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Review

The Potential of Omics in Biological Dosimetry

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Simple Summary: Biological dosimetry is used to detect and quantify a radiation exposure using biological indicators. Classically, cytogenetic methods are used for dose estimation in a nuclear incident. However, as these methods are very time-consuming, new techniques for dose estimation are being sought, especially in the case of a large radiation accident involving several thousands of people. This review describes the potential use of omics-based technologies such as transcriptomics, proteomics, and metabolomics for dose estimation.

Abstract: Biological dosimetry is an internationally recognized method for quantifying and estimating radiation dose following suspected or verified excessive exposure to ionising radiation. In severe radiation accidents where a large number of people are potentially affected, it is possible to distinguish irradiated from non-irradiated people in order to initiate appropriate medical care if necessary. In addition to severe incidents caused by technical failure, environmental disasters, military actions, or criminal abuse, there are also radiation accidents in which only one or a few individuals are affected in the frame of occupational or medical exposure. The requirements for biological dosimetry are fundamentally different for these two scenarios. In particular, for large-scale radiation accidents, pre-screening methods are necessary to increase the throughput of samples for a rough first-dose categorization. The rapid development and increasing use of omics methods in research as well as in individual applications provides new opportunities for biological dosimetry. In addition to the discovery and search for new biomarkers, dosimetry assays based on omics technologies are becoming increasingly interesting and hold great potential, especially for large-scale dosimetry. In the following review, the different areas of biological dosimetry, the problems in finding suitable biomarkers, the current status of biomarker research based on omics, the potential applications of assays using omics technologies, and also the limitations for the different areas of biological dosimetry are discussed.

Keywords: biological dosimetry; omics; transcriptomics; proteomics; metabolomics

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1. Introduction

"Omics" is the generic term for the analysis of molecular biological processes at different regulatory levels such as that of DNA, mRNA, proteins, and metabolites. Technologies for the analysis of omics data are high-throughput methods that can be used to image many molecular events simultaneously. This has enabled an improved understanding of biological processes in their entirety. The development of omics methods has significantly contributed to the elucidation of key players and their regulation in biological and pathological situations, which is crucial for the development of novel therapeutic agents. Due to the enormous development of these technologies and the significant decrease in their costs, they have also become attractive for daily clinical practice. The ability to generate large amounts of multi-omics data on an individual basis provides great potential for developments in personalized medicine, which is seen as the future of novel therapies [1,2].

Besides its use in research and clinical applications, omics methodology has also become interesting for biological dosimetry [3–5].

Biological dosimetry is an internationally recognized method for the qualitative and quantitative detection of suspected or actual overexposure of individuals to ionising radiation based on biological events. The overexposure is caused, for example, by a nuclear radiation accident, the use of radioactive warfare agents, or accidental radiation exposure in medicine or industry. The methods are based on the detection of radiation-induced changes in the cells on the molecular or cytogenetic level.

Established cytogenetic methods, such as the quantification of dicentric chromosomes, can reliably estimate radiation exposure but have the disadvantage of being relatively time-consuming. Therefore, there is a need for research on new biomarkers as well as novel methods that ensure rapid dose categorization, especially in the case of a large radiation accident involving several thousands of people, in order to be able to initiate appropriate medical care for those affected [6]. Omics methods can potentially contribute to the discovery of new radiation-dependent biomarkers as well as to the development of novel analytical methods for biological dosimetry in order to fill this research gap.

This review discusses the state of the art in omics-based biomarker research, the challenges for biological dosimetry, and the potential use of novel omics-based techniques in various radiation scenarios.

2. Fields of Application of Biological Dosimetry

Biological dosimetry can provide valuable impact on the field of radiological emergency management and supplement the clinical categorisation of victims. Nuclear and radiological incidents are relatively rare but can have tremendous effects on health and the environment when they occur. Basically, a distinction is made between two scenarios: the large-scale radiation event and the small-scale radiation event [6].

