Editorial

Epigenetic modification by galactic cosmic radiation as a risk factor for lung cancer: real world data issues

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Man's curious nature has led to many discoveries and inventions. Space exploration had always been a dream and this urge to explore has gotten stronger after revolutionary developments in the means of transportation to space. Like any other occupations astronauts also face several hazards, the most significant among these is the long-term health risk of cancer, which is mainly due to their exposure to galactic cosmic radiations (GCRs). In deep space, as opposed to low-Earth orbit, astronauts are exposed to significantly high dose-rates of GCRs and these several types of ionizing radiation may have total estimated energies of about 50–2,000 millisieverts. The impact of these high energy radiations on astronauts depends on the duration of their stay on the planet or at International Space Station (ISS) (1-3). Typically, the duration of these deep space expeditions is very long, thus, in addition to the intensity of these radiations, the longer duration of exposure is also a major challenge for astronauts (4). The National Aeronautics and Space Administration has defined carcinogenic risks of radiation as a type 1 risk, which means it is a serious health problem in nature that does not have a concept of countermeasure. Such risks can be a significant reason for delaying and even halting long-duration space missions.

The research of Kennedy *et al.* [2018] is a tremendous effort towards understanding the impact of cosmic rays on human epigenome, especially in context of the association of lung carcinomas and the effect of the dose of radiations on human in both short and long terms with an emphasis on epigenetic 'memory' of space radiation exposure, in spite of the limitation i.e. an unavailability of large human data for the estimation of carcinogenic risk due to the real exposure of complex GCRs. In particular, a statistical modelling analysis for comparing epigenetic methylation profiles of triplicate cultures of immortalized human bronchial epithelial cells revealed that genetic loci with persistently differential methylation levels after radiation exposure can discriminate normal cells from lung adenocarcinoma cells, suggesting their potential as biomarkers of cancer risk.

The cancer cell lines used in this study were cultured by the introduction of two genes, cdk4 and hTERT, from the mouse model to the normal human bronchial cells. Since cell and tissue study in humans after radiation exposure is difficult to obtain, the risk estimation from space travel has been limited to mechanistic understanding. At present, the researcher relies on animal models like the one used in this research. Fortunately, lung radiosensitivity exhibited by most of the available animal models, including mouse models, has been observed to be equivalent to that of human lungs (5). Moreover, transgenic mouse models have also been widely used to investigate functional roles of genetic alterations involved in the spontaneous tumorigenesis, however, it can be highly complicated, since effects of radiation on the human being are far more complex in comparison to the mouse or any other animal models typically used. Statistical approaches to identify biomarkers with concordant genetic profiles across different species such as mouse and human can be utilized to triage preclinical epigenetic biomarkers relevant to a human study (6,7).

As far as the functional anatomy of the lung is concerned, it is very complex because of its strong volume effect and highly heterogeneous regional radiosensitivity (8,9). Additionally, the lung appears to respond to the injury of other organs

as well, by increasing its sympathetic activity (10), which involves various complex genetic components (11). Although, vast historical research has entailed well-characterized morphological endpoints of lung and a relatively broad database for the lung response to radiations it is still highly problematic to develop a comprehensive strategy to model targeted or lung-specific responses (11).

In animal models, radiation-induced inflammatory pneumonitis has been observed to take about two to four months to develop, while fibrosis develops at around four to six months after irradiation (12). This significant variation in the duration can be caused by differences in strains of animal species and irradiation doses. In humans, a comparable time course is observed after a fractionated radiation course, but considerable variations are seen in both dose-response and temporal course after an exposure to a single high dose-rate radiation (12). Therefore, while investigating the effectiveness of an agent that can be used to mitigate pulmonary side effects of irradiation, it is important to consider differences in morphological and temporal development phases between fibrosis and pneumonitis.

Harnessing animal models for medical countermeasures to estimate risks associated with radiation exposure in humans is still debatable. Since human data is not available yet on cancer incidence as an outcome of exposure to the radiation particle with high charge and energy, animal models cannot be used as a one-to-one comparison with a human for the risk assessment of such radiation exposure (13). These preclinical animal models should therefore be used strategically and consistently in terms of irradiation parameters, animal species and strains as an effort to conduct highly reproducible translational studies for the inference of human risk due to radiation exposure (13).

The use of various animal species in the studies can introduce considerable inherent biological variations because response and sensitivity to radiations can be significantly heterogeneous among different animal species (14). The rodents can be used for initial characterization of the biological and physiological mechanisms underlying the responses to radiation, but the generalization of the observed response in these models to human can introduce bias. To minimize the interpretation bias and to detect more precise statistically significant associations, research studies can consider using a larger sample size of those animal models, which have more human-like physiology to assess specific outcomes. Similarly, the variation of lifespan among different species is also considerable. Exposure of astronauts to GCR takes place on a time scale of days or months, harnessing animal models for exploring outcomes after long duration of radiation exposure at low dose-rate is questionable as the lifespan of most experimental animals is remarkably shorter than the human lifespan (14).

Another aspect that can be explored further is assessing the challenge of multiple organ systems in response to concurrent exposure to various stressors that are seen in an actual flight in space. Survivors of atomic bombing and nuclear disaster were victims of whole-body irradiation, which occurred at remarkably high dose-rates. Such circumstances or situations do not typically occur in space flights. Various other environmental factors along with these disparities may result in significant uncertainty in the outcome of radiobiological studies. Hence, it is challenging to interpret the results based on the use of animal models or analogs that may not precisely mirror the environment of operational space radiation or complex human physiology. Evaluating complex energy spectra composed of various ions and dose-rates can be a future research consideration to mimic the actual space environment exposures.

Furthermore, family history, genetic predisposition to specific cancer types, and environmental factors including diet and lifestyle are also very important aspects to consider because they can impact the assessment of possible causality. For instance, a cigar smoking is known to cause lung cancer, head and neck cancer, and other cancers. In addition, the reproductive history influences the risk of breast cancer in women (15). These factors can bias a risk evaluation of a radiation exposure and should thus be considered in an experiment design or multivariable statistical analysis of non-experimental data.

In the future, advancements in the deep space exploration projects in this modern era of science and technology will lead to the benefits of the availability of real human data with radiation exposure, owing to two major facts. First, now larger population of astronauts flies to the deep space and get exposed to real space radiation dose environment. Second, close monitoring of epidemiological and medical records of these astronauts (14) and data collection of various biochemical components and biomarkers at several time-points over pre-, peri-, and post-flight (16), especially for repeat ISS flyers, can be a breakthrough for radiobiological research studies. It can prove to be critical for the evaluation of this complex association of unidentified carcinogenic and degenerative outcomes as a long-term risk of real space radiation by using actual human data that can enhance our understanding of the real risk of GCR in space.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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