mediated pathway (Philipp et al. 2017).

The transcriptome profiles of other irradiated cardiac cells have not been frequently studied. The transcriptomic response of human-induced pluripotent stem cells (hiPSC)-derived cardiomyocytes to 5 Gy was also examined by RNA sequencing. The study identified alterations in genes involved in oxidative stress and cardiac calcium homeostasis (Becker et al. 2018). Analysis of the genes of neonatal rat cardiac myocytes and fibroblasts after 8.5 Gy of X-ray irradiation revealed alterations in the genes responsible for oxidative stress, the p53 signaling pathway, as well as cholesterol and fibrosis (Boerma et al. 2005). Fibrosis was also an identified endpoint in whole heart tissue transcriptome performed on 8–12 weeks old male C57BL/6 mice several weeks after local exposure to 16 Gy (Seemann et al. 2013; Subramanian et al. 2017). The studies identified alterations in several genes related to TGF beta signaling, leading to increased collagen deposition and the onset of fibrosis (Seemann et al. 2013; Subramanian et al. 2017).

The transcriptomic data showed changes in the expression levels of several genes involved in the response of the cardiovascular system to radiation including DNA damage, cell–cell adhesion, inflammation, fibrosis, and senescence. It is important to note that radiation-induced changes in the transcriptome related to dose and dose rate, as well as time after irradiation and radiation quality, need to be further investigated.

miRNA

Besides protein-encoding RNAs, a plethora of non-coding RNAs is transcribed. One group are small, non-coding microRNAs (miRNAs) involved in post-transcriptional gene regulation. The impact of miRNAs on the cellular response to radiation has been described (Moertl al. 2016). They have been suggested to be predictive biomarkers of response to RT as well as potential drug targets to modulate radiosensitivity (Moertl et al. 2016). miRNAs also contribute to a broad spectrum of physiological processes in the cardiovascular system and aberrant expressions are linked with pathologic developments (Nouraee and Mowla 2015; Zhou et al. 2018). The role of miRNA alterations in initiation, progression, diagnosis, and prognosis of a broad range of CVD including heart failure, acute myocardial infarction, and arrhythmia is described (Zhou et al. 2018). Several mRNA and proteins involved in cardiac cell biology, cell survival and apoptosis, autophagy, and cytoskeleton organization have been reported as targets for up- or downregulation of miRNAs in the heart (Zhou et al. 2018).

There were 7 studies published from 2011 to 2022 that analyzed the deregulation of miRNAs in cardiovascular cells in in vitro or in vivo models after irradiation. A summary of these studies is presented in Table 2. Several of these studies investigated the role of selected CVD-related miRNAs. Alterations in miRNAs including miRNA-1, -15 b,

Table 2. List of the miRNA analyses of radiation-induced CVD.

Experimental model	Radiation Dose	Radiation quality	Time after irradiation	Analytical platform	Main observations	Reference
HDMEC	2 Gy	Photon	6 h	Locked nucleic acid (LNA)-based miRNA microarrays	Upregulation of miRNA let-7g, −16, −20a, −21, and −29c, and downregulation of miR-18a, −125a, −127, −148 b, −189, and −503	Wagner-Ecker et al. (2010)
EA.hy926 cells and HUVECs	2.5 Gy	X-rays, 0.94 Gy/min	4 and 24 h	TaqMan® Low-Density Array A v.2	Alterations in several miRNAs in different time points	Kraemer et al. (2011)
6–8-week old female C57BL/6 J mice	1, 2, 4, 8, 12 Gy.	X-rays, 1.05 Gy/min	48 h	Agilent Mouse miRNA arrays	Upregulation of miR-149-3p, −6538, −8101, −7118-5p, −211-3p, and −3960 after 12 Gy	Aryankalayil et al. (2021).
HCAEC	0.2 Gy	^{60}Co	4 and 24 h	TaqMan® miRNA assay	Downregulation of miRNA-21 at 4 h and upregulation of miRNA-146b after 24 h	Barjaktarovic, Anastasov, et al. (2013)
EA.hy926	2.5 Gy	X-rays, 0.94 Gy/min	4, 12, and 24 h	In silico interactions between miRNA and proteins	Overlap between radiation-responsive miRNAs or proteins at different time points	Sriharshan (2014)
Human heart autopsies	<0.1, 0.1–0.5, >0.5 Gy	TBI	Chronic	TaqMan® miRNA assay	Upregulation of miRNA-21 and miNA-146a in group exposed to doses >0.5 Gy	Azimzadeh, Azizova, et al. (2017)
HUVEC	2 Gy	X-rays	2 and 24 h	TaqMan® miRNA assay	Time dependent-alterations in miRNA-146a, −155, −221, and −222 in	Esplugas, Bellés, et al. (2019)

-21, -208, -133, -29, -199 b, -221, -222, and -155 have been detected in various irradiated cells/tissues of the cardiovascular system (Kura et al. 2017; Chen Y et al. 2021).

Espluggas et al. analyzed the radiation-induced changes in miRNA-146a, -155, -221, and -222 in HUVECs at 2 and 24 h after 2 Gy exposure (Esplugas, Bellés, et al. 2019). These miRNAs are involved in CVD and contribute to endothelial dysfunction, lipid metabolism, inflammation, oxidative stress, apoptosis, and angiogenesis. In good agreement with these findings, the changes in the same miRNAs were found in the blood of RT-treated women with breast cancer (Esplugas, Arenas, et al. 2019).

The changes in miRNA-17-5p, -21, -7 b, -125a, -146 b-5p, and -10a were investigated in irradiated primary HCAEC at 4 and 24 h after irradiation with 0.2 Gy. Among these miRNAs, miRNA-21 was significantly downregulated at 4 h after irradiation and miRNA-146b was significantly upregulated at 24 h after irradiation (Barjaktarovic, Anastasov, et al. 2013). The authors found a negative correlation between miR-21 levels and the structural proteins as the predicted targets.

An increased level of miRNA-21 was identified in cardiac mouse tissue after local high dose (16 Gy) irradiation (Subramanian et al. 2017). Kura et al. reported downregulation of miRNA-1 and miRNA 15b and upregulation of miRNA-21 in the rat heart exposed to a single dose of 25 Gy (Kura et al. 2016). Azimzadeh et al. analyzed the alterations of miRNA in heart autopsies of plutonium enrichment plant workers by TaqMan-miRNA assays (Azimzadeh, Azizova, et al. 2017; Azimzadeh et al. 2020). The workers included in the study were occupationally exposed to low and moderate external radiation doses (<0.1 Gy, 0.1–0.5 Gy, and >0.5 Gy) throughout their working life and were later diagnosed and later died with ischemic heart disease similar to the unexposed control group. Increased levels of miRNA-21 and −146 as potential biomarkers of CVD were also reported in an analysis of a group of workers exposed to the highest chronic dose (>0.5 Gy).

Only a few studies applied array platforms to analyze the effect of irradiation on global miRNA profiles. Aryankalayil et al. used Agilent Mouse miRNA arrays to investigate changes in miRNA in mouse cardiac tissue at 48 h after TBI with 1, 2, 4, 8, and 12 Gy. The authors identified significant upregulation of miR-149-3p, -6538, -8101, -7118-5p, -211-3p, and -3960 in irradiated hearts at the highest dose (12 Gy) (Aryankalayil et al. 2021).

Wagner-Ecker et al. analyzed 315 miRNAs in human microvascular endothelial cells (HDMEC) after 2 Gy irradiation. The authors found upregulated miRNA let-7g, -16, -20a, -21, and -29c, while miR-18a, -125a, -127, -148 b, -189, and -503 were downregulated 6 h after exposure to 2 Gy. Individual analysis of miR-125a, -127, -189, and let-7g by overexpression/inhibition identified miRNA changes as regulators of radiosensitivity in HDMEC (Wagner-Ecker et al. 2010).

Kraemer et al. compared global miRNA expression of sham-irradiated and irradiated EA.hy926 cells and HUVECs using TaqMan® Low-Density Array A version 2 (Applied Biosystems, Foster City, USA), at 4 and 24 h after single irradiation with 2.5 Gy. The authors found a wide range of changes in various miRNAs, including downregulation of 4 miRNAs (let-7d, -519e, -323-3p, and -517 b) and upregulation of 1 miRNA (miR-518b) both 4 and 24 h after irradiation.

The changes of other identified miRNA were transient at both time points (Kraemer et al. 2011). The predicted molecular targets of miRNAs affected by irradiation are mainly involved in the signaling pathways contributing to cardiac hypertrophy, fibrosis, and oxidative stress as well as endothelial structure and function (Sriharshan 2014; Kura et al. 2017).

The miRNA response of other cardiac cells, including cardiomyocytes and fibroblasts, to radiation exposure, remains to be investigated. The role of miRNA changes has been studied in skin fibroblasts, highlighting the potential regulatory role of miRNA in radiation response. In a microarray approach including 462 miRNAs, Maes et al. found the dose- and time-dependent changes in human fibroblasts in response to low (0.1 Gy) and high (2.0 Gy) X-ray doses (Maes et al. 2008). Changed miRNAs were predicted to act in typical radiation response pathways, such as apoptosis, cell cycle regulation, and DNA repair but also in cell adhesion or cytoskeleton biosynthesis (Maes et al. 2008).

In summary, changes in the miRNA profiles after irradiation is an established component in cellular radiation response in several cell types of the cardiovascular system. However, the responses are highly specific for doses, time points, and cell types. Moreover, the complexity of miRNA functions makes the biological interpretation of their alterations challenging because one miRNA may target many mRNAs and one mRNA may be targeted by multiple miRNAs.

Proteomics and post-translational modifications

Alteration in the proteome of cells and tissues is tightly linked to the physiological and pathological changes in a biological system. This makes proteomics analysis a comprehensive tool enabling the identification of the biological effect of radiation exposure. The application of proteomics approaches is well established in the radiation biology field (Azimzadeh et al. 2014; Azimzadeh and Tapio 2017).

