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REVIEW

Biomarkers for human radiation exposure

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Abstract There is a concern over the potential use of radioactive isotopes as a weapon of terror. The detonation of a radiation dispersal device, the so-called "dirty bomb" can lead to public panic. In order to estimate risks associated with radiation exposure, it is important to understand the biological effects of radiation exposure. Based on this knowledge, biomarkers to monitor potentially exposed populations after a radiological accident can be developed and would be extremely valuable for emergency response. While the traditional radiation exposure biomarkers based on cytogenetic assays serve as standard, the development of rapid and noninvasive tests for radiation exposure is needed. The genomics based knowledge is providing new avenues for investigation. The examination of gene expression after ionizing radiation exposure could serve as a potential molecular marker for biodosimetry. Microarray based studies are identifying new radiation responsive genes that could potentially be used as biomarkers of human exposure to radiation after an accident.

Keywords Biomarkers · Biodosimetry · Radiation effects

Concerns for human radiation exposure

There is concern over the potential use of radiation as a means of terrorizing public. Terrorism is not a new phenomenon as it dates back to Roman times and perhaps even further in world history. It is a deliberate warfare against civilians with the purpose of destroying their will to support their policies. Acts of violence have been reported in several parts of the world. The possibility of radiological terrorism and the implications of such threats for radiation accident preparedness are of concern. A radiological terrorist attack could involve the deployment of a Radiological Dispersal Device (RDD) or dispersal of radioactive material by an attack on a nuclear facility. RDD or dirty bomb combines explosives with radioactive material. Potential sources of radioactive materials to be used in a RDD could be from hospitals, research facilities or industrial and construction sites. Radioactive materials, dispersed in the air, could contaminate up to several city blocks, creating fear and possibly panic and will require costly cleanup. The extent of contamination would depend on the size of the explosive, the amount and type of radioactive material used, and weather conditions. A terrorist's attempt to detonate a RDD can have serious impact. It is estimated that a small-scale accident would lead to significant panic in the public. Hundreds of people could rush to the hospital emergency departments to seek medical help and would be concerned with the long-term health effects of radiation exposure.

Medical emergency preparedness and response

To decrease the vulnerability, the medical community should be familiar with basic understanding of radiation hazards and its management. Furthermore care providers should be prepared to interact with appropriate government agencies to facilitate emergency response. The care and treatment of an accidentally or intentionally irradiated person requires an assessment of their exposure. Victims of radiological terrorism events require prompt diagnosis and

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treatment of medical and surgical conditions as well as conditions related to radiation exposure. Radiation dose can be estimated by rapid-sort, automated biodosimetry and lymphocyte depletion kinetics and subsequently confirmed with chromosome-aberration bioassay. For first responders new standards, corresponding tests and evaluation protocols have been developed for the detection of radioactive materials [1]. The medical management of radiation-exposed individuals involves monitoring the exposed individual for prodromal signs/symptoms and erythema, determining blood cell counts, administration of colony stimulating factors, which decrease the duration of radiation-induced neutropenia and stimulate neutrophil recovery and assessing chromosome-aberration based cytogenetic bioassay for dose assessment [2]. The ability to treat acute and chronic radiation injuries is of prime importance and a number of therapeutic agents are being developed [3].

Biological effects of ionizing radiation

Radiation can cause both non-stochastic (cell-killing) effects, leading to burns, epilation, immune system damage and lens opacities, and stochastic or mutational effects due to low dose damage to single cells. Ionizing radiation is known to potentially interfere with cellular functions at all levels of cell organization. However, the path from irradiation of the cells to the induction of biological effects comprises several complex steps. The first step involves interactions between radiation and the cellular environment. These consist of physical and chemical reactions, which produce ions, excited molecules and radical species [4]. Excitations and ionizations are followed by a chemical thermal equilibrium of the species produced. These species then diffuse from their site of production and provoke alterations to a variety of cellular components [5]. This damage is detected by cellular surveillance systems, which in turn activate cell signaling, gene transcription and enzyme recruitment [6]. Complex cascades of signal transduction pathways respond to the radiation-induced stress [7]. In most cases, cell cycle arrest occurs, allowing, according to the biological relevance of the DNA damage, either a process of DNA repair or programmed cell death (apoptosis) [8]. The accuracy of DNA repair depends on the complexity of the DNA lesion [9] and on the fidelity of the DNA repair machinery itself. Ionizing radiation-induced biological effects are diverse including sister-chromatid exchanges, chromosome aberrations and micronucleation [10], apoptosis [11], transformation [12], mutations [13], bystander effect and gene expression alterations [14]. These effects can cause cell death or can be carried through generations causing cancer.

