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CURRENT OPINION

DNA damage-associated biomarkers in studying individual sensitivity to low-dose radiation from cardiovascular imaging

Won Hee Lee[1,2,3]*, Patricia K. Nguyen[1,2,3], Dominik Fleischmann[2,3], and Joseph C. Wu[1,2,3]*

[1]Department of Medicine, Division of Cardiology; [2]Department of Radiology; and [3]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA 94305, USA

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Introduction

The use of diagnostic imaging and image-guided interventions using low-dose ionizing radiation has increased dramatically in recent years. This is explained by dramatic advances in imaging technology which provide invaluable diagnostic information for clinical decision-making.[1] Although the benefits of appropriate use of advanced imaging technology outweigh the risks, the medical use of X-ray-based imaging techniques has become a leading source of man-made radiation exposure to the general population. According to a recent report by the National Council on Radiation Protection and Measurements, the total radiation exposure from medical imaging has increased six-fold from the early 1980s to the present, and currently almost 40% of medical radiation exposure (excluding radiotherapy) comes from cardiovascular imaging and image-guided interventions.[2,3] This has prompted renewed interest in the potential long-term risks of low-dose radiation exposure for patients, physicians, and technical staff members.[4,5] Clinical decision-making inherently requires balancing the potential benefits of e.g. a cardiac-imaging procedure and intervention with the projected risks, including those from radiation exposure. Although risk estimates for low-dose radiation exposures and international guidelines exist,[6,7] these have been developed predominantly for the purpose of radiation protection and the development of occupational dose limits for radiation exposed workers (such as some physicians). Risk estimates for medical low-dose radiation exposure are associated with substantial uncertainties—to some extent this is due to the fact that our understanding of the biological effects of low-dose radiation exposure in humans is incomplete.[6,8]

Radiation dose from medical imaging, commonly referred to as effective dose, is expressed in units of millisieverts, which is the weighted average of the absorbed dose in mGy multiplied by two weighting factors that depend on the type of tissue irradiated and the specific type of radiation.[9] The effective dose allows for a rough estimation of the risk of a partial or whole body exposure to ionizing radiation.[10] Cardiovascular imaging may involve considerable radiation exposure. For example, coronary computed tomographic angiography (CCTA) is commonly used to manage patients with suspected coronary artery disease (CAD), new-onset heart failure with reduced heart function, and for a wide range of acute indications such as acute aortic syndromes, pulmonary embolism, as well as surgical or transcatheter treatment planning of aortic diseases.[11] Typical effective doses from CCTA can range from 0.06 to 18.0 mSv with a median of 12 mSv.[12–14] For patients at intermediate risk for obstructive CAD, single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) with injected radioactive tracers has also been the cornerstone for diagnosis, risk stratification, and management. The median effective dose for SPECT MPI was reported to be 10 mSv (range, 10–25 mSv).[15] The effective doses from these medical radiation exposure are equivalent to having hundreds of chest X-rays. Of note, patients undergoing cardiac imaging may undergo not one but a series of tests or procedures involving ionizing radiation exposure, which can result in cumulative exposure of $>$100 mSv, a threshold-level documented to increase potential cancer risk.[8,16,17] It should be noted, however, that these effective doses are only gross estimates, especially for partial body exposures, and may suffer from inherent relative uncertainties of about $\pm$40% due to methodological limitations.[18,19]

Current recommended models for assessing radiation risk

Current cancer risk models for low-radiation exposure often use the linear no-threshold (LNT) model, which assumes that the risk of cancer increases linearly with the exposure, and that the

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* Corresponding author. Email: joewu@stanford.edu (J.C.W.); Email: whlee11@stanford.edu (W.H.L.)

