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PERSPECTIVE

Low dose radiation effects on the brain – from mechanisms and behavioral outcomes to mitigation strategies

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ABSTRACT

Based on the most recent estimates by the Canadian Cancer Society, 2 in 5 Canadians will develop cancer in their lifetimes. More than half of all cancer patients receive some type of radiation therapy, and all patients undergo radiation-based diagnostics. While radiation is one of the most important diagnostic and treatments modalities, high-dose cranial radiation therapy causes numerous central nervous system side-effects, including declines in cognitive function, memory, and attention. While the mechanisms of these effects have been studies, they still need to be further elucidated. On the other hand, the effects of low dose radiation as well as indirect radiation bystander effects on the brain remain elusive.

We pioneered analysis of the molecular and cellular effects of low dose direct, bystander and scatter radiation on the brain. Using a rat model, we showed that low dose radiation exposures cause molecular and cellular changes in the brain and impacts animal behavior. Here we reflect upon our recent findings and current state of knowledge in the field, and suggest novel radiation effect biomarkers and means of prevention. We propose strategies and interventions to prevent and mitigate radiation effects on the brain.

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Radiation effects

Ionizing radiation (IR) is often referred to as a double-edged sword. On one hand, it is one of the indispensable mainstream diagnostic and treatment modalities; on the other, it is a potent DNA-damaging agent that causes as single- and double-strand breaks, base and nucleotide damages, and DNA and protein crosslinks.[1,2] In addition to causing DNA damage, radiation exposure also disrupts a variety of processes in exposed cells. It can trigger changes in gene expression and cell cycle control, disrupt mitochondrial processes, lead to differentiation and apoptotic cell death, and affect global genome instability.[3,4] Radiation effects are also epigenetically mediated.[3,5,6]

Radiation effects on the brain

Recent studies have proven that the brain is, indeed, sensitive to irradiation. Cranial radiation therapy impacts a wide array of brain functions, causing cognitive decline, memory deficits, fatigue, and brain tumors in exposed individuals.[7] The extent and severity of radiation's effects on the brain depend upon the radiation dose. Exposure to high-dose IR can cause profound functional and morphological changes in brain tissues, leading to cognitive decline.[8,9] Low doses can also induce a wide array of cognitive impairments and deficits, even without any significant morphological alterations.[8,10]

While the effects of high doses of radiation on the brain have been studied and are reasonably well understood, the effects and mechanisms of the brain's responses to low doses of radiation remain rather obscure. Recent studies have proven that radiation effects are age-, brain region-, and sex-specific.[7,11,12] Among the brain regions, the prefrontal cortex (PFC) and the hippocampus are the most sensitive to irradiation.[13-18]

The hippocampus is one of the 2 active sites of neurogenesis in the mammalian brain.[19] The proliferation of neuronal precursors in the subgranular zone of the dentate gyrus generates cells that migrate further to the granule cell layer and differentiate into mature neuronal and glial phenotypes.[20] The PFC is a key regulatory region that collects inputs from all other cortical regions and then plans and directs an array of motor, cognitive, and social behaviors.[21]

Bystander effects

Radiation effects span beyond the irradiated cells and tissues, and cells that are not directly exposed to radiation – 'bystander cells', demonstrate responses that are characteristic of directly irradiated cells.[22] Radiation-induced 'bystander' effects have been observed in both naïve cells that come into contact with directly irradiated cells and naïve cells that receive irradiation "distress" signals from directly exposed cells via the growth medium, in tissue explants, spheroids, and 3-dimensional artificial human tissue models, and are commonly accepted as a ubiquitous outcome of IR exposure.[5,6,22,23]

Bystander effects also occur in the context of the whole organism. Radiation exposure causes the release of soluble

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factors into the circulating blood that are capable of inducing chromosomal damage in cultured cellsand tissue explants. Such factors have been reported in the plasma of radiation therapy patients and individuals who have been accidentally exposed to ionizing radiation,[24,25] also reviewed in.[6,23]