Radiobiological studies have shown that the effects of ionizing radiation on cells are mainly explained by modification of DNA [15]. Numerous studies over the past 50 years have accumulated clear evidence to support the cause-effect relationship between damage to DNA and the cytotoxic and mutagenic effects of ionizing radiation [16]. Damage to DNA is produced mainly by reactive oxygen species (ROS). Background radiation generates suprabasal ROS bursts along charged particle tracks several times a year in each nanogram of tissue, i.e., average mass of a mammalian cell. For instance, a burst of about 200 ROS occurs within less than a microsecond from low-LET irradiation such as X-rays along the track of a Compton electron (about 6 keV, ranging about 1 micron) and one such track per nanogram tissue gives about 1 mGy to this mass [17]. The number of instantaneous ROS per burst along the track of a 4-MeV α-particle in 1 ng tissue reaches some 70,000 [17]. Although estimates vary widely, between 10,000–1,50,000 DNA lesions are produced per human cell per day [18]. A number of these DNA lesions are stable and hence contribute to the biological consequences of ionizing radiation exposure [19].

Biomarkers for human radiation exposure

The long-term consequences from exposure to ionizing radiation are unclear, but clearly of concern to the public. Understanding of cellular responses to ionizing radiation is essential for the development of predictive markers useful for assessing human exposure. Molecular indicators that are useful in assessing human radiation exposure are lacking. Biomarkers to monitor potentially exposed populations after a radiological accident would be extremely valuable. Recent studies have attempted to find predictive markers of intrinsic radiosensitivity in healthy individuals to monitor occupational or environmental radiation exposure and to predict a patient's response to radiotherapy [20]. The most commonly used indicators of exposure are cytogenetic measures [21]. Traditional radiation exposure biomarkers based on cytogenetic assays, are time consuming and do not provide rapid results. The micronucleus (MN) assay is also widely used in the biomonitoring of human populations [22]. New methods are being developed for biodensitometry [23]. All these methods have their advantages, disadvantages and uncertainties, such that better biological estimators of the absorbed dose, especially in the low dose range, are being sought. While the primary biomarker for ionizing radiation has been DNA damage and genetic/chromosomal mutations, possible effects on apoptosis and epigenetic processes have been examined [24]. The search for biomarkers of cytotoxic (apoptotic) and epigenetic events induced by low-level ionizing

radiation is thought to be difficult in view of the fact that controlled apoptotic and epigenetic events occur constantly in a healthy body exposed to background radiation. It has been suggested that gene expression alterations could be used as a biomarker for radiation biodosimetry [25].

The lack of widespread radiation biodosimetry capabilities combined with the inability to triage in most of the current programs for dealing with the nuclear terrorism requires new developments. If a major radiation terrorist event occurs, the lack of biodosimetry and treatment capabilities will be compounded by widespread public fear of 'radiation'. To help the nation prepare for the possibility of a terrorist attack using radiological and nuclear devices, the government has given high priority to developing biomarkers for biodosimetry [26]. There is a need to enhance the current national resources to provide suitable dose assessment and diagnoses. The establishment of deployable hematology, cytogenetic biodosimetry, radiation bioassay, radioactivity-counting bioassay laboratories has been proposed [27]. Efforts to identify novel radiation biomarkers and develop applied biological dosimetry assays should lead to the development of biodosimetry devices or diagnostic tests.