Among the studies reported from 2011 to 2022 that applied proteomics platforms to investigate the cell and tissue response to radiation exposure, 27 studies analyzed the proteome response of cardiac tissue, vascular system or cardiac cells, and cell compartments using a broad range of quantitative proteomics platforms. A summary of these studies and their findings are presented in Table 3.

Mitochondrial proteins were the most sensitive protein cluster affected in irradiated hearts (Barjaktarovic et al. 2011; Azimzadeh et al. 2013; Azimzadeh, Azizova, et al. 2017; Azimzadeh, Subramanian et al. 2021). The analysis of cardiac mitochondrial proteome in C57BL/6 mice at 4 and 40 weeks after local heart exposure to moderate or high doses of X-rays (0.2 or 2 Gy) showed significant downregulation of several subunits of mitochondrial complexes I, III, and V after irradiation. The number and extent of downregulation increased over time (Barjaktarovic et al. 2011; Barjaktarovic, Shyla, et al. 2013). Mitochondrial proteins were also downregulated in the proteome profile of the murine hearts at 16 and 20 weeks after a high dose (16 Gy) of local heart irradiation (Azimzadeh et al. 2013; Xu et al. 2021). Cardiac mitochondrial proteins were also mainly affected short-term (4 and 24 h) after TBI (3 Gy) (Azimzadeh et al. 2012). The long-term effect of chronic exposure on cardiac mitochondria proteome and acetylome was exclusively studied in apolipoprotein E (ApoE)-deficient C57BL/6J female mice exposed to low-dose-rate (0.02 Gy/d) gamma radiation for 300 days using label-free proteomics (Barjaktarovic et al. 2019). This study showed that changes in mitochondrial acetylation after irradiation were associated with impaired cardiac metabolism (Barjaktarovic et al. 2019). The effect of chronic exposure was also analyzed in heart autopsies of Russian Mayak nuclear workers who were exposed only to external gamma radiation. A dose-dependent downregulation of mitochondrial proteins was observed in the heart of all exposed groups (<0.1 Gy, 0.1–0.5 Gy, and >0.5 Gy, chronic TBI) in comparison to the controls (Azimzadeh, Azizova, et al. 2017). The radiation-induced downregulation of mitochondrial proteins is accompanied by alteration in ultrastructure and reduced activity of oxidative phosphorylation subunits (Barjaktarovic et al. 2011; Barjaktarovic, Shyla, et al. 2013; Barjaktarovic et al. 2019).

Radiation-induced mitochondrial dysfunction increases the reactive oxygen species (ROS) production (Barjaktarovic et al. 2011; Barjaktarovic, Shyla, et al. 2013) and the level of oxidative stress-induced protein modifications (Azimzadeh et al. 2013; Azimzadeh et al. 2015). Although the oxidative stress is immediately measurable in the irradiated heart in the form of oxidized proteins (Azimzadeh et al. 2011; Barjaktarovic et al. 2011; Azimzadeh et al. 2013; Barjaktarovic, Shyla, et al. 2013; Azimzadeh, Subramanian et al. 2021), the expression of antioxidant defense proteins differs in the cardiac proteome in a dose- and time-dependent manner (Azimzadeh and Tapio 2017). Analysis of the mouse heart proteome, short (24 h) after 3 Gy TBI showed upregulation of acute-phase proteins involved in the oxidative stress response including peroxiredoxin, hemopexin, ferritin, transferrin, and murinoglobulin1 (Azimzadeh et al. 2011). Proteomics analysis of mouse hearts irradiated locally at a high dose (16 Gy) showed radiation-induced upregulation of proteins involved in oxidative stress response 16 weeks after irradiation (Azimzadeh et al. 2013) but downregulation after 40 weeks (Subramanian et al. 2017; Azimzadeh, Subramanian et al. 2021). The analysis of the proteome of heart autopsies from Mayak workers showed a dose-dependent reduction of several antioxidant defense proteins including catalase, superoxide dismutase, peroxiredoxins, and glutathione-S-transferase in the highest dose group (>0.5 Gy, chronic TBI) (Azimzadeh, Azizova, et al. 2017).

Physiological cardiac function depends on consistent energy production through oxidative phosphorylation in mitochondria: therefore, alterations in cardiac energy metabolism have been reported in various cardiac diseases (Wang Y et al. 2013; Guo et al. 2017). In good agreement with this, alteration in the energy metabolism has been described in the irradiated heart (Azimzadeh et al. 2012; Azimzadeh et al. 2013; Barjaktarovic, Shyla, et al. 2013; Azimzadeh, Azizova,

Table 3. List of the proteomics studies on radiation-induced CVD.

Experimental model	Radiation dose	Radiation quality	Time after irradiation	Analytical platform	Main observations	Reference
human endothelial cell line EA.hy926	0.2 Gy	^{60}Co 0.02-0.19 Gy/min	4 and 24 h	MALDI-TOF/TOF tandem mass spectrometry	Alterations in Ran and RhoA pathways, fatty acid metabolism, and stress response	Pluder et al. (2011)
C57BL/6 mice	3 Gy TBI	γ-rays	5 and 24 h	Isotope-coded protein labeling (ICPL) and 2-dimensional difference-in-gel-electrophoresis (2-D DIGE)	Alterations in mitochondrial proteins, inflammation, antioxidative defense, and structural reorganization	Azimzadeh et al. (2011)
C57BL/6N mice mitochondrial	0.2, 2 Gy Local heart	X-rays, 1.5 Gy/min Fe ions, 1.5 Gy/min	4 weeks	ICPL and DIGE	Alterations in oxidative phosphorylation, the pyruvate metabolism, and the cytoskeletal structure	Barjaktarovic et al. (2011)
Human endothelial cell line EA.hy926	2.5 Gy	γ-rays	4 and 24 h	Stable isotope labeling with amino acids in cell culture (SILAC) and 2 D-DIGE	Alterations in glycolysis/gluconeogenesis and synthesis/degradation of ketone bodies, oxidative phosphorylation, Rho-mediated cell motility, and non-homologous end-joining	Sriharshan et al. (2012)
C57BL/6 mice FFPE heart tissue	3 Gy TBI	γ-rays	24 h	Label-free quantitative (LFQ)	Alterations in the respiratory chain, lipid metabolism, and pyruvate metabolism	Azimzadeh et al. (2012)
Primary human coronary artery endothelial cells	0.2 Gy	^{60}Co	94 h	2D-DIGE and miRNA analysis	Alterations in cellular assembly and organization, cellular function and maintenance, and molecular transport	Barjaktarovic, Anastasov, et al. (2013)
HUVECs	4 Gy	X-rays, 4.1 mGy/h	1, 3, and 6 weeks	Isotope-coded protein label (ICPL) proteomics	Alterations in cytoskeletal organization, cell–cell communication, and adhesion, inflammation, and induction of premature senescence	Yentrapalli, Azimzadeh, Barjaktarovic, et al. (2013)
C57BL/6 and ApoE$^{-/-}$ mice	0.2 and 2 Gy	X-rays	40 weeks	ICPL	Alterations in the mitochondria-associated cytoskeleton, respiratory chain, ion transport, and lipid metabolism	Barjaktarovic, Shyla, et al. (2013)
C57BL/6 mice mice, 8 weeks old, male	8 and 16 Gy	X-rays (local heart)	16 weeks	ICPL	Alterations in lipid metabolism and oxidative phosphorylation	Azimzadeh et al. (2013)
NMRI mice (neonatal)	0.02, 0.1, 0.5, and 1.0 Gy	^{60}Co	7 months	ICPL	Alterations in metabolic processes, inflammatory response, and cytoskeletal structure	Bakshi et al. (2013)
HUVECs	0.24, 1.41, and 2.35 Gy at 1.4 mGy/h 0.40, 2.41, and 4.03 Gy at 2.4 mGy/h	X-rays, 1.4 and 2.4 mGy/h	1, 6, and 10 weeks	ICPL and revers protein array	Inactivation of the PI3K/Akt/mTOR pathway Induction of premature senescence	Yentrapalli, Azimzadeh, Sriharshan, et al. (2013)
Isolated endothelial form C57BL/6 mice heart	8 and 16 Gy	X-ray (local heart)	16 weeks	ICPL and targeted transcriptomics	Alterations in insulin/IGF/PI3K/Akt/eNOS Induction of premature endothelial senescence, increased oxidative stress, decreased NO availability, and enhanced inflammation	Azimzadeh et al. (2015)
Human cardiac microvascular endothelial cells	2 Gy	X-rays	4 h	Acetylome and proteome	Alterations in the proteins of the translation process, the stress response, and mitochondria, cytoskeleton signaling, and cell cycle progression	Barjaktarovic et al. (2015)
Human heart autopsies	$<$0.1 0.1–0.5, $>$0.5 Gy	TBI	Chronic	LFQ	Downregulation of mitochondrial and structural proteins oxidative stress-responsive and PPAR alpha-related proteins	Azimzadeh, Azizova, et al. (2017)
Human coronary artery endothelial cell	0.5 Gy	^{137}Cs	24 h	Acetylome and proteome	Alterations in the protein synthesis, cytoskeleton-related processes, protein	Barjaktarovic et al. (2017)

