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The final frontier: Transient microglia reduction after cosmic radiation exposure mitigates cognitive impairments and modulates phagocytic activity

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Abstract:

Microglia are the primary immune element within the brain, which are responsible for monitoring synapse function and neuron health. Exposure to cosmic radiation has the potential to cause long-term cognitive deficits in rodent models and therefore indicates a difficult challenge for future astronauts piloting interplanetary travel. Here, we discuss the potential of transient microglia depletion after the injury to ameliorate the harsh microenvironment of the brain and eliminate any potential long-term cognitive effects. Repopulation of microglia enables phagocytic phenotypes to be circumvented, via the reduction of Phagocytic and lysosomal markers, potentially being responsible for increased neuroprotection. Brief depletion of microglia after irradiation mitigated the development of any long-term memory deficits, comparable to healthy animals. Chronically, microglial levels were not affected by cosmic radiation followed by temporary microglia depletion. Following repopulation, improved recognition memory was paralleled by downregulated complement receptor C5aR. Preserved synapse function also demonstrated the therapeutic ability of microglia depletion as it corresponded with fewer phagocytic microglia phenotypes. The understanding of long-term radiation-induced cognitive impairments is vital for the protection of future astronauts and equally as important for current cancer patients. Temporary microglia depletion showed promise in preventing any deleterious cognitive impairments following exposure to elements of cosmic radiation, such as helium and high-charge nuclei.

Keywords:

Galactic cosmic ray, microglia, radiation, sex dimorphism, synapse

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Introduction

The upcoming mars mission will open up the new age of human exploration, but there are many challenges that needs to be addressed. In the attempt to trade beyond the terrestrial orbit the distances journeyed and the arising challenges during the trek will be novel to humankind. Prolonged interplanetary travel, much like the imminent Mars mission, necessitates a definitive comprehension of the physical and mental effects of the space travel on astronauts. The physical stressors the astronauts may encounter during their journey are formidable and diverse, including altered sleep patterns, limited social interaction, and constraints on living and working space. These stressors run in parallel with the direct adverse effects of space travel, which includes experiencing galactic cosmic rays (GCRs). GCRs comprised helium nuclei, protons, and high-charge and high-energy nuclei

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which can cause mutations leading to changes in cellular function. Due to limited research, the short- and long-term effects of GCR are essentially unidentified. It is predicted that during interstellar travel, astronauts will be exposed to ten times the level of GCR than astronauts on the international space station. The two primary causes of this estimated exposure will be from helium nuclei and protons, thus highlighting the paramount importance of understanding the effects of these particles.[1-5]

Only within the last decade, the research has begun targeting the effects of GCR on the central nervous system (CNS), primarily focusing on identifying protective methods to prevent or recover cognitive function after exposure. Early research from our group and others has established rodent models to investigate the effects of individual particle exposure. Our group identified that exposure to protons, or protons linked with iron, can result in acute and prolonged loss of cognitive, measured by the novel object recognition task (NOR).[4] Radiation-induced loss of cognitive function is controlled in part by alterations in the vicinity or hippocampus. Notably, we have found that GCR exposure can modulate the expression of the gene *Arc*, a plasticity-related immediate early gene, and hippocampal networks responsible for spatial memory.[4,6-8] Additional rodent studies have indicated behavioral deficits accompanied by synapse alternations after exposure to various GCR particles, particularly oxygen or titanium.[9-11] Importantly, the behavioral and synapse modifications previously discussed are in parallel with an elevated inflammatory response and increased microglia levels up to 12 months following GCR exposure.[2,4,9-12] Altogether, this evidence implies that GCR exposure can negatively affect the neuronal and microglial function when radiation-induced cognitive effects are assessed.

Microglia are the residing macrophages and primary immune element within the brain, corresponding to 10%–15% of all brain cells. They function by continuously searching for indicators of infection or injury, being rapidly deployed toward the affected region once activated, which plays a vital role in neuroinflammation. The role of microglia in indirectly mediating neuron health, via a release of chemokines and cytokines, has long been accepted. However, recent studies have shown the direct effects of microglia on synapse function.[13,14] Microglia-regulated synaptic interaction is reliant on the complement cascade, including C1q and C3, which was previously believed to be only mediated phagocytosis and pathogenic immune responses. However, recent studies highlighted the ability of the complementary cascade in the mediation of synaptic elimination during brain development and neurodegenerative diseases. These studies indicated that the inhibition of C1q or C3 attenuates synapse loss in Alzheimer's models.[15,16] Similar to these reports, we and others have demonstrated that if microglia are diminished at the time radiation occurs, it can preclude loss of cognitive function and dendritic spine loss within the hippocampus following irradiation of the brain only.[17,18]