The micronucleus (MN) and G2 assays

The G_2 and the G_0-micronucleus (MN) cytogenetic assays for peripheral blood lymphocytes have been shown to be sensitive biomarkers for chromosomal radiosensitivity [28]. The MN assay is widely used in the biomonitoring of human populations [22]. The G_2 assay involves the analysis of chromatid breaks in metaphase cells irradiated in vitro during the G2 phase of the cell cycle. Some authors have doubts about the value of the G_2 assay and claim that the differential G_2 phase radiosensitivity does not reflect differences in intrinsic radiosensitivity but is caused by the heterogeneity in cellular progression to mitosis [29]. In the MN assay the cells are irradiated in vitro in G_0 phase, stimulated to divide and MN are scored in binucleated (BN) cells resulting from a cytokinesis block [28]. Ionizing radiation can induce a large spectrum of DNA lesions, but under optimal DNA repair conditions, the principal residual lesions of importance are misrepaired double-strand breaks. The biomarkers for genotoxic effects (DNA breaks and alkali-labile sites and MN and non-disjunction frequencies) have been exploited [30]. The MN assay is a useful test in measuring radiosensitivity since it reflects non-repaired DNA breaks at the time of cell division. The MN assay was used to monitor hospital workers exposed to low doses of ionizing radiation [31] and as a biological dosimeter for radiation therapy patients [32]. The MN index in human populations correlates with age, sex and life-style factors [33]. The reproducibility of individual radiosensitivity with the MN assays is questionable [34]. Spontaneous and radiation-induced MN varies greatly between individuals [30] and little is known about the molecular mechanisms underlying this variability.

Chromosome-aberration-based biodosimetry

Chromosome aberration analysis is the conventional means of assessing radiation exposure. The frequency of chromosome aberrations in circulating lymphocytes is accepted as being the most reliable indicator of the absorbed dose of radiation [35]. The recent development of computer programs now permits semi- or fully-automated analysis of chromosome aberrations [36]. Other assays employed for the analysis of chromosome aberrations include premature chromosome condensation [37] and chromosome painting that uses fluorescence in situ hybridization (FISH) [38]. The application of the recent mFISH technique, where all 23 human chromosome pairs can be distinguished, has demonstrated that many chromosome-type structural exchanges are much more complicated [39]. Biological dosimetry based on chromosomal damage to peripheral blood lymphocytes after accidental overexposure to radiation was first performed in 1962 [40]. Increased frequencies of various chromosomal aberrations in peripheral blood lymphocytes of radiation exposed individuals have been observed [41]. The FISH analysis of human tumor cell lines with a wide range of radiosensitivities revealed a dose-dependent increase in radiation-induced chromosomal aberrations [42] indicating the usefulness of chromosome aberrations as a potential predictor of intrinsic radiosensitivity. The chromosome aberrations based analysis has been applied to assess hospital workers exposed to ionizing radiation [43].

Comet assay as a biomarker

The single cell gel electrophoresis or Comet assay permits the detection of DNA damage and repair at the single level [44]. This technique is based on embedding single cells in agarose followed by cell lysis, electrophoresis, examination under a microscope and image analysis. Software have been developed to facilitate the Comet parameters and analysis [45]. Several modifications of the Comet assay have been introduced to facilitate the detection of DNA single and double strand breaks, alkali-labile sites, incomplete excision repair sites and interstrand crosslinks [46]. The sensitivity and rapidity of Comet assay has prompted an interest to employ this test as a biomarker for radiation exposure. The feasibility of such biomarkers in uranium miners has been tested [47]. The assessment of medical personnel occupationally exposed to ionizing

radiation using Comet assay as biomarker showed significant increases in levels of DNA damage [48]. Similar studies have been done to evaluate nuclear workers chronically exposed to ionizing radiation [30]. The biomonitoring studies involving Comet assay have practical advantage over cytogenetic analysis. While Comet assay can be applied to both proliferating and non-proliferating cells, the cytogenetic techniques are only limited to proliferating cell populations.

Apoptosis as a predictive marker

Apoptosis and several proteins involved in the regulation of apoptosis could be possible indicators of irradiation after low doses of X-rays [49]. Apoptosis was used as a short-term biological dosimeter in human peripheral blood lymphocytes irradiated in vitro. Induction of apoptosis was proportional to the dose and was detected following exposures as low as 0.05 Gy. While lymphocytes from individual donors showed reproducible dose responses, there were variations between donors [50].