					folding, calcium signaling, and RhoA/actin cytoskeleton	
C57BL/6J mice, 8 weeks old, male	16 Gy	X-rays	40 weeks	LFQ and Transcriptomics	Alterations in PPAR alpha and TGF beta pathway	Subramanian et al. (2017)
Human coronary artery endothelial cell	0.5 Gy	X-rays	1, 7, and 14 d	ICPL	Alterations in the Rho GDP-dissociation inhibitor (RhoGDI) and nitric oxide (NO) signaling pathways, reduced proteasome activity, enhanced protein carbonylation indicating augmented oxidative stress, and senescence	Azimzadeh, Subramanian, et al. (2017)
Human telomerase-immortalized coronary artery endothelial cells	10 Gy	X-rays	14 d	LFQ and targeted transcriptomics	Induction of inflammatory response, induction of interferon type I-related proteins, and activation of the STAT3 pathway	Philipp et al. (2017)
Human telomerase-immortalized coronary artery endothelial cells	2 Gy	X-rays, 1.5 Gy/min Fe ions, 1.5 Gy/min	24 h 7 d	ICPL and transcriptomics	Induction of endothelial inflammation and adhesiveness	Baselet, Azimzadeh, et al. (2017)
C57BL/6J mice, 8 weeks old, male (wild type (+/+), heterozygous (+/−) or homozygous (−/−) PPAR alpha genotype)	16 Gy	X-ray (local heart)	20 weeks	LFQ	PPAR alpha is necessary for activation of noncanonical TGF beta signaling in irradiated heart	Subramanian et al. (2018a)
ApoE-deficient C57Bl/6J mice	6 Gy (chronic)	20 mGy/d) gamma	300 d	Acetylome and proteome	Alterations in the TCA cycle, fatty acid oxidation, oxidative stress response, and sirtuin pathway	Barjaktarovic et al. (2019)
Formalin-fixed paraffin-embedded (FFPE) human heart autopsies	> 0.5 Gy	TBI	Chronic	LFQ	Alterations in the lipid metabolism, sirtuin signaling, mitochondrial function, cytoskeletal organization, and antioxidant defense	Azimzadeh et al. (2020)
Human coronary artery endothelial cells (HCECest2)	0, 0.25, 0.5, 2.0, and 10 Gy	^{60}Co	20 weeks	LFQ	Activation of DNA-damage repair, inflammation, and oxidative stress pathways	Philipp et al. (2020)
Serum of C57BL/6J mice, 8 weeks old, male	16 Gy	X-ray (local heart)	20 weeks	LFQ	Alterations in the acute phase response, inflammation, and cholesterol metabolism	Azimzadeh and von Toerne et al. (2021)
C57BL/6J mice, 8 weeks old, male treated with PPAR alpha agonist: fenofibrate	16 Gy	X-ray (local heart)	20 weeks	LFQ	Restored lipid metabolism, mitochondrial respiratory chain, redox response, tissue homeostasis, endothelial NO signaling, and the inflammatory response after fenofibrate treatment	Azimzadeh, Subramanian et al. (2021)
3D aggregates of human embryonic stem cell-derived cardiomyocytes	0.1 − 2 Gy	X-rays	1. and 7 d	LFQ	Alterations in the structural proteins, contractile sarcomere, and cardiac toxicity-related signaling	Smit et al. (2021)
C57BL/6J mice, 8 weeks old	16 Gy	X-ray (local heart)	5 months	Tandem mass tag (TMT) labeling	Alterations in the mitochondrial proteins, proteins involved in the fibrosis and energy metabolism	Xu et al. (2021)

et al. 2017; Subramanian et al. 2017; Xu et al. 2021). Analysis of the formalin-fixed paraffin-embedded (FFPE) heart proteome shortly (24 h) after (3 Gy) TBI of mice showed that several enzymes involved in fatty acid oxidation, pyruvate metabolism, and citric acid cycle were significantly downregulated in irradiated hearts (Azimzadeh et al. 2012). Similarly, lipid metabolism enzymes were downregulated in the proteome of locally irradiated (2 Gy) mouse hearts at 40 weeks after radiation (Barjaktarovic, Shyla, et al. 2013). The majority of the dysregulated proteins in the heart after local high-dose irradiation (16 Gy) were also associated with the regulatory network of peroxisome proliferator-activated receptor alpha (PPAR alpha) (Azimzadeh et al. 2013), a key regulator of cardiac fatty acid oxidation, lipoprotein assembly and lipid transport (Watanabe et al. 2000; Finck 2007). The bioinformatic analysis of the proteome of the irradiated heart predicted the deactivation of PPAR alpha (Azimzadeh et al. 2013; Subramanian et al. 2017; Azimzadeh, Subramanian et al. 2021). In good agreement with this finding, the analysis of the cardiac proteome of the PPAR alpha null mice, at 20 weeks after exposure to the local high dose (16 Gy) showed the least changes, demonstrating the central role of PPAR alpha in cardiac response to ionizing radiation (Subramanian et al. 2018; Azimzadeh, Subramanian et al. 2021). Disruption of the PPAR alpha pathway has previously been described in a variety of heart diseases (Dewald et al. 2005; Finck 2007). It has been recently shown that the effect of high-dose irradiation on the heart can be ameliorated by the activation of PPAR alpha (Azimzadeh, Subramanian et al. 2021).

The impact of vascular injury and endothelial dysfunction in the pathogenesis of radiation-induced CVD has been described in animal and human data (Boerma and Hauer-Jensen 2010; Baker et al. 2011; Seemann et al. 2012; Azimzadeh et al. 2013). The effects of radiation exposure on the proteome of different endothelial cell models have been studied. Proteomics analysis of both in vivo and in vitro models indicated significant changes in the proteins involved in the structure and function of cardiac endothelial cells. The Impairment of PI3K/Akt/NO signaling and alteration in NO availability are characteristics of endothelial dysfunction (Wiench et al. 2013). The RhoA pathway was affected in the proteome of irradiated transformed human umbilical vein endothelial cell line (HUVEC; EA.hy926) after high (2.5 Gy) (Sriharshan et al. 2012) and moderate-dose radiation (0.2 Gy) (Pluder et al. 2011). Both RhoGDI and PI3K/Akt/NO signaling pathways were affected following irradiation in the proteome of endothelial cells exposed to the dose of 0.5 Gy as well as the proteome of endothelial cells isolated directly from locally irradiated (16 Gy) mouse hearts (Azimzadeh et al. 2015; Azimzadeh, Subramanian, et al. 2017). Proteomics analysis of the chronically irradiated HUVECs (1.4 and 2.4 mGy/h) indicated the involvement of PI3K/Akt/mTOR pathway inhibition in the radiation-induced endothelial senescence (Yentrapalli, Azimzadeh, Sriharshan, et al. 2013).

Cardiac tissue integrity, as well as cardiac cell interaction and communication is supported by the ECM (Chang et al. 2016). Changes in cardiac ECM are known to contribute to heart pathologies (Westermann et al. 2008; Diez 2010) including cardiac fibrosis (Westermann et al. 2008) and cardiac remodeling (Chang et al. 2016; Lindsey et al. 2016). Deposition of collagen, excessive fibroblast proliferation, and upregulation of TGF beta are all characteristics of radiation-induced heart fibrosis (Gao et al. 2012; Seemann et al. 2012; Sun et al. 2016). The expression of ECM proteins, such as biglycan, decorin, fibrinogen, and collagen was shown to be increased in the cardiac proteome, at 16, 20, and 40 weeks after local heart exposure to 16 Gy (Azimzadeh et al. 2013; Subramanian et al. 2017; Azimzadeh, Subramanian et al. 2021; Xu et al. 2021). Proteomics analysis of the FFPE hearts of Mayak workers (>500 mGy, chronical TBI) showed significant changes in the expression of ECM proteins in the chronically irradiated hearts. The collagen isoforms were all upregulated in irradiated samples (Azimzadeh et al. 2020).

Taken together, the proteome response of irradiated heart is well characterized and supports several KEs in CVD AOP including mitochondrial dysfunction, metabolic alterations, and structural remodeling.

Secretome

The secretome is the entirety of all biomolecules released from a cell to the extracellular space, where it has indispensable functions in cell-to-cell and cell-to-ECM communication. The exploration of the secretome includes molecular and functional effects of released factors and offers unique insights into the molecular interactions between cells. Autocrine, paracrine, and endocrine secretome-mediated intercellular communication occurs by the release of individual soluble components, such as chemokines, cytokines, and growth factors, but also by extracellular vesicles (EVs) that transport a variety of active macromolecules, including nucleic acids, metabolites, and lipids (Mukherjee and Mani 2013).

For the dynamic equilibrium of cells that compose the cardiovascular system, fine-tuned communication via the secretome is essential (Tirziu et al. 2010; Liu Q et al. 2021). Under stress conditions, an orchestrated crosstalk between cardiovascular cells is of particular importance to sustain efficient responses (Martins-Marques et al. 2021). Especially for regenerative processes after heart injury, effects from secreted factors are intensively discussed. In this context EVs secreted from mesenchymal stem cells indicated high potential (Gallina et al. 2015). Intercellular communication is one of the proposed mechanisms of radiation-induced atherosclerosis (Ramadan et al. 2019, 2020; Ramadan, Baatout, et al. 2021).

The secretome is a vital component for communication during the radiation response of cells to radiation-induced damage as well as for mediating non-targeted effects (Yahyapour et al. 2018; Dawood et al. 2021). A specific type of secretome is released by radiation-induced prematurely senescent cells and consists of a collection of cytokines, chemokines, proteases, and growth factors. This senescence-associated secretory phenotype (SASP) can contribute to

different cellular responses (Coppe et al. 2008). Amongst others, the adoption of this phenotype is described in endothelial cells, fibroblasts, and cardiomyocytes (Li M et al. 2018).

Several studies described radiation-induced changes in secreted chemokines and interleukins from cardiovascular cells. For example, the interleukins IL-6 and IL-8 and the chemokines CXCL5/8 are released from endothelial cells after various radiation doses and timepoints (Van Der Meeren et al. 1999; Baselet et al. 2019). Likewise, for fibroblasts, the secretion of individual SASP-factors, like IL-1, IL-6, and IL-8 were described after irradiation (Coppe et al. 2008; Isermann et al. 2020). Only two studies were found that employed an omics approach for the unbiased identification of radiation-induced changes in the secretome. Philip et al. quantified around 1000 secreted endothelial proteins, from which 338 were dysregulated 14 d after exposure to 10 Gy. Pathway analysis of these proteins revealed inflammatory response and identified interferon Type I as the main pathways of the radiation-deregulated proteins (Philipp et al. 2017). Proteomic data were also reported for radiation effects on the secretome of fibroblasts where more than 500 upregulated proteins in the secretome of irradiated fibroblasts with 10 Gy were documented in the 'SASP atlas' (Basisty et al. 2020). They also made a distinction between radiation-dysregulated soluble factors and factors released within EVs. The main pathways covered by the secreted factors included tissue and cell structure effects, such as ECM organization, actin cytoskeleton, integrin interactions, and peptidase regulation. In contrast to endothelial cells and fibroblasts, there was no information on the effect of irradiation on the secretome of cardiomyocytes.