Bystander effects have been shown to be important within organs when one organ part is exposed and within organisms when one paired organ is irradiated. In a rat model, when one lung is irradiated, a significant increase in DNA damage can be found in the unexposed shielded bystander lung.[26] Bystander effects have been noted in liver in the Chinese hamster model upon in vivo exposure to α particles.[27] Moreover, bystander effects also occur when one part of the animal's body or head is exposed to radiation while another part is protected by a lead shield.[28-31] In several rodent model-based experiments, cranial exposure is caused by molecular bystander effects in animals' shielded spleens, livers, and gonads. IR-induced bystander effects persist for a long time following irradiation.[28-34] The bystander effects may be related to the abscopal effects observed in clinic, whereby radiation treatment of one tumor site may lead to clearance of tumors in other locations within the organisms.[35] Bystander effect signals still remain enigmatic, but, similarly to the abscopal effects, they may in turn be associated with immune response.[35,36]

On a molecular level, bystander effects manifest as increases in DNA damage and mutations, changes in gene expression, and altered levels of cellular proliferation and apoptosis, and are epigenetically regulated, asreviewed in.[6,37,38]

Bystander effects in the brain

While cranial exposure has been shown to cause bystander effects in somatic organs, very little is known about the existence or impact of bystander effects on a shielded brain upon the irradiation of distal somatic organs. Bystander effects were reported to occur the astrocytes, microglia and cells from the cortex, cerebellum and hippocampus in culture upon exposures to low and high doses of IR. A handful of studies have shown that such effects do exist. For example, a report by Mancuso and colleagues showed the occurrence of radiation-induced bystander responses in the neonatal murine cerebellum following the X-ray exposure of the remainder of the body using radiosensitive Patched-1 (Ptch1) heterozygous mice.[39] The same group showed the induction of bystander effects in the brain using the connexin43 mutant mouse.[40] Still, there is a great deal to learn about the existence, magnitude, mechanisms, and consequences of radiation-induced bystander effects on the brain and their contributions to the side effects of radiation therapy.

Direct, bystander, and scatter low-dose radiation effects on the brain

To further explore the existence and mechanisms of low dose radiation-induced direct and bystander changes, we analyzed the effects of radiation on the brain, focusing on the hippocampus and the PFC due to their pivotal roles in memory, learning, and executive functions. We compared direct radiation and bystander radiation effects. Our recent study published in the *Oncotarget* (2016) was the first to conduct a large-scale analysis of the molecular, neuroanatomical, and behavioral consequences of direct and bystander low-dose irradiation on the rodent brain.[41] The key findings were that: (i) direct head exposure to radiation doses as low as 24.5 cGy induced persistent, albeit small, increases in DNA damage, as measured by levels of γH2AX and effects on gene expression in the PFCs of exposed animals; (ii) bystander effects exist in the brain following liver irradiation and manifest as small increases in DNA damage, as measured by levels of γH2AX and alterations to gene and protein expressions; (iii) both head and liver irradiation reduce dendritic space (and, thus, synapse numbers) in measures of spine density, dendritic complexity, and dendritic length; (iv) the neuroanatomical effects are brain region-specific and are more pronounced in females; and (v) both head and liver irradiation alter behavior.[41]

These intriguing bystander effects may be caused by certain blood-derived factors or by very small, scattered irradiation doses received by the brain. Therefore, we continued to study radiation effects on the brain, focusing on scatter irradiation using an animal model. One animal received direct liver irradiation while its body and the body of an adjacent "bystander" animal were fully covered by a medical-grade lead shield. The brain of the adjacent animal was found to receive scatter irradiation. Our study is the first to show that very low, clinically relevant doses of "bystander" scatter irradiation alter gene expression, induce changes in dendritic morphology, and lead to behavioral deficits in exposed animals. The key outcomes of this study are that: (i) "bystander" scatter irradiation affects the brain; (ii) "bystander" scatter irradiation at a clinically relevant dose as low as 0.115 cGy causes changes in gene expression in the PFC tissues of females, but not males; (ii) "bystander" scatter irradiation reduces spine density, dendritic complexity, and dendritic length; (iii) "bystander" scatter-induced neuroanatomical changes are brain region-specific and are much more pronounced in females; and (iv) "bystander" scatter irradiation causes behavioral deficits in female animals, but not in male animals.[42]