Gene expression as a biomarker

A number of processes are involved in the cellular response to radiation-induced damage, and variation in gene expression related to these cellular pathways could be linked to individual radiosensitivity. It has been suggested that the fate of ionizing radiation exposed cells may depend on changes in gene expression [51]. The real-time quantitative fluorogenic 5′-nuclease polymerase chain reaction (Q-PCR) or TaqMan assay was used to identify radiation-responsive molecular biomarkers, including gene expression targets and DNA mutations [20]. Expression analysis of 12 genes involved in DNA repair and apoptosis using Q-PCR from ex vivo irradiated blood samples obtained from 32 donors showed that the variability among the subjects appeared to be of the same magnitude or higher than that found for spontaneous or radiation-induced MN frequency [52]. A similar Q-PCR assay of *GADD45* gene expression alterations as a biomarker for radiation biodosimetry has been developed [25]. Using a model system of in vitro human peripheral blood lymphocytes, the examination of the effects of low-dose radiation on the expression of several proto-oncogenes (*c-Hras, c-src, c-met, c-jun, c-fos, c-myc*) and β-actin [53] concluded that the level of *c-Hras*, might be useful as an early diagnostic molecular biomarkers for biodosimetry applications. New investigations employing a combination of bioinformatics and functional genomics approaches to examine stress gene responses as molecular markers for radiation exposure are being developed [54]. The application of cDNA microarray identified potential biomarkers in the human peripheral blood lymphocytes after ex vivo irradiation. *XPE, XPC* and *C1P1/WAF1* genes were identified as candidates for estimating the environmental radiation exposures [55]. In other studies *XPC* gene induction was measured in vitro in irradiated lymphocytes from prostate cancer patients using reverse transcription and quantitative real-time PCR to develop a possible biomarker [56]. Interestingly the exposure of human blood cells to low doses of γ-radiation decreased the expression of both *hOGG1* and *XRCC1* repair genes [57]. Potential biomarkers in human peripheral blood lymphocytes after 1 Gy irradiation ex vivo identified TRAIL receptor 2, *DRAL* (also known as *FHL2*), cyclin G, and cyclin protein gene as highly expressed genes [58]. Investigation of peripheral blood mononuclear cells for radiation-related expression patterns identified that phospholipase C gamma 2 (*PLCG2*) and cytosolic epoxide hydrolase (*EPHX2*), were increased at 12 h after gamma-radiation and could be useful as a predictive biomarker [59]. Goldberg et al. [60] investigated the effect of low-dose ionizing radiation on gene expression in human skin biopsy samples and identified changes in the expression profiles of *TP53*, *CDKN1A*, *GADD45A*, cyclin B and cyclin D. Quantitative real-time PCR to confirm the gene expression profiles of lymphocytes irradiated (before PHA stimulation) with 50 cGy of gamma rays and analyzed 48 h after irradiation indicated a down-regulation of *XAB2* and an up-regulation of *RAD51L1* [61].

A snapshot of various studies aimed to identify biomarkers to estimate human exposure to radiation (Table 1) indicates a variety of results obtained for sets of modulated genes. Although majority of studies were done using peripheral blood lymphocytes, a wide variety of radiation quality, doses, dose rates, times after irradiation when the gene expression was monitored and analysis methodologies were employed (Table 1). There were marked differences as far as the identification of radiation-responsive genes is concerned. Few studies were corroborated among various studies. The modulation of *GADD45* was identified by Grace et al. [25] and Goldberg et al. [60], *CDKN1A* was reported by Amundson et al. [55] and Goldberg et al. [60] and finally the expression of *XPC* was communicated by Amundson et al. [55] and Wiebalk et al. [56]. These observed differences could be attributed to the different experimental conditions employed in these investigations. While most of the studies have described gene induction after irradiation (Table 1), Sudprasert et al. [57] reported the repression of *XRCC1* and *hOGG1* in peripheral blood lymphocytes.