detriments (solid cancers and leukaemias) associated with high-dose and high-dose rate exposures in atomic bomb survivors and from accidental high-dose occupational exposures can be extrapolated to the low-dose range.[20,21] The use of this model is reasonable for purposes of developing dose limits for occupational exposure—where erring on the side of higher risk is desirable—but whether the LNT model accurately describes the relationship between low-dose exposure and the development of cancer remains unclear and controversial. Other models, for example, assume that a dose below a certain threshold is not harmful, and the hormesis model, even posits that low-dose radiation might sometimes be beneficial. Estimating the radiation risk of low-lose radiation (≤100 mSv), thus, remains challenging due to the lack of sufficiently large and well-controlled cohorts for epidemiological studies to quantify a likely small excess cancer risk at low doses, relative to the high 'natural' cancer rate of 40%.[8,22,23] Since the 1970s, the current risk estimates that inform health protection strategies are based on the LNT model, an approach recommended by the International Commission of Radiological Protection[6] and endorsed by the Biological Effects of Ionizing Radiation VII report of the US National Academy of Sciences.[7] In fact, a significantly increased cancer risk of developing both solid cancers and leukaemia is observed in epidemiologic studies of atomic bomb survivors, in those exposed to lower doses of radiation (5–150 mSv) and in a major international study of >400 000 nuclear industry radiation workers who were exposed to low-dose radiation (5–150 mSv) and an average dose of radiation of 20 mSv.[20,24,25] Although some studies have shown the extent of DNA damage to cells is linearly related to dose,[26,27] others show that there may be threshold effects,[28] highlighting that cellular and tissue-level responses to radiation-induced damage are not always linear. In addition, recent studies have challenged the validity of the LNT model for evaluating radiation at low doses because of differences in biological responses of living cells and tissues to low- vs. high doses of radiation. Consequently, the use of biomarkers to measure the cellular effects of low-dose radiation exposure has emerged as an alternative approach to assess the potential risk of radiation.[29,30]

Utilizing biomarkers for estimating biological effects of low-dose radiation exposure

Different types of biomarkers have shown promise as predictors of radiation dose and risk, including chromosome damage (e.g. aberrations and micronuclei), post-translational modification, changes in gene expression and protein synthesis, and epigenomic modifications (*Figure 1*, *Table 1*). Exposure of cells to therapeutic doses of radiation initiates a large-scale activation of specific DNA damage signalling and repair mechanisms, a process known as the DNA damage response (DDR) pathway. This leads to the activation of a number of genes and proteins whose products trigger apoptosis, cell-cycle arrest, chromatin remodelling, and DNA repair, which minimize the risk of heritable mutations implicated in the process of carcinogenesis in human.[31,32] Misrepair of these DNA double-strand breaks (DSBs) can produce many different types of chromosomal aberrations. Cytogenetic biomarkers that can be used for

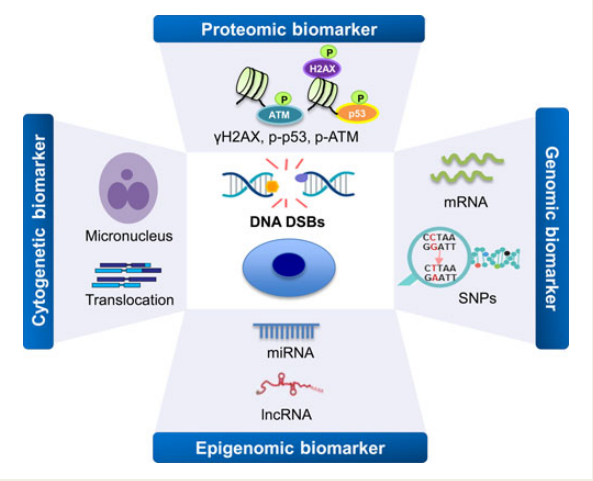

Figure 1 Overview of the DNA damage-associated biomarkers of ionizing radiation. Multiple types of biomarkers are available for measuring radiation exposure and monitoring the DNA damage and repair, such as cytogenetic, proteomic, genomic, and epigenomic biomarkers. ATM, ataxia-telangiectasia mutated; DSBs, double-strand breaks; lncRNA, long non-coding RNA; miRNA, microRNA; p, phosphate group; p53, tumour protein p53; SNPs, single nucleotide polymorphisms.

analysis of these aberrations (e.g. dicentrics, translocations, premature chromosome condensation, and micronuclei) in peripheral blood lymphocytes have been extensively validated as biomarkers of somatic chromosomal damage and intermediate end points in carcinogenesis after radiation exposure. For example, studies have found significantly increased chromosome abnormalities in blood lymphocytes obtained from adult and paediatric patients after CT scans.[33,34] However, because of low sensitivity, long processing time, and tedious scoring methods of these chromosomal aberration biomarkers after radiation exposure, the application of these markers to doses <100 mGy is limited at the present.[35,36]