A large-scale radiation event is defined as an incidence that exceeds the local medical resources [7]. Major mass-casualty events such as those that happened in Chernobyl in 1986 and Fukushima in 2011 were caused by the accidental release of nuclear material. Moreover, accidents can have a military background, as in the case of the atomic bombs dropped on Hiroshima and Nagasaki [8]. In the case of a mass-casualty incident, victims initially receive medical care from emergency services based on their medical symptoms and the local distance to the exposure site [9,10]. However, the symptoms caused by radiation are often similar to those caused by anxiety and stress [11]. Therefore, the distinction between irradiated and non-irradiated persons is difficult to perform but essential in order to avoid unnecessary medical care and thus save on medical capacities [6]. A lesson learned from previous incidents is the importance of identifying those who "worried well"—distressed people who had not been irradiated—in order to prevent the healthcare infrastructure from being overwhelmed and to minimise socio-economic harm [12]. Biodosimetric measurements are often carried out in specialised laboratories that are far away from the sampling site. In the event of a major radiation accident, it would be a great advantage to have a test that can be performed quickly on site without causing delays in transporting samples to central labs. This would provide a quick classification of those involved into irradiated and non-irradiated persons. Therefore, the development of point-of-care (POC) diagnostics is urgently needed. Omics-based biomarkers provide a good basis for this, which is already being applied in the field of transcriptomics [13].

Small-scale radiation accidents involve the overexposure of a single person or a small group of people. The approach to the handling of minor radiation accidents differs significantly from that of major nuclear disasters. These actual or suspected radiation exposures occur in medical, industrial, and residential settings. In most of these cases, biodosimetry techniques do not detect increased radiation exposure or only very low dose exposure and thus provides evidence to rule out false alarms, to reassure the victims, to clarify compensation issues in occupational accidents, and if necessary, to initiate medical follow-up measures [14].

3. The Prerequisite of Suitable Biomarkers for Biological Dosimetry

The basis of biological dosimetry is the quantification of changes in specific biomarkers induced by ionising radiation. Biomarkers are defined as measurable parameters of biological processes that have prognostic or diagnostic significance and therefore, in the case of biological dosimetry, serve as indicators of acute or previous exposure to ionising radiation [15].

In recent years, much research has been conducted on the effects of ionising radiation on humans, leading to the discovery of numerous new radiation-specific biomarkers. While basic radiobiological research focuses on the radiation response of specific organs or tissues, biological dosimetry is more interested in biomarkers found in materials that require less invasive analyses such as blood or urine. Due to their high sensitivity to radiation and their minimally invasive collection, peripheral blood lymphocytes are the material of choice in classical biodosimetry assays such as the quantitative analysis of dicentric chromosomes [16]. For the discovery of new biomarkers and the study of the effect of ionising radiation on humans, the most reliable model would be the acquisition of samples from healthy humans irradiated in vivo. However, the availability of such biological material from people who were irradiated accidentally or unintentionally, such as the Mayak workers, is very sparse [17]. Therefore, cancer patients undergoing radiation therapy provide another opportunity to study the effects of radiation exposure. These studies have already contributed significantly to biomarker research, but trials are severely limited by treatment schedule and are often influenced by health status and parallel therapies such as chemotherapy. Moreover, mice and rats serve as model organisms. In principle, these mammals are good models for the study of basic mechanisms in humans, but it has often been shown that the expression of genes and proteins is fundamentally different from that in humans [18]. To overcome this problem, biomarker research is also performed in non-human primates (NHP) [19]. Another widely used option is the irradiation of blood ex vivo and then examining the biological consequences. For cytogenetic methods such as the quantification of dicentric chromosomes or micronuclei in lymphocytes, the results are similar to those obtained from in vivo irradiated lymphocytes that come from peripheral blood [20]. However, the disadvantage of ex vivo studies is that it is not possible to study systematic and long-term effects. To overcome this problem, Lee et al. developed a model that allows for the effects of irradiation on human lymphocytes to be studied in vivo. To this end, they developed humanized mice whose murine lymphocytes had been replaced by human CD45+ cells. At specific time points after irradiation, these lymphocytes could be isolated and studied for radiation-induced proteome changes ex vivo (Lee et al., 2018). This example shows that there is a general need for innovative model systems to study the acute and long-term effects of radiation on humans in order to identify novel biomarkers for biological dosimetry.

Biological markers and their analysis need to fulfil specific prerequisites and requirements that are necessary for reliable dosimetry. The following points are the key criteria for suitable biomarkers and analytical methods used to estimate radiation exposure [21]:

- Specific to ionising radiation;
- Clear dose–effect relationship for different radiation qualities and dose rates;
- Low background level;
- Stable appearance without temporal fluctuations and stable base values;
- Reliable for a large dose range;
- Possibility to distinguish different radiation exposures (dose rate, partial irradiation, radiation quality);
- Good reproducibility;
- No influence of gender, age, and health status;
- Comparability of in vitro and in vivo results;
- Rapid sample processing and evaluation of received doses;
- Minimally invasive sample collection;
- Cheap and simple analysis.