Factors secreted from irradiated cardiovascular cells can affect recipient cells. We found one study which performed a medium transfer from irradiated endothelial cells to non-irradiated cells followed by proteome analysis. Induction of interferon Type I-related proteins and activation of the STAT3 pathway were identified as the main affected pathways in endothelial cells 14 d after exposure to 10 Gy X-rays (Philipp et al. 2017). Most other studies were restricted to the description of functional alterations as consequences of secretome exposure and provided no omics data.

Radiation effects on the cardiovascular structure may also be triggered by secreted factors from cell types that are not the main constituents of the cardiovascular system, such as adipocytes, mesenchymal stem cells, tumor cells, and blood cells. For example, endothelial cells and cardiomyocytes were recipients of EVs from mesenchymal stem cells and tumor cells. RNA sequencing of these EVs identified a large number of radiation-deregulated miRNAs which were related to CVD (Jabbari et al. 2019; Luo et al. 2021). On the other hand, several studies identified peripheral blood mononuclear cells (PBMC)-secreted EVs as mediators of radiation effects in cardiovascular cells. By RNA-sequencing and label-free proteomics, Moertl et al. showed dose-dependent changes in the miRNA and proteome cargo of EVs derived from irradiated PBMCs. Integrated pathway analysis of the radiation-triggered EV proteins and miRNAs consistently predicted an association of deregulated molecules with apoptosis, cell death, and survival (Moertl et al. 2020). Further omics analysis demonstrated large increases in the miRNA and protein content of EVs secreted from PBMCs after high dose exposure (60 Gy) (Wagner et al. 2018). Consistently, both studies showed that radiation-triggered EV changes induced pro-survival and angiogenic effects on endothelial cells. In the meantime, the secretome of irradiated PBMCs was shown to improve cardiac performance in a porcine infarction model. Transcriptional analyses of PBMC secretome effects identified the regulation of genes that were essential for cardiomyocyte function and the downregulation of pro-inflammatory genes (Mildner et al. 2022).

In summary, there is very limited omics data on the secretomes released from cardiovascular cells after irradiation. However, this knowledge is an indispensable tool to understand the crosstalk between different components of the heart in response to radiation exposure.

Metabolomics and lipidomics

Metabolomics and its subcategory lipidomics aim to identify and in some cases quantify small molecules called metabolites in cells, tissues, and biofluids. These small molecules can serve as the building blocks to maintain structural, genetic, signaling, and metabolic integrity. Both metabolomics and lipidomics have gained traction in radiation biology and are now considered optimal integral-omics technology in a systems biology approach. Targeted and untargeted approaches in both metabolomics and lipidomics have distinct pros and cons, including positive metabolite identification and coverage of different classes, or sensitivity and absolute quantification levels. Although the applied detection methods in the mainstream of metabolomics have also evolved and become more sensitive, there are still challenges where some methods (e.g. nuclear magnetic resonance [NMR]) that provide important structural information need to be yet improved as they identify only the most abundant molecules.

Among studies that applied metabolomics or lipidomics in radiation research from 2011 to 2022, 9 publications (including 2 reviews) focused on profiling small molecules related to CVD. A summary of these studies and their findings is presented in Table 4.

Gramytyka et al. exposed human cardiomyocytes to 2 Gy (CLINAC 600 6 MV photons, 1 Gy/min) and evaluated metabolic levels at 48 h afterwards with high-resolution magic-angle spinning (HR-MAS) NMR (Gramatyka et al. 2018). Significant differences were identified between exposed and unexposed groups, specifically related to oxidative stress, energy metabolism, membrane integrity, and amino acids (Gramatyka et al. 2018). The investigators extended their work to study mice following TBI (0.2 or 2 Gy, Varian CLINAC 23006 MV photons, 300 MU/min) and analyzed the heart metabolites at 48 h or 20 weeks after exposure. Metabolomic analysis with ^{1}H NMR spectroscopy showed that most changes occurred at the earlier time point

Table 4. List of the metabolomics studies on radiation-induced CVD.

Experimental model	Radiation dose	Radiation quality	Time after irradiation	Analytical platform	Main observations	Reference
C57BL/6 male mice	2 Gy	CLINAC 600 6 MV photons; 1 Gy/min	48 h	HR-MAS NMR	Changes in the metabolites associated with oxidative stress, energy metabolism, membrane integrity, and amino acids	Gramatyka et al. (2018)
Nonhuman primates, primarily male *Macacca mulatta* (heart tissue)	7.2 Gy TBI	0.6 Gy/min	Survivors vs. non-survivors, 60-day end of the study	UPLC-QTOF MS	Alterations in the long-chain acylcarnitines, fatty acid amines	Cheema et al. (2019)
C57BL/6J male mice (heart tissue)	0.1, 0.25, and 1 Gy TBI	600 MeV/n ^{16}O, NSRL	14 and 90 days	UPLC-MS/MS	Changes in the transsulfuration pathway and cystathione	Miousse et al. (2019)
C57BL/6NCrl female mice (heart tissue)	0.2 or 2 Gy, TBI	Varian CLINAC 2300 6 MV photons	48 h or 20 weeks	1H NMR	Alterations in pantothenate, glutamate, alanine, malonate, acetylcarnitine, glycine, and adenosine	Gramatyka et al. (2020)
CD2F1 male mice (heart tissue)	9.6 Gy, TBI, and treatment with amifostine	0.6 Gy/min ^{60}Co	4 and 9 d	UPLC-QTOF MS	Alterations in Hydroxyprostaglandin E1 and fatty acids	Cheema et al. (2020)
Nonhuman primates, *Macacca mulatta* (heart tissue)	12 Gy, 2.5% bone marrow shielding	0.8 Gy/min 6 MV photons	4 d and 3 weeks	Biocrates AbsoluteIDQ kit with targeted LC-MS/MS	Changes in the fatty acid oxidation, phospholipid biosynthesis, phenylacetate metabolism, pyrimidine metabolism, glucose-alanine cycle, arginine and proline metabolism, and seleno-amino metabolism.	Kumar et al. (2021); Zalesak-Kravec et al. (2021)

with the higher dose, with pantothenate, glutamate, alanine, malonate, acetylcarnitine, glycine, and adenosine as the most abundant markers. Glutamine and acetylcarnitine were significantly reduced in the 2 Gy irradiated group at 20 weeks after exposure, while the exposure to 0.2 Gy showed no statistically significant effects on heart metabolomics. Treatment of mice with resveratrol before exposure to 2 Gy was able to reduce effects in glycerophosphocholine and choline compounds (Gramatyka et al. 2020). Rats exposed to gamma rays (6 Gy TBI with ^{60}Co) showed that lipid peroxidation metabolites of heart tissue were significantly increased at 24 h after exposure, although the overall levels were measured with a standard malondialdehyde (MDA) assay (de Freitas et al. 2013). The analysis of the heart metabolites in mice exposed to TBI at 9.6 Gy (0.6 Gy/min, ^{60}Co) showed changes in various fatty acids and inflammatory mediator hydroxyprostaglandin E1 in the heart (Cheema A. K. et al. 2020). The heart showed significant early responses to radiation, which were dampened quickly by day 9 after exposure. The authors showed that the administration of the radioprotective agent, amifostine partially corrects the effect of TBI on the heart metabolome (Cheema A. K. et al. 2020).

A few studies have also examined the metabolome of heart tissue of nonhuman primates (NHPs). Cheema et al. identified increased levels of long-chain acylcarnitines, particularly sterearoylcarnitine, and linoleylcarnitine, in the heart tissue of surviving and non-surviving NHPs following 7.2 Gy of TBI (^{60}Co, 0.6 Gy/min) (Cheema A. K. et al. 2019). Alteration of long-chain acylcarnitines was associated with increased hypoxia and may impact both fatty acid β-oxidation and proper mitochondrial function (Cheema A. K. et al. 2019). In addition, a decrease of fatty acid amines, the mitochondrial-regulated metabolites with anti-inflammatory properties, strongly suggests that mitochondria are implicated in radiation responses in heart tissue (Cheema A. K. et al. 2019). Two other studies in NHPs, after partial body irradiation of 12 Gy (6 MV LINAC photons, 0.8 Gy/min) identified 8 enriched metabolic pathways in the left side and 3 in the right side of the heart at 4 days after exposure, with some changes persisting at 3 weeks after exposure (Kumar et al. 2021; Zalesak-Kravec et al. 2021). Kumar et al. showed that fatty acid β-oxidation (short, long, and very long-chain fatty acids), phospholipid biosynthesis, phenylacetate metabolism, and pyrimidine metabolism were significantly enriched ($p < .05$) in the left side of the heart, while glucose-alanine cycle, arginine, and proline metabolism, and selenoamino acid metabolism were significantly enriched in the right side (Kumar et al. 2021). Metabolomics, in combination with proteomic data from the same model at 3 weeks after exposure, showed dysregulation of inflammatory, energy metabolism, and myocardial remodeling pathways, as well as retinoid homeostasis (Zalesak-Kravec et al. 2021).

These studies have focused on high doses and dose rates. Radiation exposure and CVD remain a concern as well for astronauts and deep space exploration. The mitochondrial-related pathways were shown to be affected by both spaceflight (da Silveira et al. 2020) and space radiation (Vernice et al. 2020; Barnette et al. 2021; Laiakis et al. 2021).

One study has investigated whether exposure to ^{16}O (0.1, 0.25, or 1 Gy, 600 MeV/n) would alter specific metabolic pathways in heart tissue. The investigators (Miousse et al. 2019) identified changes in the transsulfuration pathway with high levels of cystathione, while the homocysteine remethylation pathway was unaffected.