The measurement of γ-H2AX foci formation has been applied as a biomarker of human low-dose radiation exposure that is more sensitive than quantification of cytogenetic biomarkers (e.g. dicentric chromosomes, micronuclei, and translocations), as foci formation can be detected at lower doses, <10–20 mGy.[37–44] Although the overall γ-H2AX levels in cells and/or tissues can be obtained by using immunoblotting or the enzyme-linked immunosorbent assay,[45,46] detection of individual DSBs by microscopy through foci counting is still the prevailing approach for clinical application since it is the most sensitive method.[47] In response to DSB generation, histone H2AX is phosphorylated within seconds to form γ-H2AX, with γ-H2AX levels peaking at ~30 min. Subsequent to this phosphorylation event, modifications to several other proteins, including phosphorylation of tumour protein 53 (p53) and ataxia-telangiectasia mutated (ATM), have been reported by our group and others as useful biomarkers for low-dose radiation exposure in lymphocytes and fibroblasts.[28,39,42,48] Upon rapid activation by ionizing radiation, the kinase activity of ATM leads to phosphorylation and activation of a number of DNA repair and

Table I Radiation biomarkers used for studying the risk after different diagnostic procedures

Procedure	Biomarkers	References
[^{18}F] FDG PET/CT (~5 mSv)	Proteomic marker (γ-H2AX foci)	May *et al.*[93]
CCTA (~8 mSv)	Proteomic marker (γ-H2AX foci)	Grudzenski *et al.*[94]
CCTA (~36.9 mSv)	Proteomic and genomic markers	Nguyen *et al.*[28]
CCTA (~11.4 mSv)	Proteomic marker (γ-H2AX foci)	Kuefner *et al.*[95]
CCTA (~6.4 mSv)	Proteomic marker (γ-H2AX foci)	Brand *et al.*[54]
CT (~6.3 mSv)	Proteomic marker (H2AX foci)	Rothkamm *et al.*[38]
Invasive angiography (~18.2 mSv)	Proteomic and genomic markers	Lee *et al.*[39]
Invasive angiography (~12 mSv)	Cytogenetic marker (MN assay)	Andreassi *et al.*[96]
SPECT MPI (~10.0 mSv)	Proteomic and genomic markers	Lee *et al.*[39]

PET, positron emission tomography; CT, computed tomography; CCTA, coronary computed tomography angiography; SPECT-MPI, single-photon emission computed tomography myocardial perfusion imaging; MN, micronucleus.

checkpoint proteins, including p53, H2AX, Chk2, and SMC1.[49] For example, a high frequency and similar kinetics of co-localization of γ-H2AX and p53 with pATM foci were observed following exposure to irradiation.[50–52] Although phosphorylation of H2AX may not exclusively reflect DSBs, it is still the best biomarker based on its cell cycle-independent induction, strong correlation with repair kinetics, and repair pathway independence. However, the extensive use of phosphorylated DNA damage marker proteins (e.g. γ-H2AX, p53, and ATM) alone as biomarkers of direct radiation exposure in biological samples is limited due to several factors including the transient character of foci formation, the lack of specificity for radiation, and the variation of foci frequencies between individuals.[53] Despite these limitations, these biomarkers have the potential to reveal heightened sensitivity against low-dose radiation if samples can be collected at multiple time points within appropriate time windows. For examples, the biological effect of different scan modes in different CT generations was reliably compared using γ-H2AX immunofluorescence microscopy.[38,40,54] Our recent studies also demonstrated the distinct levels of phosphorylation of H2AX, p53, and ATM in lymphocytes isolated from adult patients undergoing several cardiac medical imaging tests such as CCTA, SPECT MPI, and invasive X-ray angiography.[28,39] Specifically, the loss of foci has been demonstrated to be correlated with DSB repair, suggesting that the kinetics of foci loss of these protein biomarkers might be also used as an indicator of individual susceptibility to low-dose radiation exposure *in vivo* or *in vitro* studies.[28,38–40,43] With the demonstrated utility of γ-H2AX foci measurements in clinical application, multiple evaluation procedures such as cytometric assessment,[39] automated assay and image processing,[55] and image analysis algorithms[56,57] have been developed for optimizing the methods of foci assessment and detection. For example, recently, a fully automated, high-throughput analysis platform, the Rapid Automated Biodosimetry Tool, was developed to screen γ-H2AX fluorescence labelling in fingerstick-derived blood samples and allows the analysis of up to 30 000 samples per day.[58] To further increase the speed, throughput, and reliability of automated analysis, optimization of the protocols and regular calibration or adequate concurrent analysis of reference samples is necessary.

