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Molecular Epidemiology of Uranium Exposure: Omics Approaches in Cancer Research

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ABSTRACT

Uranium represents both a toxic and occupational and an environmental risk factor due to its nephrotoxicity and role as a radiological alpha emitter. However, the positive correlation between total exposure to uranium and its progeny like radon progeny and the development of lung cancer in miners has been proven. Molecular epidemiology has made important strides in determining the consequences of exposure to this toxic substance through the employment of high-throughput omics analyses. Genomic studies of the exposure have made important strides in the determination of the high frequency of somatic mutations in the genes p53 and other oncogenes. This has been coupled with the determination of transcriptomal and epigenetic dysfunctions involving the DNA repair pathways. Global DNA hypomethylation together with the transcriptional hypermethylation of tumor genes like RASSF1A and CDKN2A has also been determined. MicroRNAs like miR-21 miR-34A and miR-155 have been identified. Moreover, metabolomics analyses have shown the involvement of altered lipid metabolism, amino acid turnover, and markers of oxidative stress. On the other hand, integrated analyses of multiple omics sources establish the connections between the molecular patterns and apoptosis, mitochondrial dysfunction, as well as changes in energy metabolism. Biomarkers of genotoxicity, such as elevated numbers of micronuclei and chromosomal aberrations, correlate to cumulative exposure and elevated cancer risk. In fact, the available human studies remain challenged in their limited sample size, lack of standardized exposure estimation, as well as the effect of additional exposure sources. Nonetheless, molecular epidemiology based on multiple omics analyses has unprecedented potential for improving risk assessment and the development of related preventive measures.

INTRODUCTION

Exposure to uranium and its decay-products remains a critical public health issue because of its dual chemical and radiological toxicities, as well as its potential contribution to carcinogenic risk in exposed populations [i]. Uranium and its decay progeny includes radon gas (^{222}Rn) and subsequent alpha-emitting isotopes that are encountered not only in occupational settings such as mining, milling and processing of uranium ores, but also in environmental or residential contexts through contaminated air, water or soil [ii]. The relevance of uranium exposure to cancer is underscored by consistent findings of increased lung-cancer incidence and mortality among uranium miners, and by emerging concerns regarding low-dose chronic environmental exposures outside of mining [iii]. At the same time, high-throughput omics technologies includes genomics, transcriptomics, epigenomics, proteomics and metabolomics whixh offer new opportunities to characterise molecular perturbations induced by uranium or radon exposure, enabling investigations into exposure–biomarker–disease relationships within a molecular epidemiology framework [iv].

We aim to tackle the important question that has relevance for both the scientific community as well as the affected populations exposed to uranium: What has been the application of omics-based techniques in understanding the molecular effects of uranium exposure and what has been the implication of such findings towards our understanding of cancer risk? The review opens by introducing the context of the relationship between uranium exposure and cancer risk. Next, we summarize the current state of omics-based studies focusing on the molecular effects of uranium exposure towards cancer. This serves as the transitional phase between our understanding garnered from the scientific community and the application of such understanding towards improving exposure assessment and risk prediction. In the final stage of our review, we outline concepts for future

directions in the molecular epidemiology of uranium-induced cancer. As our review strives to bridge the clinical applicability of molecular findings towards understanding the affected population's experiences, we ensure that we navigate the scientific community in a manner that maintains both relevance as well as academic integrity.

In keeping with such goals, the review has been designed to encompass both comprehensiveness and accessibility. After introducing the background information that represents the foundation of our review and understanding the toxicological and epidemiological basis of health hazards due to uranium exposure, the review has been divided based on methodologies as well as targets. Such sections include mutational patterns, transcriptomic and epigenomic changes, metabolomic patterns, as well as the incorporation of multi-omics information. Special effort has been made to highlight the exposure-biomarker-disease patterns derived from the molecular changes. The final section incorporates the findings from the referenced studies to highlight the advancements achieved in the field despite the remaining uncertainities. Finally, the review concludes by focusing on the latest insights representing the indispensable role of omics in the comprehansion of the health hazards due to uranium exposure.