The existing cytogenetic methods need skilled staff for analysis and involves a time-consuming procedure. New approaches are necessary to increase the throughput in the case of a large-scale accident. The rapid development and increasing use of omics methods in research as well as individual applications have not stopped at biological dosimetry. In addition to the discovery and search for new biomarkers, dosimetry assays based on omics technologies are becoming interesting and hold high potential, especially in biological dosimetry for large-scale incidents.

4. Radiobiological Biomarkers Based on Omics Technologies

Omics analytics provides insights into an entire network of regulators and cellular signalling pathways and have therefore become increasingly important in biomedical research (Figure 1). Genomics refers to the systematic analysis of the complete genome or all active genes of a cell, a tissue, an organ, or an entire organism. In the context of biomarker screening for biological dosimetry, this area of omics is not relevant. Transcriptomics is the qualitative and quantitative analysis of mRNA. The alterations in RNA content are measured either by quantitative real-time polymerase chain reaction (qRT-PCR), which enables an accurate quantification of single RNAs, or via microarrays that offer a global scale analysis [22,23]. In proteomics, the composition of proteins in a target tissue is examined. The general workflow of proteomic analysis involves the isolation and protease digestion of proteins, followed by the determination of the relative amount of each peptide by high-performance liquid chromatography (HPLC) in combination with high-resolution mass spectrometry (MS/MS). The MS spectra obtained are analysed with the use of bioinformatics programmes and database research to identify the proteins involved and their molecular role in the radiation response [24]. In metabolomics, the metabolic products of a specific body fluid, tissue, or organ are quantified. The specific methods used for metabolic profiling are liquid or gas chromatography, followed by mass spectrometric analysis as it is used in proteomic approaches. An omics approach allows for the simultaneous quantitative analysis of thousands of different mRNAs, proteins, or metabolites in a given sample and provides information on whole transcriptome, proteome, or metabolome changes compared to untreated controls. This has an enormous advantage compared to analyses of individual markers, as the complex relationships can be better mapped. However, the enormous amount of data generated in this context requires computational and storage capacity as well as know-how of complex methods in statistics and bioinformatics.

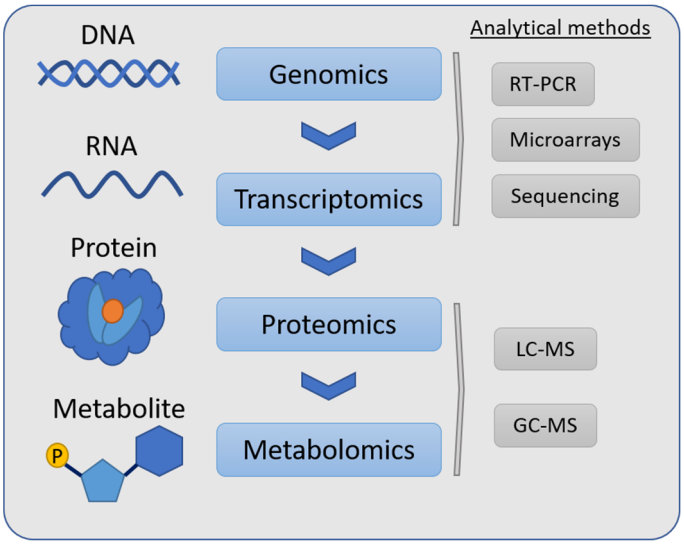

Figure 1. Overview of different omics sciences and their analytical methods.

4.1. Transcriptomics

Transcriptomics assesses shifts in RNA content following exposure to various adaptive stimuli and events. In reaction to ionising radiation exposure, a complex response occurs, which involves multiple cascades of transcriptional signalling pathways and key regulators in a cell to induce the cell cycle arrest and repair of DNA damage in order to prevent cell death. The ability to detect and quantify these radiation-responsive transcriptome shifts using molecular methods holds potential for biological dosimetry by correlating gene expression levels with ionising radiation doses under different scenarios (Badie et al., 2013; Paul and Amundson, 2008). Therefore, most research in omics-based biological dosimetry currently focuses on new biomarkers and gene expression-based methods.