The transcriptional changes related to DNA damage are also central components of the DDR.[59] Previous studies investigating the influence of dose and dose rate on radiation-induced gene expression profiles have found that a dose as low as 10 mGy can trigger gene expression modifications in human cells, and that low-dose transcriptional responses (25–100 mGy) may differ from those observed at high-dose (>100 mGy) radiation.[60,61] For example, a linear increase in genes involved in p53-regulated pathways such as cyclin-dependent kinase inhibitor 1A (C*dkn1a*), growth arrest and DNA-damage-inducible protein 45 alpha (*Gadd45a*), and Mdm2 p53 binding protein homolog (*Mdm2*) was found between 25 and 500 mGy, whereas at 25 mGy, only genes involved in the regulation of cell death processes were induced.[61,62] Consistent with these findings, we recently demonstrated a concerted elevation in the gene expression of six DNA damage response genes (e.g. *Bax*, *Ddb2*, *Mdm2*, *Tp53*, *Bbc3*, and *Atf6*) in T-lymphocytes isolated from a small subset of adult patients post-SPECT MPI, most patients after radiation exposure from CCTA, and all undergoing invasive X-ray angiography.[28,39] These changes were measureable as early as 2 h after radiation exposure and in some patients were extended to 48 h. Thus, changes in gene expression profiling may be potentially useful to estimate radiation exposure, providing several advantages over the more traditional cytogenetic assays that are more labour-intensive and time-consuming, and requiring relatively long-lived (>24 h) changes and γ-H2AX foci analysis that shows normally a very early and transient response of cells to DSBs, with the caveat that accurate measurements must be performed within a shorter window of exposure when using gene expression profiling as well as taking into account inter-patient variability which may potentially be resolved by having a large enough group size.

Exposure to radiation is also known to lead to epigenomic alteration, which will affect gene regulation after DNA damage induction. MicroRNAs (miRNAs) have recently emerged as promising biomarkers for the detection of various pathological conditions, including post-exposure to radiation.[63,64] After DNA damage induction, post-transcriptional regulation by miRNAs occurs between transient post-translational protein modifications (seconds/minutes) such as phosphorylation and ubiquitination, and gene transcriptional

events (hours/days).[65] Serum miRNAs that fall under the 'omics' biodosimetry approach provide simple and attractive biomarkers that may effectively determine individual radiation exposure because of their inherent stability.[66–68] Previous studies have shown modulated expression profiles in miRNA expression following exposure to low- and high-dose radiation.[69,70] For example, miR-150 demonstrated a dose and time-dependent depletion in serum from mice irradiated at a range of 1–8 Gy.[71] A significant modification of expression upon radiation exposure was also observed for miR-34-a-5p and miR-182-5p in human T lymphocytes, which exhibit strong pro-apoptotic and anti-proliferative properties,[72] and dual properties as both an oncogene and tumour suppressor depending on the cellular model, respectively.[73] In addition, the expression of miR-20 and miR-21 was significantly decreased in low dose (50 mGy) irradiated human B lymphoblast cell lines,[74] thus indicating potential key roles of miRNAs in estimation of the dose and the regulation of cellular response to which the individual was exposed. In addition to miRNAs, long non-coding RNAs (lncRNAs) are a less investigated class of mRNA-like transcripts and their expression has been shown to be associated with cellular response to radiation-induced DNA damage. So far, only a few radiation-responsive lncRNAs have been found. For example, the expression of several lncRNAs such as lncRNACCND1, gadd7, ANRIL, and PANDA were found to be induced by DNA damage, and lncRNA-RoR, loc285194, and lncRNA-p21 were shown to be regulated by the p53 pathway, which is involved in the DDR.[75] The two other lncRNAs (e.g. TP53TG1 and FAS-AS1), direct target of TP53, were also up-regulated by radiation exposure in human T lymphocytes.[76] Although the deregulation and biological functions of radiation-responsive miRNAs and lncRNAs remain largely unknown considerable evidence suggests that miRNAs and lncRNAs may serve as a potentially rich source of biomarkers for studying radiation exposure, predisposition, and individual susceptibility.[68,77]

