

## Molecular Pathways: Radiation-Induced Cognitive Impairment

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### Abstract

Each year, approximately 200,000 patients in the United States will receive partial- or whole-brain irradiation for the treatment of primary or metastatic brain cancer. Early and delayed radiation effects are transient and reversible with modern therapeutic standards; yet, late radiation effects ( $\geq 6$  months postirradiation) remain a significant risk, resulting in progressive cognitive impairment. These risks include functional deficits in memory, attention, and executive function that severely affect the patient's quality of life. The mechanisms underlying radiation-induced cognitive impairment remain ill defined. Classically, radiation-induced alterations in vascular and neuroinflammatory glial cell clonogenic populations were hypothesized to be responsible for radiation-induced brain injury. Recently, preclinical studies have focused on the hippocampus, one of two sites of adult neurogenesis within the brain, which plays an important role in learning and memory. Radiation ablates hippocampal neurogenesis, alters neuronal function, and induces neuroinflammation. Neuronal stem cells implanted into the hippocampus prevent the decrease in neurogenesis and improve cognition after irradiation. Clinically prescribed drugs, including PPAR $\alpha$  and PPAR $\gamma$  agonists, as well as RAS blockers, prevent radiation-induced neuroinflammation and cognitive impairment independent of improved neurogenesis. Translating these exciting findings to the clinic offers the promise of improving the quality of life of brain tumor patients who receive radiotherapy. *Clin Cancer Res*; 19(9); 2294–300. ©2013 AACR.

### Background

The majority of cancer patients undergo some form of radiation therapy. For those with primary or metastatic tumors in the brain, radiation can be delivered to the lesion(s), for instance stereotactic radiosurgery, or to part or all of the brain in smaller fractions [whole-brain irradiation (WBI); fractionated whole-brain radiation (fWBI)]. Improved anti-cancer therapies have resulted in increased long-term brain tumor patient survival (1), so that the patient population experiencing significant late effects is growing rapidly. Radiation-induced cognitive impairment occurs in up to 90% of adult brain tumor patients who survive more than 6 months after fWBI (2, 3). The hallmarks of radiation-induced cognitive impairment are decrements in verbal memory, spatial memory, attention, and novel problem-solving ability (4, 5), all with incidence and severity increasing over time

(6). Cognitive impairment progresses to dementia in about 2% to 5% of long-term survivors who have received fWBI, including memory loss, ataxia, and urinary incontinence (7). These late effects can be seen without clinical or radiographic evidence of demyelination or white matter necrosis (8). Brain tumor survivors experience radiation-induced cognitive impairment, which significantly affects their quality of life (QOL); reduced QOL is now recognized as one of the most important outcome measurements, second only to survival in clinical trials (9). Successful long-term treatments or effective preventive strategies for radiation-induced cognitive impairment are sorely needed.

### Pathogenesis of radiation-induced cognitive impairment

Valuable insights have come from preclinical studies regarding potential pathogenic mechanisms involved in radiation-induced cognitive impairment; however, details of specific molecular mechanisms/pathways remain ill defined (Fig. 1A; ref. 10). Previously, late radiation-induced brain injury was viewed as solely a result of DNA damage, leading to a reduction in the proliferative capacity of vascular endothelial or brain glial cells and thus progressive and irreversible (11). This hypothesis is no longer tenable; preclinical studies conducted in the last 2 decades clearly show that radiation-induced late effects reflect complex and dynamic interactions between multiple cell types (12). In the brain, radiation-induced late effects, including cognitive impairment, are hypothesized to occur because of dynamic