These constitute seminal findings because, for quite some time, the brain has been considered a radiation-resistant organ, on which only very high doses have been thought to have harmful effects. In sum, our initial experiments present key evidence that the mammalian brain is negatively affected by direct, bystander, and scatter exposures to very low doses of radiation. The effects are sex- and brain region-specific and persistent. In addition, our data suggest that the female PFC is especially sensitive to low-dose irradiation, much more so than the male one, and that it is one of the most stress-sensitive regions of the mammalian brain. This is a novel finding because the majority of animal model-based studies have focused on the effects of low-dose irradiation on the hippocampus due to its established role in adult neurogenesis and memory formation.[13,17,43-46] By comparison, the PFC has been overlooked in animal models of radiation treatment, despite its key role in regulating crucial executive functions, such as planning, decision-making, behavioral inhibition, and working memory, among others.[21,47] In our studies, direct irradiation of the head, bystander irradiation of the liver, and scatter irradiation caused notable and persistent gene expression changes in the PFC tissues of female rats. Changes in the hippocampus tissues were small to negligible.

Future perspectives

Our analysis reveals that molecular, cellular, neuroanatomical, and behavioral changes induced by cranial, bystander, and scatter radiation treatments exhibit sex-specific differences and are much more pronounced in female animals. The majority of earlier animal studies have used male animals[46,48-52] and, thus, have not been able to provide a complete picture of the brain's response to radiation and chemotherapy treatment. Overall, brain functions are well-documented as being 'sexed' and 'gendered',[53] and numerous sex differences have been documented in autism spectrum disorder,[54,55] the development of substance use and abuse,[56] the regulation of neuro-inflammatory responses,[57] and the effects of adolescent stress,[58] among others. Synaptic patterns and neuronal densities are sexually dimorphic, and males and females display dissimilar patterns of transmitting, regulating, and processing biomolecules, including neurotransmitters, as well as different patterns of behavior in response to certain stimuli, as reviewed in.[53] Furthermore, an earlier study by Silasi et al.[12] reported significant sex differences in brain responses to single doses and multiple, fractionated doses of direct total body irradiation. Therefore, it is absolutely imperative to use both male and female animals in any model study. Specifically, the mechanisms of sex differences in radiation responses need to be studied in further detail. These mechanisms may be due to differences in hormonal status and/or to an intricate interplay between radiation and the regulation of gene expression by sex hormones.[12]

Previous studies have suggested that miRNAs play regulatory roles in gene expression in the brain's responses to total body irradiation.[7,59] Yet, nothing is known about the effects of low-dose head, bystander, or scatter irradiation on the brain's small repertoire of ncRNA. Future studies should be conducted to determine the regulation of gene expression through low doses of direct, bystander, and scatter irradiation in the brain and to discern patterns of DNA methylation and hydroxymethylation and their roles on regulating gene expression in directly exposed, bystander, and scatter-irradiated brain tissues.[60,61] To gain a full understanding of the molecular mechanisms and pathways affected by various modes of low-dose radiation exposure, the effects of bystander and scatter-radiation should be studied using tumor-bearing animals. Age bias, if any, must also be considered.

In recent years, significant effort has been devoted to developing new strategies for the prevention and mitigation of deleterious radiation effects on healthy tissues and organs, including the brain. Because radiation exposure (direct, bystander, and scatter) affects dendritic space, reduces the brain's ability to produce new neurons, and alters behavior, mitigation efforts should focus on restoring these key parameters and functions. An array of recent studies have proposed elegant and elaborate, albeit complicated, radiation mitigation strategies that include stem cell- and stem cell-derived vesicle-based approaches,[62-64] as well as approaches based on the pharmacological inhibition of adenosine kinase and elimination of microglia.[65,66] These strategies may, in the future, turn out to be very useful, although, in their current state, they are high-tech and rather costly. On the other hand, environmental enrichment and exercise may provide a feasible, easy, and cost-effective avenue for exploring ways to protect the brain from irradiation. Since environmental enrichment has been reported to have numerous positive, protective, and mitigating effects in models of neurologic diseases and animals exposed to high doses of whole-brain irradiation,[67-70] one could predict that environmental enrichments may be very effective for counteracting the deleterious neuroanatomical and behavioral effects of low-dose head, bystander, and scatter irradiation.

Analyses of the mechanisms of the effects of low-dose radiation on the brain must be continued and further substantiated. In the future, these may serve as a foundation for the development of new methods to prevent low-dose radiation from affecting the brain. Such methods may, in turn, be important for preventing the effects of low-dose brain radiation exposure that occurs during radiation therapy and diagnostics and in occupational and environmental conditions. Preclinical animal model data can serve as a foundation for the research and development of new brain radiation biomarkers.

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