Taken together, the metabolomic studies reported here highlight the involvement of mitochondrial and metabolic alterations in cardiac injury due to radiation exposure.

Biofluid

Metabolomics analysis of minimally invasive and easily accessible biofluids provides a reliable platform to monitor radiation-induced biological effects including CVD. As with tissues and cells, the vast majority of the literature on biofluids (e.g. serum, plasma, urine, saliva, and feces) focuses on high-dose exposures for biodosimetry, with increased emphasis on connecting biomarkers of delayed effects of acute radiation exposure (Pannkuk et al. 2017; Satyamitra et al. 2020; Vicente et al. 2020). The metabolomic and lipidomic studies on radiation biomarkers in biofluids at the low dose and low dose rates are limited. Nine studies that analyzed biofluids following irradiation (from 2014 to 2022) are summarized in Table 5.

McGarrah et al. (2018) reported a list of such targets in plasma including branched-chain amino acids, branched-chain α-ketoacids, ketone oxidation, long-chain acylcarnitines, tricarboxylic acid (TCA) cycle intermediates, certain amino acids, pyrimidines, pentose phosphate pathway intermediates, short-chain dicarboxylacylcarnitine, and trimethylamine N-oxide (TMAO). In particular, TMAO (a gut microbiota-derived metabolite) is emerging as a strong biomarker for CVD (Schiattarella et al. 2017), in addition to changes in short-chain fatty acids and secondary bile acids (Brown and Hazen 2018). Lipidomic changes have also been shown in patients with CAD and coronary microvascular dysfunction (Lindner et al. 2021) while decreased total bile acids are consistently shown in patients and animal models with CAD (Li, Shu et al. 2020; Chong Nguyen et al. 2021). The majority of these metabolites, lipid species, and classes could easily be measured with targeted metabolomic and lipidomic approaches.

Atherogenic lipid profiles with low high-density lipoprotein (HDL) cholesterol and hypertriglyceridemia were also found in Japanese atomic bomb survivors (Akahoshi et al. 2003). These observations have been suggested as a mechanism to link radiation exposure and coronary heart disease.

A select number of studies with internal contamination (injectable ^{137}Cs or uranium in drinking water) have assessed biomarkers in serum, plasma, or urine. Goudarzi et al. identified perturbations in amino acid metabolism, fatty acids, TCA cycle, glycolysis, and phosphatidylcholines (PCs) in mice injected with $^{137}CsCl$ (2–30 d, 1.95–9.91 Gy cumulative dose) (Goudarzi et al. 2015). A similar approach by Li et al. described oleamide and sphingosine-1-phosphate as metabolites that were perturbed irrespective of dose rate (varying dose rates from 0.16 to 1.36 Gy/d) (Li, Lin et al. 2020). Sphingosine-1-phosphate is of particular importance because of its significant role in vascular and immune systems and the metabolism of HDL (Proia and Hla 2015; Jiang XC 2017; Cartier and Hla 2019). Chronic low dose exposure to uranium on the other hand showed significant changes in the nicotinate-nicotinamide pathway and unsaturated fatty acid biosynthesis, reflected in the urine of male and female rats (Grison et al. 2019), which could be due to the dual toxicity of uranium (radioactive and a heavy metal). The estimated absorbed dose rate to the kidneys at 9 months of age was estimated to be 5.4×10^{-7} Gy/d, with a cumulative dose of 0.15 mGy under the assumption of a constant dose rate over 9 months.

While internal exposures demonstrated significant changes in metabolomics and lipidomics, external exposures to low dose rate photons showed similar results. TCA cycle and fatty acids were the most dysregulated pathways in the urine of high dose rate exposed mice (3.09 mGy/min) (Goudarzi et al. 2014), with a novel metabolite, hexosamine-valine-isoleucine-OH (Hex-V-I), increased 150-fold in low dose rate exposed (variable 0.1–1 Gy/d) mice vs. an 80-fold increase in mice exposed at higher dose rate (~0.8 Gy/min) (Pannkuk et al. 2021). The role of this novel metabolite remains to be elucidated, including whether persistent changes may have a role in the delayed effects of acute radiation exposure. A common theme emerging from the published studies is alterations in energy metabolism showing the most significant changes in TCA and mitochondria (Jang et al. 2016; Pannkuk et al. 2017; Kawamura et al. 2018; Livingston et al. 2020). Studies on human exposures are limited to biofluids, focusing primarily on samples from cancer patients with doses outside the scope of this review.

Nonetheless, mitochondrial dysregulation, and pro-inflammatory metabolites were prominent results in biofluids (serum and urine) from TBI human cohorts (Laiakis et al. 2014; Laiakis et al. 2017; Vera et al. 2020).

Interestingly, alterations in fatty acids, various lipids, glycerol, glycolate, and choline-containing phospholipids were described in serum analysis of breast cancer and head and neck cancer patients who received RT (Shaikh et al. 2017; Jelonek et al. 2020; Boguszewicz et al. 2021). Changes in circulating levels of lipids were reported as a biosignature of radiation exposure in TBI patients before stem cell transplantation (Laiakis et al. 2017).

In contrast to urine and blood, fecal material and saliva were two largely unexplored biomaterials in low-dose radiation research, although evidence is accumulating showing that radiation doses as low as 0.5 Gy have significant effects. BALB/c mice exposed to photons (0.5 Gy) showed microbiome changes linked to the glucagon signaling pathway, central carbon metabolism in cancer, and TCA cycle (Laiakis et al. 2014; Liu X et al. 2019), while salivary metabolomics in C57BL/6 mice exposed to photons (0.5, 3, or 8 Gy) showed that the overall metabolic profile remained distinct from sham-exposed animals one week after exposure (Laiakis et al. 2016).

Table 5. List of the biofluid analyses on radiation-induced CVD.

Experimental model	Radiation dose	Radiation quality	Time after irradiation	Analytical platform	Main observations	Reference
TBI patients	1.25 Gy, 1.25 × 3 Gy	∼0.1 Gy/min Clinical exposures 15 MV photons	Pre, ∼6, ∼24 h	UPLC-QTOFMS	Octanoylcarnitine, hypoxanthine, trimethyl-L-lysine, acetylcarnitine, decanoylcarnitine, uric acid, and xanthine	Laiakis et al. (2014)
C57BL/6 male mice Saliva	137Cs external TBI 0.5 Gy	γ-ray 1.4 Gy/min	1 and 7 d	UPLC-QTOFMS	Changes in polar metabolites	Laiakis et al. (2016)
Human breast cancer radiotherapy patients Serum	6 cycles of radiotherapy, unreported dose	Unreported	Controls, pre and end of radiotherapy cycle	GC-MS	Changes in fatty acids	Shaikh et al. (2017)
TBI patients	1.25, 2, 1.25 × 3 Gy	∼0.1 Gy/min Clinical exposures 15 MV photons	Pre, ∼6 and ∼24 h	LC-MS, GC-MS	Eicosanoids, monoacylglycerols, triacylglycerols, phosphatidylcholines, phenylalanine, and phosphatidylglycerols	Laiakis et al. (2017)
Outbred Sprague-Dawley male and female rats Plasma and urine	Chronic exposure in drinkable water	Uranium	∼9 months	LC-microTOF-MS	Changes in nicotinate-nicotinamide pathways and unsaturated fatty acid biosynthesis	Grison et al. (2019).
BALB/c male mice Feces	0.5 Gy acute and fractionated	γ-ray ^{60}Co	7, 21, and 35 d	GC-MS	Alterations in glucagon signaling pathway, central carbon metabolism, TCA cycle	Liu X et al. (2019)
C57BL/6 male mice Serum	^{137}CsCl injections (4 Gy total dose)	γ-ray 0.16 Gy/d, 0.69 Gy/d, and 1.25 Gy/d	2, 3, 5, 7, and 14 d	UPLC-QTOFMS	Changes in Oleamide, sphingosine-1-phosphate irrespective of dose rate	Li HH et al. (2020)
Head and neck radiotherapy patients	Conventional radiotherapy and				radiatio + concurrent chemotherapy (cisplatin)	Clinical exposures
Pre, 2 weeks, end of treatment	LC-MS	Reduced choline-containing phospholipids	Jelonek et al. (2020)			
C57BL/6 male and female mice, Urine and serum	TBI (1–9.7 Gy)	^{137}Cs, ∼1–0.1 Gy/d, 0.8 Gy/min	1, 2, 3, 5, 20, and 30 d	UPLC-QTOFMS	Alterations in ketoglutaric acid, 1-methylnicotinatime, TML, carnitine, trigonelline, indoleactic acid, Hex-V-I, citric acid, and xanthurenic acid	Pannkuk et al. (2021)

Integrative multi-omics

A deep understanding of the biological effects of radiation exposure is greatly facilitated by a systems biology multi-omics approach. As described in the previous sections, each omics technique provides a picture of one specific aspect of how the biological system changes in response to radiation exposure. To achieve a comprehensive understanding of the systemic impact on cells or tissue, it is necessary to integrate findings from different omics approaches to resolve the complexity of the organization of biological processes. The current status of the systems biology multi-omics approach in CVD research has been recently well-reviewed, including the limitations and advantages (Joshi et al. 2021). Currently, specific multi-omics studies to look at radiation impact on the cardiovascular system are lacking. Only a few studies have so far been performed using at least two omics platforms (Subramanian et al. 2017; Papiez et al. 2018; Cheema et al. 2022). As stated above, literature exists for multi-omics studies related to CVD in general. On the other hand, multi-omics studies on radiation are limited but show the power of these studies.

Papiez et al. analyzed the proteomic and RNA sequencing data of the postmortem cardiac left ventricle samples from Mayak workers exposed to a dose >0.5 Gy (Papiez et al. 2018). The analysis revealed that a systemic response as a function of dose caused alterations in glycolysis, oxidative phosphorylation, the TCA cycle, and PPAR alpha signaling pathways to be dominantly impacted in the cardiac tissue from the Mayak nuclear workers. The study confirmed the previous findings on Mayak heart autopsies (Azimzadeh, Azizova, et al. 2017) where the metabolic and mitochondrial proteins were highly impacted in the cardiac tissue from the nuclear workers exposed to radiation.