Global gene expression arrays initially serve as a research platform for finding appropriate marker genes that are suitable for biodosimetric applications. This means that the changes are detectable in a relevant dose range and have a dose–response relationship so that the expression values for the respective genes can be assigned to a specific radiation dose.

In general, radiation-specific genes and signalling pathways are part of DNA repair and cell survival processes. In peripheral blood lymphocytes, most of the changes correlate to the well-studied p53 pathway [3,25,26]. P53 maintains genome stability by preventing the occurrence of mutations caused by cellular stress or DNA damage. In addition, p53 is involved in regulating the expression of a variety of genes involved, for example, in apoptosis, cell differentiation, growth arrest, or accelerated DNA repair [27,28]. Genes suitable for dose estimation that belong to this pathway and have been found to be deregulated by irradiation are, for example, FDXR, DDB2, MDM2, ACTA2, ASCC3, BAX, AEN, BBC3, CDKN1A, CCNG1, GADD45, MDM2, and PCNA [4,29–32]. Other candidate genes include PHPT1, XPC, PCNA, SENS1, MYC, PFKP, and ZMAT3 and have been identified as promising for biological dosimetry [4,33]. Manning et al. showed that deregulation in the expression of FDXR, DDB2, and CCNG1 indicate exposure to low-dose ionising radiation, whereas the combination of FDXR, DDB2, and PHPT1 is useful for determining high-dose exposures [34].

In a comparison of laboratories belonging to the RENEB network (Running the European Network of Biodosimetry and Retrospective Physical Dosimetry), Abend et al. were able to show that dose reconstruction based on FDXR and DDB2 is reproducible across different methods, protocols, and laboratories. However, they clearly noted that success in identifying ex vivo protracted radiation is strongly dependent on the exposure and incubation time (at least 4 h) and a constant temperature of 37 °C in order to allow for the biological response to manifest as gene expression changes [35].

In addition, in the case of a mass-casualty incident, sending blood samples to well-equipped laboratories is time-consuming and complicated due to strict regulations. However, Cruz-Gracia et al. investigated the possibility of using nanopore sequencing in biodosimetry, a method that offers the possibility of on-site analysis using portable measuring devices. The shift of a specific gene cluster and dose correlation was most significant for FDXR and APOBEC3H in human peripheral blood mononuclear cells 24 h after 2 Gy ex vivo irradiation [36].

Until now, the most promising and most frequent gene identified as a suitable biomarker is FDXR [37,38]. Although due to the complexity of the molecular reaction caused by ionising radiation, dose estimation based on single changes in gene expression is not optimal. Therefore, the use of panels of radiation-sensitive genes are more promising for improving the accuracy of the estimation [39–41]. More research must be performed to define such gene signatures for different dose rates and radiation qualities in order to apply gene expression in biological dosimetry, especially for POC usage [13].

4.2. Proteomics

Proteomics is a snap shot of all proteins expressed at a certain time and under specific environmental conditions, which can be analysed qualitatively and quantitatively. In combination with bioinformatic analysis, conclusions can be drawn about functional regulatory

mechanisms, signalling pathways, and key proteins responding to external stimuli [42]. Following changes induced by ionising radiation in the transcriptome, the deregulation of proteins occurs and can be measured by high-throughput methodology. Additional posttranslational modification such as phosphorylation following the activation of proteins can be analysed.

Protein expression studies following ex vivo irradiation of human lymphocytes or in non-human primate (NHP) models have identified several proteins that exhibit a linear dose–response relationship or dose specificity. The following marker proteins were identified as promising for biodosimetry: AACT, ATM, BAX, CCL2, CDKN1A, CRP, DDB2, FDXR, FLt3L, H2AX, IL6, LBP, MYC, LCN2, TNF, TP53, TSPYL2, XRCC6 [5,43,44]. An interaction analysis of these proteins was performed using the STRING-db. The light-green cluster represents the inflammatory cluster, while the red-green cluster consists of proteins that belong to DNA repair and cell cycle arrest (Figure 2). These proteins are involved in cell cycle regulation, DNA repair, apoptosis signalling pathways, or early inflammation induction and, comparable to the biomarker genes for gene expression analysis, belong to the TP53 pathway, as demonstrated in [5,43,45].