Obtaining a global perspective of genes expressed in irradiated peripheral blood lymphocytes is considerably more informative in terms of risk assessment. The

Table 1 Possible gene expression markers to assess human radiation exposure

Analysis system	Radiation type	Radiation dose/ dose rate	Analysis time post irradiation	Validated genes	Analysis method	References
Whole blood	^{60}Co γ-radiation	3 Gy 0.1 Gy/min	24, 48 h	GADD45	Real-time RT-PCR	Grace et al. [25]
PBL	250-kVp X-rays	0.25–1.5 Gy	0.25–17 h	c-Haras	Northern blot	Miller et al. [53]
PBL	^{137}Cs γ-radiation	0.2–2 Gy 60 cGy/min	24, 48 h	DDB2 (XPE) CDKN1A XPC	RNA dot blot	Amundson et al. [55]
PBL	^{137}Cs γ-radiation	5 Gy 10.1 Gy/min	4 h	XPC	Real-time RT-PCR	Wiebalk et al. [56]
PBL	^{137}Cs γ-radiation	5–50 cGy 20 cGy/min	48 h	XRCC1 hOGG1	RT-PCR	Sudprasert et al. [57]
PBL	^{137}Cs γ-radiation	1 Gy 3.81 Gy/min	12 h	TRAIL receptor 2 DRAL (FHL2) Cyclin G Cyclin protein gene	RT-PCR	Kang et al. [58]
PBMC	^{137}Cs γ-radiation	2–16 Gy Not available	12 h	Phospholipase Cγ2 (PLCG2) Cytosolic epoxide hydrolase (EPHX2)	RT-PCR	Park et al. [59]
Skin biopsy	X-rays	1, 10, 100 cGy 80 cGy/min SSD = 100 cm	1, 4, 24 h	TP53 CDKN1A GADD45A Cyclin B Cyclin D	Real-time RT-PCR	Goldberg et al. [60]
PBL	^{60}Co γ-radiation	25 cGy 91 cGy/min	48 h	XAB2 RAD51L1	Real-time RT-PCR	Fachin et al. [61]

PBL, peripheral blood lymphocytes; PBMC, peripheral blood mononuclear cells

identification of genes involved in cellular responses to ionizing radiation could lead to the development of novel biomarkers suitable for human biodosimetry. We recently employed microarray technology to examine radiation-induced gene expression profile of human cells grown in culture and identified several radiation responsive genes [62]. We monitored the expression of several of these genes in irradiated HeLa, HFL1, TK6, and Jurket human cell with relative quantitative RT-PCR (Chaudhry, submitted for publication). The results indicated a cell line specific modulation of gene expression after exposure to ionizing radiation with the exception of *MADH7* (also known as *Smad 7*). *MADH7* was induced in all the cell lines exposed to ionizing radiation and could be used as a universal biomarker for examining radiation exposure in human populations. To develop a useful gene expression biomonitor, however, human gene expression changes occurring in response to irradiation in vivo must be measured directly. The cancer patients visiting a radiation therapy clinic could serve as an ideal population to investigate the suitability of biomarkers of radiation exposure. The results obtained from the patient population can be extended to identify individuals exposed to radiation in a radiological accident.

Conclusion

Public is concerned about the effects of radiation and risks associated with an accidental exposure due to terrorist activity. Government agencies are taking necessary steps to develop strategies in order to combat radiological terrorism threat. Scientific community has taken measures to develop markers for biodosimetry purposes. The research focus has been on the inclusion of biomarkers such as the G_2 and the G_0-MN cytogenetic assays, chromosome aberration analysis and apoptosis. Gene expression offers a viable tool to serve as a new development in biomarker discovery. As a result of microarray based genome-wide expression monitoring research, many new genes have been identified. Our laboratory has identified several radiation responsive genes that could serve as a potential biomarker of human

radiation exposure and to identify victims of radiological terrorism. Initial data involving various human cell lines grown in culture to evaluate the suitability of these markers is providing promising results. Current studies in our laboratory involving cancer radiotherapy patients as representative radiation exposed populations are aimed at validating gene expression markers to assess human radiation exposure.

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