The cardiac proteome and transcriptome were analyzed in male C57BL/6 mice at 40 weeks after an acute local high-dose heart exposure (16 Gy) (Subramanian et al. 2017). Although the integrative analysis of gene expression array and proteomics data showed a modest direct correlation between gene and protein expression, it demonstrated that cardiac TGF beta signaling and PPAR alpha signaling were affected by irradiation at both the mRNA and protein levels (Subramanian et al. 2017).

Proteomics and transcriptomics were also used to compare the endothelial cell responses at 1 and 7 d after exposure to a single 2 Gy dose of X-rays or iron ions (Baselet, Azimzadeh, et al. 2017). The analysis showed alterations in genes and proteins involved in cell-cell adhesion, endocytosis signaling, and inflammation. The inflammatory response and adherence properties of endothelial cells were decreased after iron ion exposure, whereas they were increased by X-rays (Baselet, Azimzadeh, et al. 2017).

A recent study utilized a multi-omics approach with metabolomics, proteomics, and lipidomics to assess acute radiation injury in the serum of male and female NHP models following exposure to 6–8.5 Gy with ^{60}Co (Cheema et al. 2022). The study showed alterations in the circulating levels of lipids, metabolites, and proteins. The analysis demonstrated a blood-based multi-omics biomarker panel that contained four analytes that could stratify individuals as a function of dose. The panel of analytes was comprised of PC (16:0/22:6), acetyl carnitine, suberyl glycine, and serpin family A protein. Among these metabolites, acetyl carnitine (Dundar et al. 2016), suberyl glycine (Lu et al. 2017), and serpin family A protein (Li et al. 2016) have been previously reported as decent cardiac toxicity markers. Interestingly, all 4 analytes are heavily related to the metabolic, mitochondrial, and glycolytic functions. By using this multi-omics approach, the authors were able to provide a focused and targeted list of biomarkers that can potentially be utilized for therapy with further research.

The ultimate example of a comprehensive multi-omic analysis of radiation impact on the cardiovascular system is the NASA Twin Study which entailed studying samples obtained from two identical twins, with one twin being exposed to space radiation at low Earth orbit onboard the International Space Station (ISS) compared to the identical twin on Earth (Garrett-Bakelman et al. 2019). This is an important example of demonstrating how a comprehensive multi-omics approach can provide a complete map of the systemic biological impact. In this study, Garrett-Bakelman et al. performed transcriptomics, epigenetics, proteomics, metabolomics, and microbiomics on multiple time points from blood (i.e. multiple cell types isolated from the blood), urine, and fecal samples. Although the focus of that study was not specifically on cardiovascular health risks associated with spaceflight, utilizing this multi-omics approach revealed that cardiovascular changes occur during spaceflight. Specifically, markers associated with inflammatory cytokines and chemokines and oxidative stress were increased for the twin in flight, while no changes occurred for the control ground twin. In combination with the proteomic data, the authors found alterations in the proteins involved in the vascular structure and function. From this comprehensive multi-omics study, it was determined that vascular changes or adaptations occurring during spaceflight might have an impact on cardiovascular health due to the combination of space radiation and microgravity.

Discussion

Radiation omics support CVD AOP development

The application of omics in the context of hazard and risk assessment has already been discussed in toxicology (Bridges et al. 2017; Sauer et al. 2017; Aguayo-Orozco et al. 2019). Omics data offer great potential for the discovery of reliable biomarkers and biomarker arrays, as well as for integration into weight-of-evidence approaches to interpreting the mode of action of toxic substances (Bridges et al. 2017; Sauer et al. 2017; Aguayo-Orozco et al. 2019). Interest in the application of the AOP approach to radiation protection has increased greatly, drawing on experience gained in the field of chemical toxicology (NCRP 2020; Chauhan, Hamada, et al. 2021; Chauhan, Leblanc, et al. 2021; Chauhan, Sherman, et al. 2021; Chauhan, Stricklin, et al. 2021; Chauhan, Wilkins, et al. 2021; Chauhan, Beaton, et al. 2022). This review aimed

to describe the potential of radiation omics to be incorporated into the AOP framework.

The studies reviewed here are representative of omics data that have been generated over the last two decades in the context of radiation-induced CVD. The literature review was conducted by experts in related fields and the relevance of the findings related to adverse effects introduced in CVD AOP (Chauhan, Hamada, et al. 2021) was highlighted. Data discussed here collectively showed the potential to support different KEs in the hypothetical CVD AOP previously proposed by the authors (Chauhan, Hamada, et al. 2021). However, the studies discussed here need to be comprehensively evaluated to fulfill B-H criteria. The development and progression of radiation-induced CVD is a multidimensional phenomenon, so studying the interaction between genes, proteins, metabolites, etc., at all levels of biological organization is crucial.

Interestingly, some of the omics findings are consistent following different radiation scenarios at different time points, suggesting common AOs of radiation exposure to the heart (Figure 1 and Supplementary Table 1). There were several omics data showing the changes in oxidative stress, mitochondrial dysfunction, metabolic, and ECM remodeling, and endothelial signaling pathway. The change in cardiac energy metabolism is known as a hallmark of different heart pathology including those induced by irradiation. Identification of the different genes, proteins, and metabolites associated with heart metabolism offers an attractive panel of potential candidates for biomarker profiling, diagnosis, and risk assessment of radiation-induced CVD.

Transcriptomics data discussed here point to the importance of DNA damage in the progression of vascular pathology and open the debate on the inclusion of these cellular events as KEs in the proposed CVD AOP. Changes in the inflammatory response have also been reported by several radiation omics studies, but further studies are needed to establish a relationship between inflammatory status and biological effects of radiation exposure.

The proposed CVD AOP contains several bidirectional relationships between major KEs emphasizing molecular and cellular interplay in the cardiovascular system. The omics data on secretomes and exosomes can provide evidence for such cross-talks between pathological processes contributing to heart injury after irradiation. Such data may fill the knowledge gaps in the potential interplay between endothelial dysfunction, and cardiac metabolic and structural changes.

Systems biology: a path forward for comprehensive AOP

The integration of findings generated by different omics platforms is key for a systems biology approach to gain a full understanding of how radiation exposure impacts the cardiovascular system. Integrating systems biology into the AOP framework can potentially enrich AOP features by expanding the linear abstraction behind KEs to a more complex network of those biological events. To achieve a comprehensive picture of the radiation effect, non-omics findings, such as pathologic images, clinical measures, and epidemiological information as well as other biochemical and biological assays and arrays are necessary to fill the gaps in assessing risk-related outcomes. Figure 2 illustrates a proposed multidisciplinary and multidimensional systems biology approach, ranging from high-throughput data to

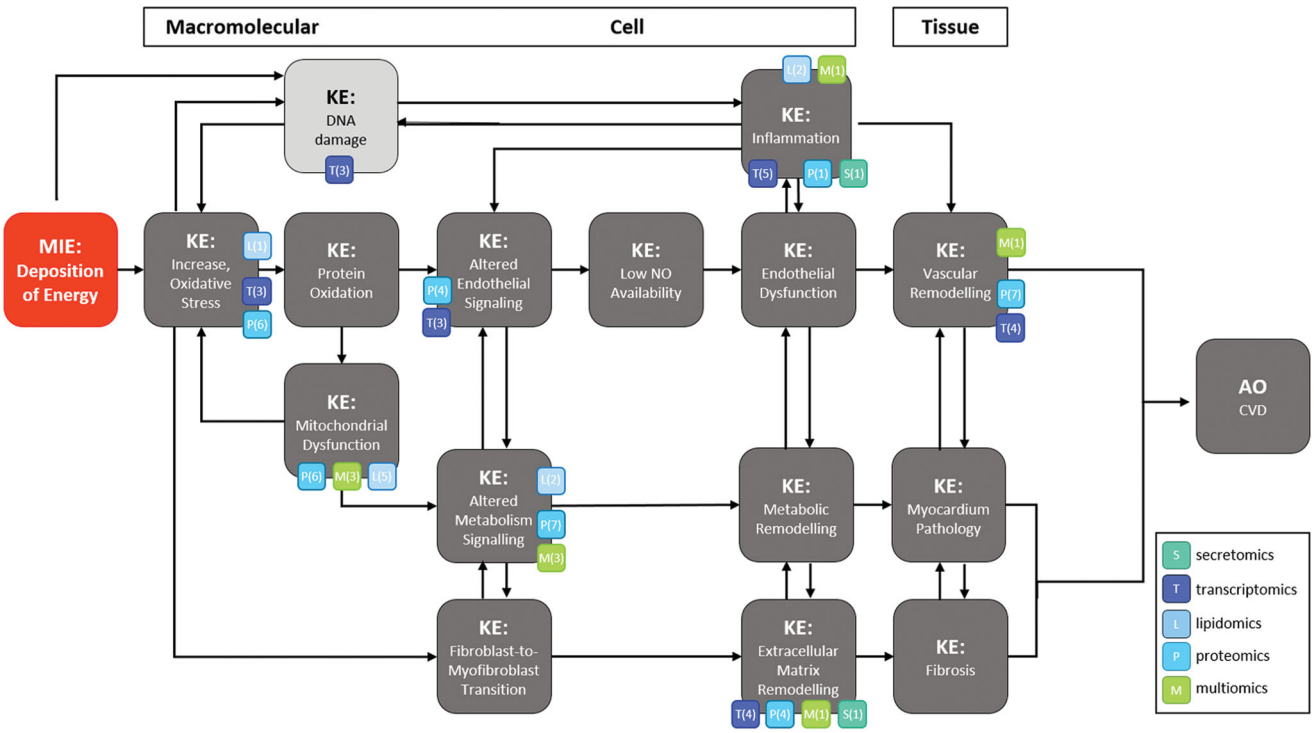

Figure 1. Categories of radiation omics studies to support proposed CVD AOP. Available types of omics data are represented across key events in the CVD AOP network as colored boxes (modified from Chauhan, Hamada, et al. (2021)).

