Cancer risk from exposure to galactic cosmic rays - implications for human space exploration

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Abstract:
Current space programs are shifting toward planetary exploration, and in particular towards human missions to the moon and Mars. However, space radiation is a major barrier to human exploration of the solar system because the biological effects of high-energy and charge (HZE) ions, which are the main contributors to radiation risks in deep space, are poorly understood. Predictions of the nature and magnitude of the risks posed by space radiation are subject to very large uncertainties. Great efforts have been dedicated worldwide in recent years toward a better understanding of the oncogenic potential of galactic cosmic rays. A review of the new results in this field will be presented here.
Introduction

Space exploration is a grand adventure for humankind with the potential for exciting discoveries that capture our imaginations and benefit society. The benefits from exploration\(^1\) must be balanced with cost, safety and ethical concerns in deciding on acceptable levels of risks for astronauts or a no-go mission decision. The leading health concerns are exposure to galactic cosmic rays (GCR) and solar proton events, which present significant but poorly understood risks for carcinogenesis and degenerative diseases\(^2,3\). Spaceflight in low Earth orbit, such as missions on the space shuttle and the International Space Station, are partially protected by the Earth’s magnetic field and the solid shielding of the planet. The Apollo missions ventured away from the protection of the Earth but lasted only up to 12 days. Proposed missions to the moon in the next decade could last up to 200 days (\textbf{figure 1}) and a possible mission to Mars lasting as long as 3 years would lead to whole body doses around 1-sievert (Sv) or more\(^4\). However, the concepts used for risk projection on Earth, including the use of the dose unit Sv, are perhaps deceptive for GCR exposures. Efforts to improve the understanding of biological effects of densely ionizing heavy ions through biomedical research on cancer are the subject of this essay.
Space Radiation Environments and Risk Assessment

In space, astronauts are exposed to protons and high energy and charge (HZE) ions along with secondary radiation including neutrons and high linear energy transfer (LET) recoil nuclei, produced by nuclear reactions in spacecraft or tissue. The energy spectrum of the GCR peaks near 1,000 MeV/nucleon, and consequently these particles are so penetrating that shielding can only partially reduce the doses absorbed by the crew. Thick shielding poses obvious mass problems to spacecraft launch systems, and would only reduce the GCR effective dose by no more than 25% using aluminum, or about 35% using the more efficient polyethylene. Therefore, current shielding approaches cannot be considered a solution for the space radiation problem with the exception of solar proton events, which are effectively absorbed by shielding.4

In traveling to Mars, every cell nucleus within an astronaut would be traversed by a proton or secondary electron every few days, and an HZE ion about once per month.5 Whole body doses of 1-2 mSv/day accumulate in interplanetary space, and approximately half this value on planetary surfaces.6 The large ionization power of HZE ions makes them the major contributor to the risk, in spite of their lower cell nucleus hit frequency than protons. To undertake ground-based space radiation research, special facilities are needed to accelerate charged particles (from protons to iron) to relativistic energies. Only a few such facilities exist in the world, and NASA has invested in a new facility at Brookhaven National Laboratory on Long Island, NY (http://www.bnl.gov/medical/NASA/).
On Earth radiation workers or patients are most frequently exposed to low-LET $\gamma$- or X-rays. Epidemiological data, largely from the Atomic bomb survivors in Japan, provides a basis for risk estimation for low-LET radiation. However, because no human data exist for protons and HZE ions, space risk estimates must rely entirely on model systems and biophysical considerations. Using standard methods for cancer risks projections based on the double detriment life table for an average population and a radiation induced cancer mortality rate scaled to the data from Atomic bomb survivors, risks for extended missions to the moon and the Mars exploration mission are shown in Table I. In this Table, 95% confidence intervals are reported that take into account the uncertainties in epidemiology data, space environments, and radiation quality and dose-rate effectiveness factors. Maximum acceptable levels of risks for astronauts are typically set at 3% fatal risk, but the large uncertainties in projections and the likelihood of other fatal or morbidity risks for degenerative diseases precludes a go/no-go decision for Mars exploration at this time.

**Radiobiology of HZE Ions- Cellular Effect**

A necessary step for reducing uncertainties in risk assessment are studies on the molecular pathways causative of cancer initiation and progression, and to extend these studies to learn how such pathways can be disrupted by HZE ions including both genetic and epigenetic modifications (figure 2). The goal of this research is to establish a more mechanistic approach to estimating of risk, and answering questions that include: can HZE effects be scaled from those of $\gamma$-rays, is risk linear with low dose-rate, and how
does individual radiation sensitivity impact risks for astronauts, a population selected for many factors related to excellence in health.