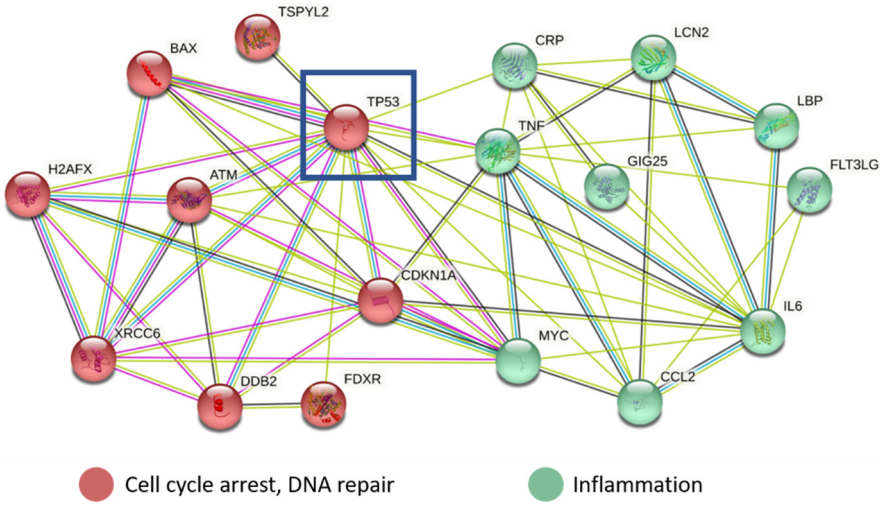

Figure 2. STRING db analysis of the top candidate proteins for biological dosimetry. The network represents the connection between the single proteins. The two clusters presented allocate the proteins to specific molecular functions such as cell cycle arrest and DNA repair in red and inflammation in green.

In a literature review, Marchetti et al. examined a set of 261 mammalian proteins for their suitability for use in biological dosimetry. Their analysis revealed that the combination of ATM, H2AX, CDKN1A, and TP53, proteins involved in early damage detection and cell cycle control, are the best candidates, exhibiting dose-dependent deregulation over a wide dose range. To improve individual dose estimation, they expanded the biomarker panel to 20 proteins [5].

Humanised mice are a promising model for finding suitable proteins as biomarkers to be used in biological dosimetry. They allow for the investigation of radiation effects on human lymphocytes in a mammalian organism. Studies using this model have identified 46 radiation-responsive proteins, with FDXR, BAX, DDB2, and ACTN1 being the strongest candidates [44]. These proteins have already been proven to be suitable for dose estimation in various experimental set-ups and also as promising biomarkers in gene expression approaches [37,38,43].

Another promising approach for early triage decisions was presented by Wang and colleagues. They developed a bioassay called FAST-DOSE (Fluorescent Automated Screening Tool for Dosimetry) that can reconstruct the absorbed radiation dose in peripheral blood samples using an immunofluorescent biomarker system. They tested a range of biomarker proteins in humanised NOD-scid-gamma (Hu-NSG) mice and NHPs up to 8 days after

exposure. In the mouse study, ACTN1, BAX, FDXR, and TP53 showed a linear dose shift up to day 3, and accurate dose reconstruction was possible. For NHPs, the biomarker panel was extended to include DDB2 and TSPYL2 and was able to discriminate samples by dose categories below or above 2 Gy, up to 8 days after whole-body exposure [46].

Balog et al. developed a blood protein marker panel for dose estimation, including AACT, AMY, FLT3L, MCP1 (CCL2), and NGAL (LCN2), which was tested on NHPs. The peak level of AMY, ACCT, and NGAL (LCN2) was reached 24 hours after irradiation, while FLT3L showed a first significant increase three days after irradiation, which lasted until the seventh day. MCP1 (CCL2) levels increased on the first day and continued to increase until the fifth day. This underlines the need for an application based on a panel of radiosensitive proteins to allow for reliable dose estimation [47].

In both studies, protein biomarker panels were analysed using immunoassays, which have great potential to be used in a POC biodosimeter.

4.3. Metabolomics

In addition to the reactions to radiation exposure at the level of RNA and proteins, exposure consequently also affects metabolic processes and the composition of metabolites. The metabolome describes the totality of low-molecular metabolites in a biological system such as tissue or body fluids. Changes in the metabolome are caused by biochemical reactions triggered by catalytic proteins in response to certain environmental factors such as exposure to ionising radiation. Shifts in metabolite concentrations in response to radiation-induced mitochondrial dysfunction, increased oxidative stress, and DNA damage therefore provide information on radiation-induced changes and could serve as suitable biomarkers for biodosimetry.