During interplanetary travel, it is predicted that the entire body will be exposed to a helium ion once in nearly every 3 weeks; however, in spite of this risk, there remain a limited number of studies evaluating its effects on CNS function.[3-5,19,20]

Irradiation and Memory

Deep-space missions into uncharted territory present a variety of potentially lethal obstacles, some of which are unknown. Preclinical studies can shed light on potential problems and formulate solutions to these issues. Here, we investigate the long-term adverse effects on memory by whole-body helium irradiation. For the first time, it has been demonstrated that short-term reduction of microglia following charged particle irradiation prevents any memory deficits when measuring >90 days after exposure. Furthermore, it has been found that rescue of memory deficit was in part due to at least these three factors: minimized neuroinflammation, modulation of the repopulated microglia phenotype, and expression of neuronal protein. Particularly, the reintroduced population of microglia showed reduced expression of phagocytic marker LAMP-1 and complement mediator C5aR. Attenuation of cognitive deficits was linked with upregulated synapsin-1 and diminished PSD-95 protein levels. These findings elucidated that the benefits of microglia reduction following irradiation could play a significant role in limiting memory deficits during space exploration.

Recognition memory is the capacity to evaluate an item as familiar following prior exposure to the object; this relies on the integrity of the medial temporal lobe.[21] The most widely accepted measure of recognition memory in rodent models is the NOR, which depends on the hippocampal function.[22] NOR evaluates recognition memory using the natural tendency of the animals to investigate novel locations and items, without the use of aversive stimuli. This behavioral task also requires limited researcher interaction, therefore minimizing possible human interference that would affect the outcome. In a recent study, NOR was utilized to evaluate GCR-induced recognition memory damage. It was reported that recognition memory was not affected shortly after GCR exposure (18 days). In congruence with other studies, when microglia were depleted, there were no measurable memory deficits.[16,21] Yet, the

whole-body helium exposure of 15cGy or 50cGy resulted in recognition memory deficits 90 days after irradiation.

Existing predictions estimate that a Mars interplanetary journey will last between 1.5 and 3 years, hence it is imperative to study the effects of deep space radiation on brain function, one of the major stressor that astronauts will encounter in deep space travel.[4] Several studies have established the prolonged GCR-induced deficits using iron, protons, silicon, titanium, oxygen, or proton with iron exposure.[4,6,8-11,23,24] A recent study has evaluated helium irradiation on rats, of the head only, and reported no significant deficits in NOR at low levels (0.1–10 cGy).[25,26] The previously mentioned study is limited in clinical application because interplanetary journeys result in whole-body irradiation. To this point, a study from Rabin *et al.* evaluated the effects of irradiation of the body only, head only, and whole body utilizing ^{16}O ions and showed that the whole-body exposure was the most significant in creating cognitive deficits.[26] Several recent reports have characterized various components of GCR, such as helium, as provoking long-term deficits, beyond 90 days of recognition memory, signifying the potential challenges for prolonged space voyages and the health of astronauts upon their return to earth.[12,19,25]

Transient depletion of microglia (via PLX) occurred 7 days after irradiation mitigates any recognition memory deficits. The ability to utilize this therapy within a broad treatment window is beneficial, further supporting the potential clinical efficacy of this therapy. Yet, further studies must be conducted before performing this procedure on astronauts. It was also found that helium irradiation modulates microglia activity in a persistent fashion without elevating the levels of microglia at 90 days after irradiation. It has been postulated that radiation-induced microglia modulation occurs in the acute stage, within 3 weeks of the initial radiation exposure as the removal of microglia with PLX from days 8 to 22 was able to protect against long-term memory deficits. Although further studies need to evaluate other treatment windows, 8–22 days provides evidence of the therapeutic potential of this treatment. Furthermore, the repopulated microglia exhibited phenotypic differences from the microglia of the animals that did not receive microglia depletion, at 90 days postexposure. Notably, once the repopulation of microglia was completed, the levels were similar to those of the healthy individuals. Hence, a key variation between 50 cGy and 50 cGy + PLX animals is the phenotype of microglia, insinuating the ability of helium radiation to induce functional alterations which lead to cognitive deficits.