As a starting point we can consider the initial biophysical events caused by HZE tracks in cells and tissue\textsuperscript{6,8,9}. Energy deposition by HZE ions is highly heterogeneous with a localized contribution along the trajectory of each particle and lateral diffusion of energetic electrons (delta-rays) many microns from the ions path. These particles are therefore characterized by a high LET, however contain a low LET component. Biophysical models have shown that the energy deposition events by high LET radiation produce differential DNA lesions, including complex DNA breaks, and that there are qualitative differences between high- and low-LET radiation both in the induction and repair of DNA damage\textsuperscript{10-13}. The number of DNA single strand breaks (SSB) and double strand breaks (DSB) produced by radiation varies little with radiation type\textsuperscript{8,10}, however for high-LET radiation, a higher fraction of DNA damages are complex, i.e. clusters containing mixtures of two or more of the various types of damages (SSB, DSB, etc.) within a localized region of DNA. Complex damage is uncommon for endogenous damage or low-LET radiation, and has been associated with the increased relative biological effectiveness (RBE) of densely ionizing radiation. The repair of DSB is known to occur through direct end-joining and homologous recombination processes. Indications are that for high-LET radiation, where complex DSB occur with high frequency, little repair occurs leading to cell death or that the mis-rejoining of un-repairable ends with other radiation-induced DSB lead to large DNA deletions and chromosome aberrations. While the high effectiveness in cell killing provides the rationale for heavy-ion cancer
therapy (hadrontherapy)\textsuperscript{14}, residual damage in surviving cells is of concern for carcinogenesis.

Heavy charged particles are very effective at producing chromosomal exchanges with RBE values exceeding 30 in interphase (as visualized using premature chromosome condensation) and 10 at the first post-irradiation mitosis for energetic iron ions\textsuperscript{15}. The detailed RBE versus LET relationship found for total exchanges is similar to earlier studies of mutation\textsuperscript{16} and in vitro neoplastic transformation\textsuperscript{17}. For all of these endpoints, RBE peaks around 100-200 keV/\textmu m, and then decreases at very high LET. However, the quality of chromosome damage is different when heavy ions are compared to sparsely ionizing radiation. Large differences in gene expression are observed between X-rays and HZE ions reflecting differences in damage response pathways\textsuperscript{18,19}. Qualitative differences in the type of gene mutations have also been reported\textsuperscript{20}. Novel multi-color fluorescence painting techniques of human chromosomes have clearly demonstrated that high-LET $\alpha$-particles\textsuperscript{21} and iron ions\textsuperscript{22,23} induce many more complex-type chromosomal exchanges in human cells than low-LET radiation (figure 3). Most of these complex chromosomal rearrangements will ultimately lead to cell death. In fact, only a small fraction of the initial damage is transmitted in mice 2-4 months after the exposure to energetic iron ions\textsuperscript{24}. A low RBE for the induction of late chromosomal damage has also been measured in the progeny of human lymphocytes exposed in vitro to energetic iron ions, with the interesting exception of terminal deletions, that occurred with much higher frequency in the progeny of cells exposed to heavy ions compared to $\gamma$-rays\textsuperscript{25}.

The presence of chromosomes lacking telomeres in the progeny of cells exposed to heavy ions is particularly interesting. Sabatier \textit{et al.}\textsuperscript{26} found that rearrangements
involving telomere regions are associated with chromosomal instability in human fibroblasts many generations after exposure to accelerated heavy ions. Telomere dysfunction play a crucial role in initiating or sustaining genomic instability\textsuperscript{27-28}, which is a major step in cancer progression. Heavy ion-induced effects on telomere stability has also been studied using siRNA knockdown for components of DNA-dependent protein kinase (DNA-PK) in human lymphoblasts\textsuperscript{29}. Differential results where found for γ-rays and high-LET radiation, with iron nuclei being much more effective in producing DSB-telomere fusions after knockdown of DNA-PK. Cells containing telomere-deficient chromosomes will either senesce, or undergo B/F/B cycles, promoting genetic instability. The fate of normal cells containing a single terminal deletion is not known, but it has been shown that the loss of a single telomere in cancer cells can result in instability in multiple chromosomes\textsuperscript{30}. These recent results suggest that telomere instability could be an important early event in the pathway to cancer induction by HZE nuclei.

**Radiobiology of HZE Ions- Tissue Effects**

The possibility of heavy ions causing unique tissue damage at low dose was noted after the Apollo astronauts’ observed of light flashes during dark adaptation\textsuperscript{31}. These visual sensations are related to the passage of HZE particles through the retina, or proton-induced nuclear interactions in the eye\textsuperscript{32}. The micro-lesion concept considers stochastic tissue events that occur with HZE tracks and the possibility of unique types of tissue damage\textsuperscript{9}. Micro-lesion formation is of especial concern for damage to the brain or central nervous system (CNS), where fully differentiated structures are present. However, it
could also play a role in increased effectiveness for HZE ions in highly structured tissues. CNS effects that have been observed in animal models include altered motor function or performance\textsuperscript{33}, accelerated striatal aging\textsuperscript{34}, late degradation of DNA\textsuperscript{35}, altered dopamine function\textsuperscript{33}, and neurodegeneration\textsuperscript{36}. The Casarett model\textsuperscript{37,35} predicts that the appearance of late degenerative effects to the CNS and other tissues could be advanced by many years after radiation exposure in what has been called “radiation accelerated aging”. This effect would have an increasing severity with increasing HZE fluence, and appears to be relevant in describing the increased incidence of cataracts observed in astronauts exposed to higher doses of space radiation\textsuperscript{38}.