Radiation-induced metabolomic changes have been studied in biological fluids such as urine, blood, and saliva as well as in subcutaneous fat and organ tissues from relevant models. Most studies show promising results, especially in urine and serum, which could be measured up to seven days after exposure [48].

Pannkuk et al. have made an important contribution to finding relevant biomarkers in response to radiation exposure. The metabolites citric acid, creatine, citrulline, taurine, carnitine, xanthine, creatinine, hypoxanthine, and threonine were shown to respond most strongly to ionising radiation. Studies on NHP have shown that these metabolites can be detected as deregulated in urine or serum after a single whole-body irradiation of 2–10 Gy, up to 7 days post exposure. For some candidates, a clear dose-response relationship could be demonstrated, providing the basis for retrospective dose estimation. Using all members of this metabolite cluster, it is possible to distinguish the exposed from unexposed samples, which is particularly important in the acute phase of a mass-casualty event [49–52]. Metabolites were also found to be affected at a similar dose range after irradiation in mice and rats [53–58].

The analysis of the urine of patients who had received total body irradiation with 1.25 Gy as part of a bone marrow transplant revealed deregulation patterns similar to those already shown in animal studies. Carnitine, xanthine, and hypoxanthine were found to be deregulated compared to non-irradiated controls [59]. In further studies, a strong sex-specific effect was observed, which was also shown in a biomarker study with NHPs [51]. Therefore, it is necessary to establish gender-specific biomarker panels.

The utility of metabolite biomarkers for the various measures of biodosimetry needs to be further explored. Nevertheless, the ease and non-invasiveness of obtaining samples and the relatively long detection time of up to seven days after exposure make metabolome-based strategies for dose estimation very promising.

4.4. Opportunities and Limitations of Omics-Based Biological Dosimetry

Until now, counting dicentric chromosomes has served as the gold standard method for determining exposure doses of ionising radiation [60]. Dicentric chromosomes are almost exclusively caused by ionising radiation, with low background levels, a clear dose–response

relationship, and a detection limit of approximately 100 mGy for low LET gamma rays acute whole-body exposure and 1000 manually scored cells [61]. Due to these attributes, the method has proven itself to be the most stable and reliable within all biological dosimetry methods [60,62–65]. Due to new technical developments such as software-based automated analysis procedures, the method has further evolved in recent years [66,67].

However, this analysis method is still time-consuming, with a processing time of at least 2–4 days, and requires qualified and trained specialists [62]. Hence, it is only suitable to a limited extent for rapid dose determination in larger samples/numbers of people. Therefore, there is a great need for rapid and robust analysis strategies in the case of large-scale radiation events that allow for immediate discrimination between exposed and unexposed individuals, followed by more detailed analyses based on traditional methods whenever required.

Omics approaches offer novel biomarker research and methodology that could be useful for biological dosimetry in these cases. On the one hand, intensive research is being conducted to develop a POC device based on omics biomarkers in order to allow for a rough differentiation between unexposed, low-exposed, and highly exposed individuals on site. On the other hand, high-throughput methods are also needed for laboratories to estimate the approximate dose, with the possibility of processing a large number of samples in a very short time window to ensure rapid medical interventions.

In addition to the development of fully automated methods, the use of artificial intelligence offers new possibilities for the analysis and integration of omics data. Machine learning-based techniques greatly facilitate the search for specific biomarker panels and will strongly support omics-based biodosimetry in the future [68,69].

Although current data appear quite promising, there is still a long way to go before these techniques can be used routinely in biological dosimetry practise. Due to the dynamics of gene, protein, and metabolite expression, the time frame for dose estimation is relatively short, so it will be very difficult to determine the correct dose in situations where the time of exposure is unclear. Compared to cytogenetic methods such as the analysis of dicentric chromosomes, where the signal might be stable for up to 3 years [70], omics approaches show deficits in terms of signal stability. In addition, it was revealed in some studies that many genes of interest show the saturation of expression levels above 1000 mGy, which is a highly limiting factor for dose estimation [34,37,71]. Another problem is specificity. As it has been demonstrated, most deregulated parameters are in some way related to the p53 pathway and could be influenced by a variety of different situations and internal as well as external stressors in addition to ionising radiation. Therefore, a biomarker panel that is deregulated almost exclusively following ionising radiation needs to be developed. Specific irradiation modalities cause different omics signatures that need to be taken into account when creating biomarker panels [72]. In addition, health status, age, and gender influence the changes in radiation-induced gene, protein, or metabolite expression. Therefore, individualised omics expression-based dosimetry models need to be developed for different population subgroups.