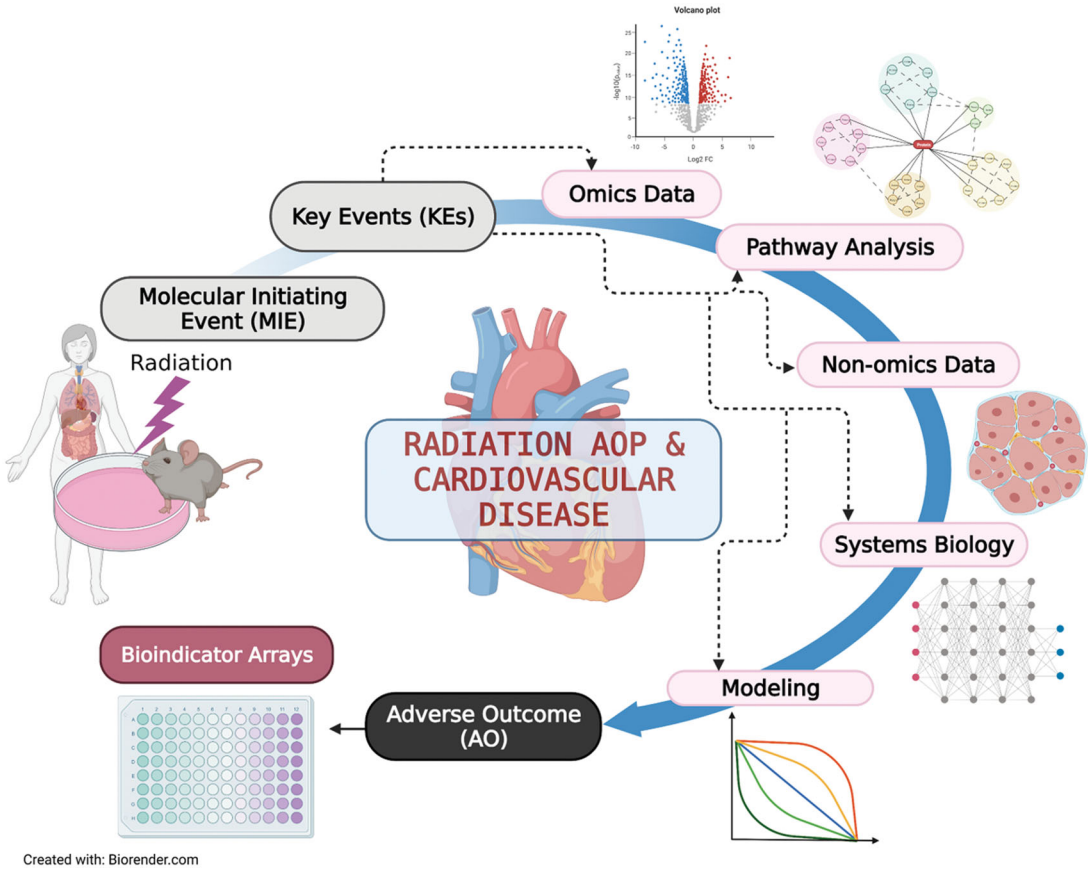

Figure 2. The application of omics data in the development of AOP for radiation-induced CVD. The different levels of omics data obtained from the cell, animal, and human samples can enrich the AOP framework alongside available knowledge from non-omics data, epidemiological findings, and mechanistic, and mathematical modeling. Together, this information can be integrated across biological levels of organization and provide confident bioindicators for the development of bioscreening tools that can support radiation risk assessment. MIE: molecular initiating events; KE: key events; AO: adverse outcome. The figure is created with BioRender.com.

modeling. The approach is designed to integrate omics and non-omics results to understand the biological response of a biosystem (e.g. cardiovascular system) to radiation exposure (Figure 2). Applying the systems biology approach within the established AOP framework should facilitate the development of a reproducible bioassay to measure endpoints relevant to risk assessment (Figure 2).

The evolving radiomics are a good example to meet such an interactive approach (Sotoudeh et al. 2021). The platform extracts a wide range of features of the medical images and translates them to algorithms that can be combined with those from other analytical platforms including omics (Zanfardino et al. 2019). The compiled information can further support the various components of the AOP framework where omics results alone cannot do so.

Understanding CVD as a complex disease requires the investigation at different biological levels of the cardiovascular system. The application of systems biology has recently received increasing attention. The platform provides a pragmatic but sophisticated approach to understanding the changes in the heart tissue during the development and progression of CVD. The various cellular components of the cardiovascular system have been studied by systems biology (Joshi et al. 2021). The integration of omics data and non-omics clinical findings through advanced computational methods and mathematical algorithms provides a highly interactive biological network that can advance our understanding of CVD.

Although there are not many multi-omics studies currently published on the impact of radiation on the cardiovascular system, there are many individual omics studies with strong potential to be integrated into a systems biology approach. A systems biology approach needs an optimal collection of radiobiological samples and data following the FAIR Data Principles (Findable, Accessible, Interoperable, and Reusable) to facilitate sharing and integration of data in the radiation research field (Subedi et al. 2022). To perform optimal re-analysis of data, accessibility to the user-friendly and well-designed repository is crucial. The STOREDB database (https://www.storedb.org) hosted by the German Federal Office for Radiation Protection (BfS) is one of a few available databanks designed for such purposes which include managing, sustaining, and sharing data generated by different platforms of radiation research (Schofield et al. 2019).

Although maintaining linear and simplified biological pathways is the main philosophy behind the AOP approach, systems biology can provide the opportunity to give more mechanistic information, fill gaps in biological data, and translate them at different levels of the organism from molecule to cell up to the individual organism. The integrated approaches may facilitate profiling of the radiation response

in a dose- and time-dependent manner to identify the critical exposure criteria leading to the adverse effect on individuals and populations. To fully translate this information at a population level, further research is needed on molecular epidemiology to test and validate the proposed connections between the AOPs and actual health outcomes. Such 'big data' approaches would typically use information from omics platforms, biobanks, and health registries. Such a comprehensive platform can identify attractive genes, proteins, or metabolites as measurable bioindicators for screening and risk assessment.

In this context, a recent study used a systems (radiation) biology approach, by integrating experimental data on different cellular endpoints, including cellular functions, such as proliferation, senescence, and angiogenic properties, as well as transcriptomics and proteomics data, in order to more comprehensively understand the mechanisms underlying the endothelial response after chronic low-dose gamma irradiation (0, 1.4, 2.1, and 4.1 mGy/h) (Babini et al. 2022).

The mathematical model applied in the study to integrate different datasets reproduced the experimental results and confirmed a dose-dependence for radiation-induced premature senescence, however, the molecular mechanisms differed with dose rates. The re-analysis of cell proliferation rate and the senescence status (percentage of cells responding positively to the senescence-associated β-galactosidase) using a mathematical model (a logistic curve) confirmed a decreasing trend of cell proliferation and increase of senescence as a function of the dose rate.

The study also found that different dose rates could trigger different molecular mechanisms in cells during the onset of senescence (e.g. the dose rate of 4.1 mGy/h affected cell-to-cell communication, cellular adhesion, and inflammation, while the dose rate of 2.4 mGy/h affected the expression of cell cycle-related inhibitors such as the cyclin-dependent kinase inhibitor p21 and the PI3K/Akt/mTOR pathway) (Babini et al. 2022).

Toward regulatory implementation: challenges for radiation omics to inform the AOP framework

The omics data presented here emphasized that the development of the AOP network will need measurements at several dose and time points and in different cell types because the omics profiles of phenotypic alterations may differ by the stage in the pathogenesis of the disease (NCRP 2020). Moreover, before incorporation into the AOP framework omics data need to be evaluated for a series of assessments adapted to B-H criteria including persistence and significance, reproducibility and consistency, biological plausibility, and human health relevance (Bridges et al. 2017). To meet regulatory expectations, omics analyses and related results must be standardized universally and validated effectively. Such uniform conditions enable omics science to produce consistent, reliable, reproducible, and repeatable data to be applied to decision-makers and regulatory applications. In addition, there is a need to improve understanding of the relationships between molecular changes observed in omics data and disease outcomes, as molecular (particularly transcriptional) responses are often early events that lead to overt phenotypic (apical) effects associated with disease progression.

As stated above, the poor availability of low-dose and low-dose-rate data complicates investigations in this area. It is more likely that the available high-dose data can be initially incorporated into the AOP. However, it remains debatable whether, in the absence of data for low dose irradiation, this knowledge can be applied at lower dose and dose rate/fractionation (Little 2016; Little et al. 2020).

It is important to note that ICRP recommended the nominal threshold of 0.5 Gy for DCS, independent of the rate of dose delivery (Stewart et al. 2012). This recommendation aimed basically to serve as a precaution to medical practitioners for risks posed by dose to the heart and brain of the patients. Thus far, no dose limit has been recommended for DCS, so there is no need of discussion for regulatory implementation at this stage. Nevertheless, ICRP Task Group 119 established in 2021 considers implications of the current knowledge on radiogenic DCS for the ICRP System of Radiological Protection. Such discussions are ongoing as part of the steps in preparing the next basic recommendations (Clement et al. 2021). The AOP approach is supported by the ICRP (Laurier et al. 2021) and the UNSCEAR Expert Group on Diseases of the Circulatory System (CircuDis), which encourages further efforts to develop an AOP network for DCS in which omics data can play a central role.

The omics studies discussed here emphasized the urgent need to apply an optimal animal model to study radiation-induced CVD. Such an in vivo system would be important to improve the knowledge base for environmental radiation protection, but should also provide transferable and translational data to apply to human health and human risk assessment. Although the omics data from rodent models are very informative, it is not always easy to correlate the affected pathways with pathological endpoints that are measurable in humans. The genetically modified and diseased animals are also not the best model because they do not necessarily reflect the changes that would be induced in normal animals following irradiation (Chauhan, Hamada, et al. 2021). The unexpected observations, including adaptive or suppressive effects in these mutants at low dose and/or low dose rates, must also be interpreted with caution (Hamada et al. 2014).