The identification of radiation exposure-related biomarkers will enable us to better understand how humans react to radiation exposure, and may provide a model to estimate individual sensitivity to radiation in the future. The main features of DNA damage-associated biomarkers are summarized in *Table 2*. As the formation of DNA damage is not unique to radiation, studies should take into account how the utility of these biomarkers can be affected by various factors that may affect individual sensitivity, such as age, gender, genetic susceptibility, and exposure to other environmental carcinogens such as tobacco smoke.

Strategies for assessing individual radiation sensitivity using biomarkers and cellular models

The induction or suppression of DDR pathways are important determinants of how patients respond to radiation exposure.[78] To maintain the benefits of cardiac medical imaging tests while minimizing the radiation risk, a better understanding of individual differences in radiation sensitivity and molecular events involved in cellular response to low-dose radiation is needed. The occurrence of individual variability in response to radiation sensitivity has been extensively reviewed in previously published reports.[79,80] In recent years, cell-based and genetic studies have provided the molecular and genetic basis of cellular effects of radiation by identifying the genes and pathway involved.[61,81,82] For example, genome-wide

Table 2 Principal of features of DNA damage-associated biomarkers

Biomarkers	Advantages	Limitations	Readout/time of onset	Cell types
Cytogenetic (e.g. micronuclei, translocations, dicentrics)	Standardized protocol and relatively low costs High specificity to IR and low background in non-exposed population (dicentrics) Easy identification (micronuclei) Can be used in cases of long-term IR (translocations)	Laborious, time-consuming, sophisticated, variability in scoring cells Limited sensitivity at dose <0.1 Gy High background frequency (translocation and micronuclei)	Days to weeks Retrospective (translocations)	WB PBMC
Proteomic (e.g. γ-H2AX, pATM, pP53)	Highly sensitive and linear with radiation dose : 0.01–8 Gy Can detect radiosensitive individuals Potentially high-throughput analysis	Not specific to IR (also formed in response to UV and other genotoxins) Fast decline of the signal Variation of foci frequency between individuals	Minutes to days	PBMC Fibroblasts
Genomic (e.g. mRNA, SNPs)	High-throughput analysis Linearly dose dependent to IR	Bioinformatic challenge and high cost (RNA-Seq)	1–3 days	PBMC WB Cell lines
Epigenomic (e.g. miRNA, lncRNA)	Relatively stable Potentially high-throughput analysis Cell- or tissue-type-specific expression	Lack of data on specificity and sensitivity	Hours to days	Serum PBMC Cell lines

WB, whole blood; PBMC, peripheral blood mononuclear cell; IR, ionizing radiation; UV, ultraviolet; ATM, ataxia-telangiectasia mutated; lncRNA, long non-coding RNA; miRNA, microRNA; p, phosphate group; p53, tumour protein p53; SNPs, single nucleotide polymorphisms.

transcriptomic analysis of a small area of human tissue exposed *in vivo* to low-dose radiation yielded considerable individual variability of radiation response.[83] Our recently published prospective cohort study of 63 patients undergoing SPECT MPI investigated the biological effects of low-dose radiation using proteomic and genomic biomarkers and found marked variation in individual response to low-dose radiation.[39] However, individual radiosensitivity can arise from both genetic predisposition and/or other factors (e.g. diet, tobacco use, or prescribed medications). Controlling such confounding factors is difficult, compromising assessments of *in vivo* radiation responses between individuals.

Alternatively, patient-derived primary cells can serve as a predictor of individual variability in response to low-dose radiation, providing better control of the confounding factors via standardization of cell culture conditions. Peripheral blood lymphocytes have been commonly used for identifying biomarkers and studying individual response to low-dose radiation from cardiac medical imaging, because these primary cells are easily accessible and represent one of the most radiosensitive cells types in the body.[39,62] However, such cells have limitations due to their low proliferation potential, and their use is further complicated by the fact that different cell types (e.g. proliferative vs. non-proliferative) within the same individual may show varying responses to low-dose radiation. Therefore, it is highly desirable to have an *in vitro* platform in which different cell types from the same individual can be exposed to the same *in vitro* low-dose radiation for measurement of cellular responses with sensitive biomarkers that focus on the DNA damage response, alterations in chromatin structure, gene expression, and proteomics.