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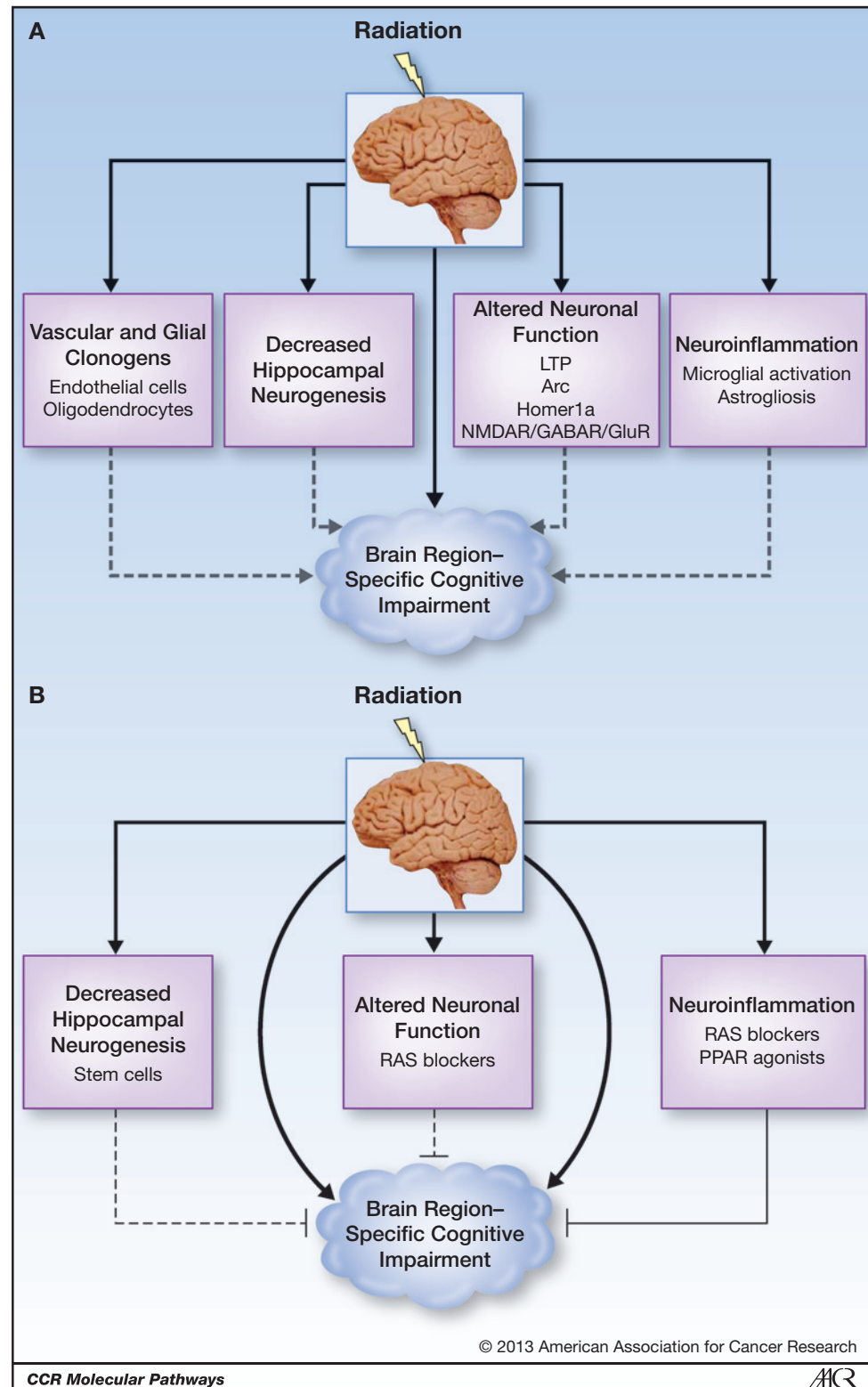
**Note:** Dr. M.E. Robbins is deceased. This article is dedicated to his memory.

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Figure 1. A, potential mechanisms underlying radiation-induced cognitive impairment. Radiation-induced cognitive impairment likely involves dynamic interactions between multiple cell types in the brain. Brain irradiation causes changes in the vasculature, glial cell populations, hippocampal neurogenesis, and neuronal function and elicits neuroinflammation. All of these pathways likely contribute to the development of radiation-induced cognitive impairment. B, potential therapeutic interventions to prevent radiation-induced cognitive impairment. Preclinical models suggest that radiation-induced cognitive impairment can be prevented or ameliorated by targeting neurogenesis or inflammation. Neuronal stem cell transplants to the hippocampus can restore neurogenesis, thus improving cognitive function. PPAR agonists and renin-angiotensin system (RAS) blockers prevent neuroinflammation and radiation-induced cognitive impairment independent of changes in neurogenesis.