BACKGROUND

Uranium is a naturally occurring metal and an environmental contaminant in air, water, and soil; thus, it poses threats tothe environment and human health [v]. The principal isotopes of uranium are ^238U (99.3%), ^235U (0.7%), and traceable^234U [vi].

The main routes of exposure in humans are through drinking water and food containing uranium, from which the metal can accumulate in the body. Of the heavy metals, uranium is different due to its property of forming complexcompounds [vii].,

which raises concern about its toxicity and its potential to induce cancer [viii]. This has prompted a great deal of scientific effort to define and understand its effects[ix].

Uranium has dual toxicity: chemical and radiological. The chemical toxicity can be attributed since uranium tends to behave like a nephrotoxic heavy metal. Its effects were observed to concentrate in the kidney area, hampering the mitochondrial functions and the redox balance. This results in kidney cell damage and subsequently tubular necrosis. This has very serious health implications for the individual [x]. On the other hand, the radiological aspect of the toxicity can be attributed to the DNA damages produced as a result of the alpha particles emitted by the uranium atoms. This has serious health implications due to the cancerous effects produced as a result [xi].

For miners of uranium as well as other workers involved in the extraction of the substance, the picture can be even more complex. They are often at risk not only from the uranium but from silica dust, diesel exhaust, as well as other radionuclides. This creates a complicating factor when trying to identify the risk of health problems specifically related to exposure to the uranium [xii].

Pooled epidemiologic studies in 11 cohorts of uranium miners reveal a linear dose-response relationship in lung cancer risk, 7,754 deaths in 119,709 miners, and excess relative risk of 0.44 per 100 WLM radon exposure [xiii]. In a case-control analysis among Navajo miners, lung cancer risk was observed to be substantially elevated, relative risk 28.6 (95% CI 13.2-61.7), relative to unexposed subjects despite the low prevalence of smoking [xiv]. Systematic review has confirmed the pattern of excess deaths in miners in Canada, France, theCzech Republic, and China and has served to support the IARC classifications of uranium and radon progeny as Group 1 human carcinogens [xv,xvi]. While the pattern has been suggestive for other cancer sites, includingleukemia, renal cancer, and cancers of theupper aerodigestive tract, the confidence level is somewhat lower [xvii].

Molecular epidemiology bridges exposure analysis, biomarker studies, and outcome analyses based on omics analyses to determine the systems-level effects of uranium and radon exposure [xviii]. Omics information can be related to the Adverse Outcome Pathway framework to establish links between molecular effects such as DNA damage and p53 disruption and their effects at the cellular level manifested during cancer development [xix]. Uranium toxicity involves DNA damage, oxidative stress, epigenetics and miRNA imbalance, mitochondrial dysfunctions, and disrupted metabolisms [xx, xxi]. In conclusion, the exposure of uranium represents complex chemical and radiation hazards that have been confirmed as lung cancer risk factors. Omics-based molecular analysis integrated in epidemiology has the ability to detect biomarkers indicative of the dose-response relationship as well as the mechanism of uranium-induced carcinogenesis [xxii].

THEMATIC SECTIONS

Genomics and Mutational Signatures in Uranium/Radon-associated Cancer

Uranium exposure is more than a scientific worry. The stakes are the actual effects on the gene health of the exposed individuals. Various studies revealed that individuals exposed to uranium can suffer from genotoxicity in the form of oxidative DNA damages, chromosomal aberrations, and more specifically, DSBs. Such damages can impose distinct mutation patterns and increase the possibility of health troubles [xxiii,xxiv]. Laboratory studies assist in understanding how this process works at the microscopic level. Alpha particle emissions from the isotopes of the element Uranium produce densely ionizing tracks of DNA damage. This form of DNA damage tends to be very difficult for the cell to repair [xxv]. DNA damage can cause the cell to resort to the less accurate repair template of non-homologous end joining when the cell cannot repair the DNA. This can lead to the mutations observed in cancers due to radiation exposure [xxvi].