In this context, human induced pluripotent stem cells (hiPSCs) are an attractive option as they are easily accessible and can be derived from fibroblasts or peripheral blood mononuclear cells. In fact, hiPSCs have greatly expanded the realm of possibilities for both basic research and potential clinical applications, including development of personalized cell-based assays and well-defined *in vitro* platforms utilizing specific types of cells derived from patients, which may help elucidate the molecular basis of diseases and lead to the discovery of clinically relevant biomarkers and potential therapeutic targets (*Figure 2*). For example, patient-specific iPSCs have been widely used as an *in vitro* platform for disease modelling, drug screening, drug discovery and toxicity assays, and precision medicine.[84,85] These iPSCs are capable of differentiating into various cell types, including cardiomyocytes and endothelial cells, providing an effective system for studying individual variability in response to low-dose radiation across various cell types. By using genetic and molecular approaches, iPSCs-based and patient-specific platforms will allow us to identify potential candidate genes that may contribute to individual variation in response to radiation. It is important to note, however, that the iPSC-based platform is in itself limited by the lack of differentiation protocols into certain cell types, as well as challenges in manufacturing scale and long-term culture. While limitations remain that prevent the full application of iPSCs at the present, such as the absence of well-defined controls, genetic aberrations caused by reprogramming factors, and lack of large numbers of iPSC lines, these hurdles are expected to be overcome in the near future with the ongoing development of more effective reprogramming methods and creation of large iPSC biobanks worldwide.

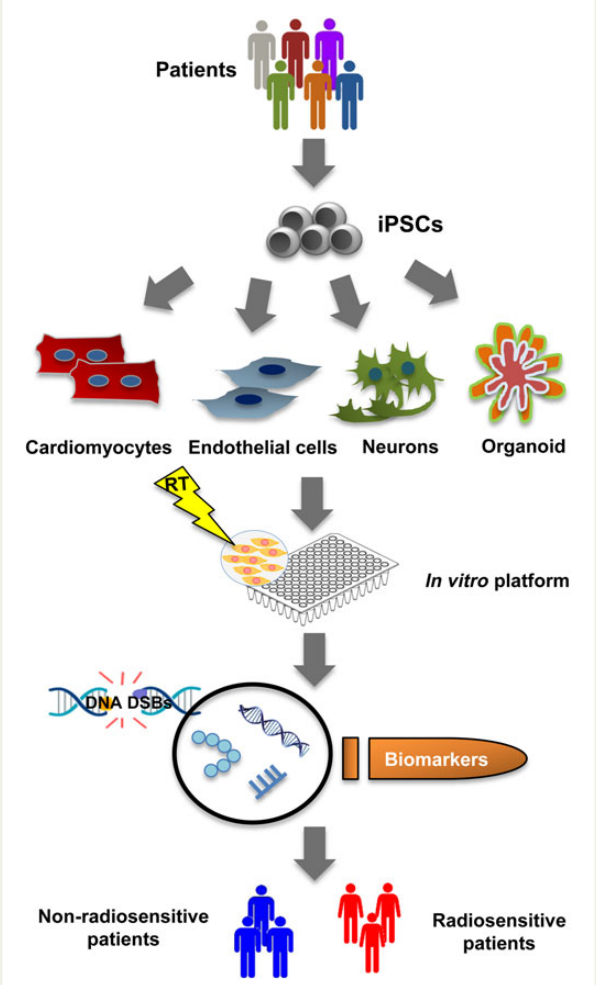

Figure 2 Schematic of a donor-specific cell-based platform for predicting individual radiosensitivity. Induced pluripotent stem cells obtained through the reprogramming of somatic cells from an individual can be differentiated into various cell types. Different cell types from the same individual can then be exposed to radiation for measurement of cellular responses *in vitro* using multiple biomarkers. iPSCs, induced pluripotent stem cells; RT, radiation; DNA DSBs, DNA double-strand breaks.