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interactions between multiple cell types within the brain (11), including astrocytes, endothelial cells, microglia, neurons, and oligodendrocytes.

#### Vascular and glial clonogens

Previous studies have indicated that irradiating the rodent brain leads to alterations in proliferative cells of the

vasculature and glial cell populations. Rats that received fWBI had time- and dose-dependent reductions in the number of brain endothelial cells, vessel density, and vessel length (Fig. 1A; ref. 13). Two months after fWBI in a mouse model, capillary rarefaction and tissue hypoxia increased in all regions of the hippocampus (14); administration of systemic hypoxia restored brain microvascular density and improved hippocampal-dependent cognitive function (15). Intravenous injections of primary cultured mouse fetal neural stem cells after each 5-Gy fraction (4 fractions total) differentiated into both brain endothelial cells, as well as a variety of other brain cells, and restored radiation-induced decreases in both cerebral blood flow and cognitive function (16). However, a variety of interventional drugs (see later text for details) prevent fWBI-induced cognitive impairment in preclinical models without altering the reduction in vascular density and length (W.R. Brown; unpublished data). In addition, radiation-induced white matter necrosis can occur in the absence of any vascular changes (17).

The oligodendrocyte type-2 astrocyte (O-2A) progenitor cell has been hypothesized to represent the primary glial target cell (Fig. 1A; ref. 18); radiation-induced loss of O-2A progenitor cells leads to a failure to replace oligodendrocytes, ultimately resulting in demyelination and white matter necrosis. Oligodendrocyte depletion has been reported in young adult rats within 24 hours of single WBI doses of  $\geq 3$  Gy and total fWBI doses of  $\geq 4.5$  Gy (19). Radiation-induced oligodendrocyte depletion may be a transient effect because no change was observed in the number of myelinated axons, thickness of myelin sheaths, or cross-sectional area of myelinated axons in middle-aged rats that were cognitively impaired 12 months after 40 Gy of fWBI was given in 5-Gy fractions twice a week for 4 weeks (20). Moreover, despite the kinetics of oligodendrocyte loss being consistent with an acute transient demyelination, it is inconsistent with late onset of white matter necrosis (21). An additional and important component of radiation injury to the brain is the relatively recent observation that brain irradiation can inhibit hippocampal neurogenesis.

### Neurogenesis

The hippocampus has been shown to play a major role in learning, consolidation, and retrieval of information (22) and thus the majority of studies have focused on the hippocampus to investigate radiation-induced brain injury (Fig. 1A). The hippocampus consists of 3 regions, the dentate gyrus (DG), CA3, and CA1, which have been implicated in both rodent and human cognition. In addition, the DG is 1 of 2 sites of adult neurogenesis in the mammalian brain. Neuronal stem cells (NSC) in the DG are capable of self-renewal, as well as generating new neurons, astrocytes, and oligodendrocytes (23, 24). Neurogenesis is dependent on a specific neurogenic microenvironment where endothelial cells and astrocytes promote and regulate neurogenesis (25). Irradiating the rodent brain has been shown to result in a dose-dependent decrease in NSCs, decreased proliferation of surviving NSC, and decreased

differentiation of NSC into neurons (26–28). Young male rats that received a single 10-Gy dose of WBI, a dose that does not cause white matter necrosis or demyelination, only produced 3% of new hippocampal neurons as compared with unirradiated rats (27). Unlike neurogenesis, gliogenesis seems to be preserved after irradiation (28). Reductions in hippocampal neurogenesis have been correlated with radiation-induced cognitive impairment. However, to date no clear mechanistic link between radiation-induced cognitive impairment and decreased neurogenesis has been shown.