An optimal experimental model should be able to account for individual susceptibility and sensitivity in response to radiation exposure, a critical aspect of human health risk assessment. Individual sensitivity to radiation varies and is correlated with genetic factors and lifestyle (De Stefano et al. 2021). Although the contribution of genetic predisposition to radiation sensitivity or radiation resistance in cancer is well accepted, the knowledge in the area of the radiation-induced non-cancer effect is not yet very well developed (Foray et al. 2016; Rajaraman et al. 2018; Barnard and Hamada 2022). The background status of the biosystem (from cell to tissue) at the time of irradiation may also impact the biological effect of radiation exposure. Radiation exposure is arrhythmogenic in healthy individuals

(Azizova et al. 2022), but anti-arrhythmogenic in individuals with cardiac arrhythmias receiving cardiac RT (Zhang et al. 2021).

The availability of human samples for omics studies is a well-known concern in CVD research, where the collection of fresh-frozen biomaterial is inconvenient for ethical reasons. In this context, the role of radiation biobanks is an important consideration for future studies. Radiobiological and clinical archives could provide a valuable source of human biomaterial for understanding the adverse effects of radiation exposure on the cardiovascular system. Omics profiling of archived biomaterial in radiation research has progressed over the past decade but still needs to be further improved (Azimzadeh, Gomolka et al. 2021). Although only a few omics datasets were generated on human biomaterial (Laiakis et al. 2014; Azimzadeh, Azizova, et al. 2017; Papiez et al. 2018; Garrett-Bakelman et al. 2019; Azimzadeh et al. 2020), these studies highlighted the impact of retrospective analysis of archival samples to investigate the adverse effect of clinical or occupational radiation exposure.

In the absence of sufficient frozen samples to study the effects of radiation exposure on cardiac tissue, formalin-fixed, paraffin-embedded (FFPE) samples may indeed represent the optimal material for such retrospective analyses given their large number, simple storage, and plentiful diagnostic records. This stresses the urgent need to improve the radiation biology biobank policy and its infrastructure (Azimzadeh, Gomolka et al. 2021).

The application of high-throughput omics data generated on in vitro systems is an important vision for toxicologists to find an alternative to animal testing (Sauer et al. 2017). However, applying an ideal cellular model to represent the cardiovascular system is not an easy task. The available commercial cellular systems (endothelial cells, fibroblasts, cardiomyocytes, and smooth muscle cells) are not the best alternative for complex and dynamic features of cardiac tissue. Consequently, the bioindicators and biomarkers identified in the in vitro systems cannot be used directly as a surrogate in humans. Using isolated cells from irradiated hearts, 3D models of interactive cells and cell co-culture in omics analysis may help to address this issue.

It is important to note that applications of omics platforms are still in their infancy in radiation research. Epigenetics, post-translational modifications (PTMs), and the secretome of cell communication are unexplored potential that needs to be further investigated to identify early and late health effects of radiation exposure.

Integration of biological and epidemiological data, a vision for risk assessment

Translating the qualitative understanding of detrimental effects into quantitative estimates of health risk remains a pertinent challenge of the AOP framework. The epidemiology-based risk assessment approach used to extrapolate from AOs assessed at higher doses to low doses is associated with significant uncertainties in estimating risk at low doses and low dose rates of ionizing radiation (Preston 2017; Preston et al. 2021).

Approaches to integrating radiation biology data and epidemiology findings for risk assessment, especially at low doses are discussed in Report No. 186 of the US National Council on Radiation Protection and Measurements (NCRP) for cancer and CVD (NCRP 2020). The biological data generated by advanced omics technologies will not only provide a better understanding of the cellular and molecular processes affected by low doses and low dose rates, but may also facilitate the development of biomarkers for radiation-related health effects. Integration of such mechanistic data with epidemiological evidence is expected to improve risk assessment for cancer and CVD (Hamada and Fujimichi 2014; NCRP 2020; Chauhan, Beaton, et al. 2022; NASEM 2022).

Among epidemiological studies with biological data or available biosamples for further examinations (reviewed in NCRP 2020), Japanese atomic bomb survivors and Mayak production association workers are the main cohorts to offer potential biomarker information usable as parameters in a predictive model for the effect of radiation on cardiovascular system (NCRP 2020; Preston et al. 2021).

The Report has clearly emphasized the potential of AOPs to inform conceptual designs of biologically based risk models (BBRMs). For radiation risk of cancer, the Report already illustrated promising BBRM prototypes which were developed for organs, such as the colon, thyroid, and lung. Kaiser et al. propose systematic approaches and appropriate study designs to harness knowledge stored in AOPs for quantitative risk assessment using (cancer-related) BBRMs as hinges (Kaiser et al. 2021). However, for radiation-induced CVD, the development of such BBRMs is still in its infancy. Previous attempts focused on the impact of cholesterol metabolism on atherosclerosis and CVD risk but did not perform model fits against epidemiological datasets (Cobbold et al. 2002; Little et al. 2009; Mc Auley 2022). On the one hand, the sheer complexity of the involved pathogenic processes prevents the development of models with a reasonably low number of parameters. Furthermore, biological and epidemiological evidence for a response at doses below 0.5 Gy is uncertain (Little et al. 2021).

High dose, fractionated RT results in an increase in the rate of major coronary events by 7.4% per Gy in breast cancer patients (Darby et al. 2013). The majority of these events arise from atherosclerosis as the main underlying disease (Rehammar et al. 2017). Thus, the risk projections from BBRMs for therapeutic doses in clinical applications may be useful. Consequently, in the EU-funded MEDIRAD project, the development of a BBRM for acute coronary events (ACEs) in breast cancer patients after RT has been proposed (http://www.medirad-project.eu/work-packages; last accessed on 25 April 2022). Motivated by the AOP framework, it was planned to inform the conceptual model design with data at molecular and vascular levels in a 'bottom-up' approach. The molecular data consisted of epigenetic (DNA methylation) and transcriptomic (miRNAs) analyses obtained from circulating blood cells which have been measured in animal

experiments and the patient samples. For the characterization of a detrimental effect at the vascular level, imaging data from echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) have been recorded. Before joining them into a common database the data are screened separately for each area of origin with standard statistical methods such as multivariate regression of single outcomes. More suited to unravel the complexity of causal relationships between different levels is bioinformatical network analysis (Schäfer and Strimmer 2005; van Wieringen and Chen 2021). This analytical tool should identify radiation-induced clusters of biomarkers linking molecular and vascular levels. Such clusters might pertain to atherogenic processes like chronic inflammation. They generate hypotheses on radiation targets in the atherogenic chain which can be implemented and tested in BBRMs.

Starting from radiation epidemiology in a 'top-down' approach, the development of a BBRM was organized into three levels. In Level I, the baseline model without risk factors described the progression and age-risk pattern of atherosclerosis in a Markov chain Monte Carlo simulation with coronary artery intimal surface area as the object of time evolution (Simonetto et al. 2021). During aging, this area is subsequently covered with atherosclerotic lesions of increasing severity. Complicated lesions appear at the end of the chain and the rate of myocardial infarction increases proportionally to the area of these lesions. Model parameters are derived from simultaneous fits to incidence rates in the German KORA cohort (Kuch et al. 2008) and the age-dependent prevalence and spatial extent of atherosclerotic lesions in the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) (1993) study (PDAY 1993).

In Level II, the model included classical risk factors, such as smoking, hypertension, and dyslipidemia from the KORA cohort (Simonetto, Heier, et al. 2022). The main target of detriment in the chain of the atherogenic process was identified by goodness-of-fit. Whereas the impact of dyslipidemia was realized along the whole atherogenic chain, smoking made its strongest impact at the chain end with complicated lesions. Finally, in Level III, the KORA cohort was replaced by a Dutch cohort of breast cancer patients to obtain a risk model for ACEs after RT. Using the same method of effect identification as in Level II, therapeutic radiation released the strongest impact on complicated lesions. Due to low case numbers, the exact shape of the post-RT age-risk pattern could not be determined. However, the risk increased significantly already in the first five years after RT (Simonetto, Kaiser, et al. 2022). These findings are in line with the observation that RT doses to atherosclerotic plaques in the left anterior descending coronary artery are enhancing cardiac toxicity (van den Bogaard et al. 2021). Moreover, Simonetto et al. proposed that the dose-response for rupture of large atherosclerotic lesions might be non-linear. These studies show that susceptibility to radiation-induced ACEs depends markedly on the atherosclerotic state of a patient (Simonetto et al. 2020). Thus, for risk reduction heart sparing techniques or proton therapy has been proposed for patients burdened with plaques within the volume of high RT doses. The outlined approach of 'Development of biologically-based models to evaluate radiation-induced disease risk' has been added to the MEDIRAD recommendations (http://medirad-project.eu/recommendations/).

Conclusions

There is a body of available data on the various omics applied in radiation research that can broadly inform the AOP framework. By comprehensive screening, omics platforms provide the opportunity to identify biological pathways indicative for risk-related outcomes. Such valuable information can be used to understand the mechanistic links between dose, dose-rate, and radiation quality and disease development and progression. Further research is needed to clarify the issues for the application of omics for regulatory purposes. The quality, accuracy, and reproducibility of omics data need to be improved. The omics data needs to be universally standardized, interpreted, and validated before they can be incorporated into the AOP framework to address radiation protection purposes. A deeper understanding of the molecular mechanism of the biological effects of radiation offers potential measurable bioindicators of radiation exposure, late and long-term effects, susceptibility, and sensitivity. In the long term, this information proposes the development of a reliable and universal bioassay for the human health effects of radiation exposure. It is important to note that the acceptance of the AOP framework in the radiation protection community will be influenced by its ability to improve quantitative risk assessment. Designed mechanistic models, potentially based on different levels of biological organization, may help in this respect.

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