Recent advances in three-dimensional (3D) culture techniques that can independently manipulate genetics and microenvironmental factors also may be used as a platform to better understand the fundamental biological response to normal and disease processes, and to test novel therapeutic strategies, often using patient-derived cells or tissues.[86] Although no approach is currently ready for routine clinical practice, 3D culture techniques may provide an integrative tool to generate individualized predictive or prognostic information for preclinical therapeutic testing, which is the ultimate objective of precision medicine and targeted therapy. There are a number of studies evaluating the effects of radiation in 3D culture models in terms of DNA damage and apoptosis. For example, treatment of organotypic slice cultures derived from human glioblastoma with the chemotherapeutic drug after irradiation-induced variable DNA damage and strongly affected proliferation and cell death

rates, making this a unique model to explore susceptibility of individual tumours for specific therapies.[87] In addition, foci formation of DNA damage marker proteins, such as p53-binding protein 1(53BP1), phosphorylated ATM, and γH2AX, was detected in a 3D tissue model after radiation, and foci diameter growth was shown to be correlated with chromatin remodelling to facilitate DNA repair.[88] Explanting the living tissue or cell of a patient into a 3D culture model will require a high degree of standardization and reproducibility across experiments. There are still important requirements to be met for drug screening application, such as the ability to replicate complex heterogeneous cell mixtures from patients and the degree of adaptability using a high-throughput screening platform.

Conclusion

Identification of biomarkers capable of providing an accurate estimation of radiation risk caused by low-dose radiation and predicting individual radiation sensitivity may improve our understanding of the biology pertaining to low-dose radiation. Using a multi-parametric approach that includes mass spectrometry, second-generation sequencing, and high-throughput evaluation of single nucleotide polymorphisms (SNPs), we may be able to identify the underlying factors that modulate radiation sensitivity. The use of various 'omics' technologies together with the emergence of public data repositories may be highly useful to reduce study bias, increase statistical power, and improve overall biological understanding of underlying factors that modulate radiation sensitivity. However, care should be taken during horizontal data integration (frequently used in meta-analysis involving the combination and multi-faceted analysis of different data sets measuring the same molecular events) or vertical data integration (combining data collected at different levels in the 'omics-cascade') in the context of (i) data management due to the sheer size of raw data generated and (ii) the complexities of existing analytical approaches especially in dealing with high-throughput studies with high dimensionality but of relatively small sample size.[89–92] Ultimately, development of cellular models that are donor-specific and obtainable non-invasively, along with use of a panel of multiple biomarkers, will provide crucial information elucidating the interplay of genes, proteins, and possible pathways responsible for individual responses to low-dose radiation. This information may provide us with a better understanding of how low-dose radiation affects living tissues so that we may develop novel strategies to minimize individual risk.

It is important to note that changes in these radiation biomarkers does not necessarily equate to increased cancer risk and interpretation of all findings using biomarkers should be limited to the cellular response to low-dose radiation-induced damage in the short-term. Measuring the potential risk of low-dose radiation-induced cancer is particularly difficult, because it is complicated by much higher potential risk of inherent risk of cancer and the omnipresent background radiation, making accurate estimates infeasible using any existing strategies.

Future directions

Despite these inherent limitations, radiation biomarkers can better inform us about the mechanisms modulating individual radiation risk, which can lead to the development and adherence to measures to minimize risk. In the past years, radiation dose reduction has been successfully achieved by several remarkable technical refinements. Future studies should focus on identifying highly sensitive cell injury biomarkers for very low-dose radiation (<3.0 mSv) and finding a rapid, practical, and quantifiable measure of biological response to low-dose radiation amiable to high-throughput population testing that can be used to rank individuals in their radiosensitivity. In addition, the expanded scale on the automated platform maintaining reduced variation will provide adequate statistical power to detect a modest effect of underlying traits of individual radiation sensitivity. Given the necessity of cardiovascular imaging, this information will be invaluable for clinicians and patients who rely on these tests to guide the diagnosis and management of complex cardiovascular disease.

Authors' contributions

J.C.W. handled funding and supervision. J.C.W., W.H.L. acquired the data. J.C.W., W.H.L. drafted the manuscript. J.C.W., W.H.L., P.K.N., D.F. made critical revision of the manuscript for key intellectual content.

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