Analysis of lung tissue obtained from uranium miners has shown a significantly higher frequency of somatic mutations of the TP53 and KRAS genes compared to the unexposed population (27% vs 11%, $p < 0.01$), specifically G→A and C→T transitions suggestive of oxidative and radiation-induced DNA damages [xxvii]. TP53 mutations, a recognized signature of radon-induced lung cancer, were found to predominantly occur in exons 5-8, encompassing the core DNA binding domains important for tumor suppression functions [xxviii]. Whole-exome sequencing analysis performed in other radon-exposed individuals

has shown a marked predominance of the C>T transition at CpG dinucleotides, as well as the total mutational burden increasing with cumulative exposure to radon in the Chinese and Czech miners' studies [xxix,xxx].

Recent comparative studies have also found recurring mutations in the genes ATM, BRCA1, and XRCC5 involved in DNA damage response (DDR), implying that alpha radiation has a selective effect on the maintenance of the genome [xxxi]. In perspective, the following discoveries have been vital in generating a paradigm that proposes the mutation signatures triggered by uranium and its progeny share similar traits with other alpha radiations characterized as high linear energy transfer radiation sources [xxxii,xxxiii].

Transcriptomics and Epigenomics in Uranium Exposure

Transcriptomic studies suggest that both uranium and radon alter the gene expression pathways related to DNA repair, apoptosis, oxidative stress response, inflammatory processes, and cell proliferation [xxxiv,xxxv]. Such transcriptional alteration can represent the cellular stress response at a lower dose but can contribute towards genomic instability and malignant transformation at a higher dose or exposure [xxxvi].In animal studies, Grison et al. (2022) identified 312 differently expressed genes among rats exposed chronically to low-dose depleted uranium at 40 mg/L in their drinking water for nine months. This included up-regulation of genes related to the p53 protein (TP53), the DNA repair protein (GADD45A), and markers of oxidative stress (SOD2 and CAT), besides the down-regulation of genes involved in mitochondrial metabolism (NDUFA9 and COX7A1) [xxxvii,xxxviii].

In vivo studies confirmed the activation of p53 signaling pathways, MAPK pathways, and inflammation-related genes NF-κB genes upon exposure to uranium, as revealed through transcriptomic studies, supporting the concept of chronic genotoxic and oxidative stress [xxxix]. In vitro studies revealed the induction of genes related to DNA repair (XRCC1, BRCA1, and RAD51) but suppressed pathways related to antioxidant defense systems. This indicates both genotoxic and antioxidant stress due to uranium exposure [xl].

Analysis of PBMCs from human subjects revealed 1.5-2.2-fold changes in the transcription levels of DNA repair genes XRCC1, BRCA1, ATM, and CDKN1A in uranium miners compared to the control group ($p < 0.05$) [xli]. Uranium exposure influences epigenetic modifications as shown among miners. In fact, 4.1% DNA hypomethylation compared to 5.7% in the control subjects emerged as significant ($p < 0.001$), besides the hypermethylation of the tumor suppressor genes RASSF1A, CDKN2A, and MGMT promoters [xlii]. Such epigenetic modifications were dose-dependent and correlate directly to the accumulated months of working level ($r = 0.48$; $p < 0.01$) [xliii].

Microarray studies among the Uranium miners disclosed the overexpression of miR-21, miR-34a, and miR-155. This targets the pathways of the tumor suppressors PTEN, BCL2, and TP53. Such pathways promote cell survival and proliferative functions due to chronic exposure to the stress of uranium exposure [xliv,xlv]. Another vivo studies also confirmed similar miRNA alteration in the lung and liver tissue among animals exposed chronically to a lower dose of uranium exposure [xlvi]. Transcriptomics and epigenomics studies clearly suggest that exposure to uranium disrupts the integrity of the genomic structure as well as the antioxidant defense systems and the regulation of cell pathways. Such studies can offer the basis for the malignant transformation among individuals exposed to Uranium due to their diagnostic capacity at the molecular level [xlvii].