Animal studies generally demonstrate that HZE nuclei have a higher carcinogenic effectiveness than low-LET radiation. RBE was measured in mice or rats for tumors of the skin\textsuperscript{39} and of Harderian\textsuperscript{40} or mammary\textsuperscript{41} gland, and reaches values as high as 25-40 at low doses. However, the risk and detriment of cancer is not fully characterized until the relationship between radiation quality and latency, where tumors appear earlier after high-LET irradiation\textsuperscript{42}, is adequately described. Recent studies have debated the relative importance of DNA damage and mutation or extracellular matrix remodeling and other non-targeted effects as initiators of carcinogenesis\textsuperscript{43}. Tissue effects independent of DNA damage that have been associated with cancer initiation or progression include genomic instability\textsuperscript{44}, extracellular matrix remodeling\textsuperscript{43}, persistent inflammation\textsuperscript{43}, and oxidative damage\textsuperscript{45}. Other studies are exploring possible relationships between radiation and the activation of dormant tumors and modulation of angiogenesis\textsuperscript{46}.

The so-called bystander or non-targeted effects\textsuperscript{45,47,48} may have enormous consequences for space exploration. Non-targeted effects may lead to supra-linear dose-
response curve at low doses, perhaps reducing the effectiveness of spacecraft shielding, but it may also be protective by removing damaged cells from the organism. Both effects challenge the conventional linear no-threshold risk model assumption\textsuperscript{49}, which is currently adopted for radioprotection on Earth and in space. They also suggest important targets for biological countermeasures likely to be more effective than countermeasures targeting DNA damage\textsuperscript{50}.

**Conclusions**

Reducing the uncertainties in risk assessment required before a mission to Mars can be undertaken has led to a great number of investigations guided by molecular and genetic research on carcinogenesis and degenerative diseases. The large uncertainties in risk projection models will only be reduced by improving basic understanding of the underlying biological processes and their disruption by space radiation. There are unique aspects involved in this approach due to the specific challenges to biological systems presented by space radiation, especially HZE ions. It is unlikely that the radiation risk problem for space exploration will be solved by a simple countermeasure, such as shielding or radioprotective drugs. The risk will be understood and controlled only with more basic research in the field of cancer induction by charged particles.
Conflict of Interest

We declare no conflicts of interest.

Acknowledgments

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References


35. Lett JT, Williams GR. Effects of LET on the formation and fate of radiation damage to photoreceptor cell component of the rabbit retina: implications for the projected manned mission to Mars. In *Biological effects of Solar and Galactic*


Table 1. Calculations of effective doses, %Risk of death from fatal cancer, and 95% CI for lunar or Mars missions. Calculations are at solar minimum where GCR fluence is highest for a 5-g/cm² aluminum shield. The absorbed dose, D and Effective dose, E are averaged over tissues prominent for cancer risk², and competing causes of death are treated in the risk calculation, compressing the distribution of risk probabilities at larger values (>5%).

<table>
<thead>
<tr>
<th>Exploration mission</th>
<th>D, Gy</th>
<th>E, Sv</th>
<th>Fatal Risk(%)</th>
<th>95% CI</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Males (40 y)</td>
</tr>
<tr>
<td>Lunar (180 d)</td>
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<td>0.17</td>
<td>0.68</td>
<td>[0.20, 2.4]</td>
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<tr>
<td>Mars swingby (600 d)</td>
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<td>4.0</td>
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<tr>
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<td>1.07</td>
<td>4.2</td>
<td>[1.3, 13.6]</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>0.17</td>
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<td>1.07</td>
<td>5.1</td>
<td>[1.6, 16.4]</td>
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</table>
Figure 1. Concept of a future moon landing. According to the new Vision for Space Exploration (January 2004), NASA plans to return on the moon within the year 2020. The current project anticipates 4-6 crewmembers performing Lunar surface operations for 60-180 days. The Earth-moon cruise lasts approximately 4 days. (Picture credit NASA/John Frassanito and associates).
**Figure 2.** Schematic of importance of uncovering basic mechanisms of cancer induction by galactic cosmic radiation. Determining role of DNA damage vs. non-targeted effects has large implications for radiation shielding, mission duration, and in approaches to design of biological countermeasures. In DNA-target model, a linear response is expected with research focus on slope of response as function of radiation quality and radiation sensitivity. In non-targeted model, shielding is ineffective and distinct target for biological countermeasures are pursued.
**Figure 3.** A karyotype of a human lymphocyte exposed to 0.3 Gy Fe-ions (1 GeV/nucleon). The cell contain a non-reciprocal exchange involving chromosomes 2, 3, and 4. Complex-type exchanges are very rarely seen after exposure to low-LET radiation at doses <2Gy, but can be induced by single traversals of heavy ions.