This suggests that novel omics-based dosimetry methods are not suitable for all radiation accidents; however, they are able to distinguish between different radiation qualities and sources and hold promise, especially as a POC strategy and for processing a high number of samples.

5. Conclusions

Omics-based methodology has brought new advances in the characterisation of radiation response to tissues, organs, and the whole organism. The application of this methodology in the identification of biomarkers that respond to radiation offers a new promising chance to develop high-throughput assays for biological dosimetry and to fill the gap with regard to strategies for large-scale incidents. However, more research is needed to incorporate omics into future accident management. Currently, most efforts have been performed to develop POC assays, especially those based on mRNA and proteins. Results

gained so far have clearly demonstrated that the goal should not be to identify individual genes, proteins, or metabolites in order to detect and quantify previous radiation exposure, but to find radiation-specific fingerprints that are exclusive to particular radiation doses, types, and rates, and ideally, also to predict subsequent medical effects. In general, the use of several parameters or methods is recommended in order to make the most accurate dose estimation possible [14,70,73,74]. A potential approach for the future would be a two-step model, with a very fast but rather inaccurate method that could make a rough division into the irradiated and the non-irradiated, followed by a more accurate, time-consuming method. For the first step, on-site POC dosimeters based on, e.g., omics-based techniques would be a suitable approach for the pre-screening of samples. This would significantly reduce the number of samples requiring more accurate dosimetry. Individuals suspected of exposure can then undergo accurate dosimetry, e.g., dicentric chromosome analysis in trained laboratories.

In summary, this novel approach has encouraging potential, especially when used for the initial subdivision of victims in large radiation accidents, which has not been possible so far in a satisfactory manner with the use of classical methods. It is therefore very important to further develop these methods, find radiation-specific biomarker panels, and develop the technical equipment for POC use.

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Abbreviations

The following abbreviations are used in this manuscript:

AACT	Alpha-1-antichymotrypsin
ACTA2	Actin, aortic smooth muscle
AEN	Apoptosis-enhancing nuclease
AMY	Alpha-amylase 1A
APOBEC3H	Apolipoprotein B mRNA editing enzyme
ASCC3	Activating signal cointegrator 1 complex subunit 3,
ATM	Ataxia telangiectasia mutated
BAX	Bcl-2-like protein 4
BBC3	Bcl-2-binding component 3
CCL2	C-C motif chemokine 2
CCNG1	Cyclin-G1
CDKN1A	Cyclin-dependent kinase inhibitor 1
CRP	C-reactive protein
DDB2	DNA damage-binding protein 2
DNA	Deoxyribonucleic acid
EPR	Electron Paramagnetic Resonance
FAST-DOSE	Fluorescent Automated Screening Tool for Dosimetry
FDXR	Ferredoxin Reductase
FLT3L	FMS-like tyrosine kinase 3 ligand
GADD45	Growth arrest and DNA damage-inducible protein
H2AX	H2A.X Variant Histone
HPLC	High performance liquid chromatography
Hu-NSG	NOD-scid-gamma
IL6	Interleukin-6 receptor

IR	Ionising Radiation
LBP	Lipopolysaccharide-binding protein
LCN2	Lipocalin-2
MDM2	Mouse double minute 2 homolog
mRNA	Messenger ribonucleic acid
NHP	Non-human primate
PCNA	Proliferating cell nuclear antigen
PFKP	ATP-dependent 6-phosphofructokinase
PHPT	Phosphohistidine phosphatase
qRT-PCR	Quantitative real time polymerase chain reaction
RENEB	Running the European Network of Biodosimetry),
TNF	Tumour necrosis factor
TP53	Cellular tumour antigen p53
TSPYL2	Testis-specific Y-encoded-like protein 2
XPC	Xeroderma pigmentosum group C-complementing protein
XRCC6	X-ray repair cross-complementing protein 6
ZMAT3	Zinc finger matrin-type protein 3

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