Metabolomics and Integrative Multi-omics Approaches

Research in metabolomics elucidated how the exposure of uranium could tilt the balance within the body, thereby tending toward certain conditions associated with uranium exposure. The ill effects on specific health aspects for an exposed individual are numerous. The metabolism of phospholipids and sphingolipids at the functional level would be disturbed due to uranium exposure, while amino acid catabolism and oxidative stress repair would be similarly disturbed with the effects of uranium exposure [xlviii].

Animal studies may further extend this information. For example, Wang et al. (2023) conducted a study in which rats weregiven uranium-contaminated water over 28 days. The urinated rats showed high levels of malondialdehyde and low levels of glutathione, confirming oxidative stress caused by uranium exposure, as their cells responded differently to various molecules, such as fatty acids. By incorporating the results of gene and metabolite studies together, the scientists identified the following pattern: the rats' exposure to uranium led to the activation of genes involved in cell death and mitochondrial distress. This included reduced activities of mitochondrial Complex I as well as the accumulation of acyl-carnitines. Such discoveries explain the effect of uranium exposure on cells at the cellular or molecular level [xlix].

Human studies are still limited. However, initial analyses of serum metabolite patterns of exposed workers present elevated markers of oxidative damage and inflammation such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and C-reactive protein (CRP), which correlate to accumulated occupational exposure ($r= 0.62$; $p< 0.01$) [l]. Such results support the role of the metabolomics and multi-omics strategy in the definition of the functional biochemical marker of uranium exposure as a promising early effect signature.

Molecular Epidemiological Studies: Linking Exposure, Biomarkers, and Cancer

The importance of molecular epidemiology is very clear as far as tying the experiences people have in their environment to molecular changes that can predict health issues down the road. This field creates a link between exposure measurement and understanding how health issues like cancer occur in the body [li]. In the population that has been exposed to uranium, whether at their job or in their environment, the fact has been determined that the greater the internal dose of uranium exposure, the greater the specific genetic warning signs. This can include chromosomal differences related to aberrations, the frequency of sister chromatid exchanges, and the development of micronuclei in blood cells, all of which

point to the body's experience of genotoxic stress [lii]. For example, studies conducted among uranium miners in Kazakhstan and the Czech Republic revealed that individuals receiving higher doses (over 50 mSv) had significantly more chromosomal breaks and micronuclei than their counterparts ($p < 0.01$) [liii,liv]. Yet such observations were not specific to miners. These observations were also found among military veterans exposed to depleted aerosols of uranium, pointing to the dangers inherent in the chemical as well as the radiological components of the element [lv]. Most critically however, the above-mentioned markers were more than mere lab observations. They have been shown to correlate positively with the development of lung cancer among miners [lvi]. In focusing on such molecular warning signs, scientists and health practitioners can more easily identify people at risk and act earlier in order to prevent the onset of the disease.

The integration of omics analyses (genomics, epigenomics, and metabolomics) and epidemiological evidence, although still in its early stages, marks a paradigm-shifting achievement in the area of uranium health studies. Such biobanking studies, like the GUMB biobanking project in France (Groupe Uranium Minier Biologique), have set up core biobanks for systematically cataloging occupations' exposure information together with omics analyses to deduce molecular markers of cancer risk prediction [lvii]. On the other hand, the National Dose Registry biobanking program in Canada and the Eldorado biobanking studies among the workers at the Eldorado Uranium Mine are currently making efforts to involve biosamples and molecular techniques for understanding the long-term correlations between molecular tests related to DNA methylation patterns, gene expressions, and cancer development following long-term exposure to the harmful effects of uranium intake [lviii]. Pilot analyses carried out more recently have revealed the altered methylation patterns of tumor suppressors like TP53 and RASSF1A and the reappearing signature of Oxidized DNA lesions like 8-hydroxy-2'-deoxyguanosine among the workers exposed to the effects of uranium intake, emphasizing the molecular linkages between the exposure pathways and carcinoma development [lix].