In addition to the hippocampus, other domains in the brain are also important for cognition and likely important in the development of radiation-induced cognitive impairment. Prior studies have suggested that conformal partial brain irradiation may not cause the same degree of cognitive impairment as large-field and/or WBI (29, 30), leading to the hypothesis that there are specific brain regions that, after irradiation, can contribute to cognitive impairment. Peiffer and colleagues (31) used dose–volume histogram analysis of 2 prospective clinical trials to show that it is not the dose to the whole brain, but rather the dose to specific regions, such as the temporal lobes and the hippocampus, that predicts subsequent radiation-induced cognitive impairment. These authors propose a neuroanatomical target theory for radiation-induced cognitive impairment; selective damage to certain brain structures may be the cause of cognitive impairment after radiotherapy. Thus, radiation-induced loss of neurogenesis alone may not accurately predict radiation-induced cognitive impairment.

### Neuronal function

Although neurons were once considered a radioresistant population because they no longer could divide, a growing interest has been expressed in radiation-induced changes in neuronal function, particularly synaptic plasticity. Irradiating the rodent brain elicits changes in hippocampal long-term potentiation (LTP; ref. 32), neuronal receptor expression of the immediate-early gene activity-regulated cytoskeleton-associated protein (Arc; ref. 33), *N*-methyl-D-aspartic acid (NMDA) receptor subunits (34), and glutamatergic transmission (35). Recently, Wu and colleagues (36) noted that irradiating isolated rat brain slices with 2 to 10 Gy led to acute (30 minutes postirradiation) decreases in tyrosine phosphorylation and removal of excitatory NMDA receptors from the cell surface while simultaneously increasing surface expression of inhibitory  $\gamma$ -aminobutyric acid (GABA) receptors. These changes corresponded with altered synaptic responses, inhibition of LTP, and reduced cognition. We have shown radiation-induced changes in gene expression of Homer1a, a synaptic plasticity early-response gene essential for the activity-dependent regulation of excitatory synaptic transmission. Homer1a exhibited decreased expression in both the hippocampus and cortex 2 m after fWBI (37; E. Moore, personal communication). Furthermore, these changes in Homer1a expression correlated with an increase in metabolic

glutamate receptor 1 (E. Moore; personal communication). These exciting findings suggest new putative mechanisms and targets and provide further evidence that fWBI alters synaptic plasticity (Fig. 1A).

### Neuroinflammation

Evidence for a chronic inflammatory response to fWBI/WBI in rodent models includes elevation of inflammatory cytokines in mouse brain up to 6 months after irradiation (38, 39), a marked increase in the number of activated microglia in the neurogenic zone of the DG (27), increased expression of the CCR2 receptor in the subgranular zone 9 months after irradiation (40), and persistent microglial and astrocyte activation (refs. 41 and 42; Fig. 1A). These results provide a rationale for the use of antiinflammatory-based interventions to prevent or ameliorate late radiation-induced brain injury, including cognitive impairment.

### Clinical-Translational Advances

Although the exact mechanisms involved in radiation-induced brain injury, including cognitive impairment, are unclear, potential therapeutic strategies to prevent radiation-induced brain injury have focused on stem cell and/or drug-based therapies (Fig. 1B). The rationale for stem cell therapies is based on results from studies correlating the radiation-induced decrease in hippocampal neurogenesis with cognitive impairment (43, 44). Following single doses of WBI, voluntary running has been shown to increase neurogenesis in the rodent hippocampus with a corresponding improvement in spatial learning and memory (45, 46). Injection of NSCs directly into rodent brains after WBI partially restores neurogenesis and hippocampal-dependent cognitive function (16, 47, 48). Interestingly, these NSCs not only differentiate into neurons but also into oligodendrocytes, astrocytes, and endothelial cells that can alter the hippocampal microenvironment (16). However, these studies involve injecting NSCs into immunodeficient mice. Previous studies by Monje and colleagues showed that inflammation impaired the neurogenic environment; thus, the transplanted syngenic NSCs cannot produce neurons (27, 49). Translating NSC transplantation to prevent or ameliorate radiation-induced cognitive impairment in patients will require considerably more research before it can be implemented in the clinic.