PLX targets colony-stimulating factor 1 (CSF-1), which is vital for the survival, differentiation, and proliferation of microglia and monocytes, and also plays a role in the CSF-1/CSF-1R signaling pathway, which is essential to promote early brain development. CSF-1-(null) mutant mice have diminished macrophages present in tissues and exhibit atypical brain development, while a CSF-1R knockout mutation is lethal before puberty.[27-29] However, CSF-1R inhibitors deplete microglia with no significant cognitive effects, and once the inhibitor is no longer administered, the CNS promptly repopulates the brain with microglia.[16-18,30,31] Several reports have demonstrated that the reduction of microglia mitigates cognitive deficits resulting from whole-brain X-ray or cesium exposure.[17,18] Intriguingly, the depletion of microglia in Alzheimer's mouse models attenuates neuronal, dendritic spine loss and cognitive deficits during the disease progression.[16,32] In addition, in a diphtheria toxin model, the reduction of microglia limited inflammatory response and encouraged brain repair.[33] Altogether, these results indicate that microglia depletion shortly after physiologically, pathologically, or chemically induced cerebral injury can attenuate the resulting cognitive deficits. However, Elmore *et al.* demonstrated that in a healthy CNS, repopulated microglia result in similar inflammatory response as the nondepleted microglia.[31] Nevertheless, this may not be indicative of pathological states as a recent study demonstrated that repopulated microglia produce reduced inflammatory response after charged particle irradiation. This alteration may be attributed to diminished complement receptor C5aR expression on microglia as these results are supported by other studies, demonstrating enhanced cognitive rescue after administration of a C5aR antagonist in rodent models.[34,35]

The repopulated microglia have exhibited diminished levels of lysosome membrane protein LAMP-1, suggesting reduced phagocytic function, resulting in a discrete functional difference from the nondepleted animals. In a previous study, the depletion of microglia had shown not to effect dendritic spine density, in healthy animals, while also preventing the significant reduction of spine density following brain-only irradiation.[17] The newly repopulated microglia limits the phagocytic phenotype induced by GRC, thus protecting against cognitive and synapse loss. The stability of synapses was evaluated, resulting in elevated and reduced levels of presynaptic protein synapsin-1 and postsynaptic protein PSD-95, respectively, in the cGy50 + PLX condition compared to the cGy50-only group. As synapsin-1 and PSD-95 are both contributors to synapse stability, fluctuating levels of these proteins suggest a change in the overall neuron function.[36,37] Early studies targeted the effects of microglia on synapse interaction and found that microglia predominately digest presynaptic terminals.[38] These results support more recent data,

suggesting that less phagocytic microglia, resulting from the repopulation of the 50 cGy + PLX condition, may cause additional presynaptic protein expression, while GCR exposure by itself will elevate PSD-95 levels, resulting in reduced dendritic spine density.[9] This effect on postsynaptic terminals corresponds to radiation-induced cognitive deficits (object-in-place and NOR).[9] Although these studies elucidate insightful details of possible mechanism responsible for the attenuation of cognitive deficits following GCR exposure, further investigations need to explore the direct interaction between microglia and synapses after GCR exposure.

Comprehending the effects of radiation exposure on cognitive function is of paramount importance not only for the future of space exploration but also for individuals receiving cancer treatment. Clinical whole-brain radiation exposure predominately involves 25–30 fractions, resulting in a total does of 55–60 Gy. There are a variety of adverse effects, inducing activation of glial cells, reduced neural regeneration, damage to the blood–brain barrier, and intrusion of peripheral immune cells, which may all or in part account for persistent cognitive deficits.[39-43] In the current study, substantial reductions of inflammatory chemokine CCL2 and scavenger receptors CD163 and CD206 were observed in 50 cGy + PLX animals compared to the 50 cGy-only group at 90 days postexposure. Along with a reduction of LAMP-1, it can be assumed that following GCR exposure, the microglia-depleted brains exhibit a more favorable microenvironment than that of nondepleted brains. These data further support the key role the microglia have in the progression of persistent radiation-induced cognitive deficits.[17,44]

Microglia-depleted animals after GCR have also exhibited reduced levels of DUSP1, an upstream inhibitor of brain-derived neurotropic factor (BDNF) signaling, indicating that PLX-mediated microglia reduction could result in a secondary upregulation of microglial BDNF signaling, potentially aiding enhanced cognitive protection.[45,46] Notably, a downregulation of DUSP1 in the 50 cGy + PLX group, but not the 100 cGy + PLX group, was observed when compared to GCR-exposed animals that did not receive microglia depletion. A mild decrease in CD163 and elevation of CD206 in microglia-depleted brains was observed when compared to the GCR-exposed (100 cGy) group with no microglia depletion. This evidence indicates that the regulation of CD163 and CD206 within the repopulated microglia is not responsible for diminished cognitive function as the 100 cGy group had no cognitive impairments.

Conclusion

Our observations in tandem with other reports strongly suggest the therapeutic efficacy of microglia depletion following radiation exposure to ameliorate cognitive deficits, as well as providing a potential mechanism of action for the function of microglia in the development of persistent cognitive impairments after GCR exposure. Understanding the intricacies of how radiation exposure affects cognitive function is vital for the exploration of inflammation-plagued disorders.

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Conflicts of interest

There are no conflicts of interest.

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