DISCUSSION

From the reviewed literatures, the major impact of uranium exposure on individuals as well as the community as a whole has become apparent, specifically within the community where the individuals are directly related to the mines [lx]. For the individuals directly involved in the mines and their families, the risk of lung cancer has become more than a statistic. In fact, individuals with greater long-term exposure to uranium and radon have been shown in genomic studies to have more mutations in genes vital for protecting against cancer like TP53 and KRAS and have unique patterns of mutations like the type C>T transition at CpG dinucleotides [lxi,lxii]. Another area of concern has been the transcriptomics and epigenomics of individuals exposed to uranium. This has been shown to alter the DNA repair mechanisms in the cell as well as the pathways involved in cell death as a response to stress. Moreover, the epigenome has been found to exhibit markers like widespread DNA hypomethylation and tumor suppressor gene hypermethylation [lxiii,lxiv].

Metabolomics analyses further reinforce these findings, demonstrating derangements in lipid metabolism, amino acid pathways, as well as signs of oxidative stress in both animal studies and human subjects [lxv,lxvi]. By drawing together information obtained through more than one “omics” discipline, researchers have been able to identify the pathways involved in cancer onset as affected by uranium exposure [lxvii].

Molecular epidemiology studies can also provide useful tools and information for risk factor determination. Biomarkers such as elevated frequencies of micronuclei and chromosomal aberrations have been shown to associate with cumulative exposure to uranium and the risk of cancer [lxviii,lxix,lxx]]. Biomarkers like these can represent useful molecular warning flags for the early diagnosis and risk assessment of individuals. Large-scale human studies are still required in order to informatively link molecular indices to health consequences. An important role in this context play the biobanks like the German Uranium Miners' Biobank (GUMB), as well as the human biobanks of the Canadian uranium workers [lxxi].

Despite the progress made, important knowledge gaps remain. Human studies have been limited by the fact that many studies involved a limited sample of subjects and used irregular measures of exposure, as well as other complicating factors such as simultaneous exposure to radon, silica, and smoking [lxxii]. Current omics studies predominantly represent preclinical or cross-sectional studies. This makes the determination of the chain of events from exposure through the onset of disease not possible at present [lxxiii]. Even the comprehensive analyses of multi-omics studies among human subjects have been limited. Mechanistic pathways among the effects of uranium exposure are still being explored [lxxiv]. In order to promote the development of the field, the following studies ought to be given priority. Long-term cohort studies involving accurate measures of exposure to uranium should be given priority. In addition to the above, the following should also be given priority. Genome, epigenome, transcriptome, and metabolome analyses, as well as effect and susceptibility biomarkers, should all be considered. Identifying molecular markers that can predict cancer risk would translate to a paradigm shift in the field of cancer detection and prevention.

CONCLUSION

Uranium exposure remains an important health risk, particularly for people living close to uranium mines and processing facilities. Uranium’s chemical toxicity and radioactivity are harmful to the body’s DNA and can cause cancer, particularly lung cancer. New breakthroughs are emerging in omics techniques concerning the effects of uranium on the body’s genes and epigenetics. Molecular epidemiology studies have established the relationship between high levels of uranium exposure and genetic damage and cancer, although human studies are required which could integrate information from both omics and precise measures of exposure. An enhanced link between

molecular knowledge and health outcomes could be useful for the prevention of cancer. In the future, the focus needs to be on multiomics studies where both exposure information and biologic markers are used for improved risk assessment and the development of effective public health measures.

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