The relative wealth of experimental data supporting a major role for neuroinflammation in radiation-induced brain injury suggests that utilization of anti-inflammatory-based approaches would be of benefit. Rather than developing novel agents, a process that would likely take considerable time and ultimately prove unsuccessful, we have focused on using clinically prescribed drugs, including PPAR $\alpha$  and PPAR $\gamma$  agonists, and blockers of the renin-angiotensin system (RAS; Fig. 1B).

PPAR $\alpha$ , PPAR $\delta$ , and PPAR $\gamma$  are ligand-activated transcription factors that belong to the steroid/thyroid hormone superfamily of nuclear receptors (50), regulate inflamma-

tory signaling, and are neuroprotective in a variety of central nervous system diseases (51, 52). Dietary administration of the PPAR $\gamma$  agonist, pioglitazone (120 parts per million), to young adult male rats starting 3 days before, during, and for 54 weeks after the completion of 40-Gy fWBI, prevented the radiation-induced perirhinal cortex-dependent cognitive impairment measured 52 weeks after fWBI (53). In addition, administering pioglitazone before, during, and for only 4 weeks after fWBI similarly prevented the radiation-induced decrease in cognitive function, indicating that continued administration of the drug for a year after fWBI may not be required (53). A phase I/II trial of pioglitazone given to patients with brain tumors before, during, and after fWBI is near completion (M.D. Chan; personal communication).

The PPAR $\alpha$  agonist fenofibrate has also been used based on its ability to cross the blood-brain barrier (BBB) and be well tolerated by patients. Dietary administration of fenofibrate (0.2%, w/w) to young adult male mice receiving a single 10-Gy dose of WBI prevented both the radiation-induced decrease in the number of newborn hippocampal neurons and increase in microglial activation (54). In addition, in a follow-up study using young adult male rats, dietary fenofibrate (0.2%, w/w) administration starting 1 week before and continuously up to 30 weeks after 40-Gy fWBI prevented perirhinal cortex-dependent cognitive impairment assessed 26 weeks after fWBI and also prevented the increase in activated microglia determined 30 weeks after fWBI (D. Greene-Schloesser; personal communication). This preservation of cognitive function was seen in the absence of any detectable decrements in hippocampal-dependent cognitive function or any protection in terms of neurogenesis, further emphasizing the need to consider other brain regions and not the hippocampus alone when studying radiation-induced cognitive impairment (D. Greene-Schloesser; personal communication).

Blockade of the RAS has proved to be one of the most effective approaches in the prevention and amelioration of radiation-induced late effects. Angiotensin II type 1 receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI) have proved highly effective in the treatment and prevention of experimental radiation-induced late effects in the kidney and lung (55). Classically, the RAS has been viewed as a complex systemic hormonal system; however, recent studies have identified several intraorgan RAS, including a brain RAS (56), clearly involved in modulation of the BBB, stress, memory, and cognition (57). Moreover, beneficial effects of RAS blockade on cognitive function have been observed in hypertensive patients using the ARB losartan independent of any reduction in blood flow (58). These findings suggest an important role for the brain RAS in normal cognitive function and potential treatment of dysfunctional memory disease states (59). Based on these findings, it is logical to investigate the use of RAS blockers in the treatment of radiation-induced brain injury, including cognitive impairment.

Administering the ARB, L-158,809 (in 20 mg/L drinking water) to young adult male rats 3 days before 40-Gy fWBI, during and for 28 or 54 weeks post-fWBI prevented the radiation-induced cognitive impairment observed 26 and 52 weeks after irradiation (60). Giving L-158,809 before, during, and for only 5 weeks after irradiation similarly prevented the cognitive impairment observed 26 weeks after irradiation, indicating that continued RAS blockade may not be required (60). Lee and colleagues extended these observations to show that RAS blockade using ramipril, an ACEI, can similarly prevent fWBI-induced cognitive impairment (61). Thus, RAS blockade with either an ACEI or an ARB seems effective at preventing radiation-induced cognitive impairment. Of note, RAS blockade did not prevent or ameliorate radiation-induced decreased neurogenesis. In contrast, both the ACEI and ARB did prevent the fWBI-induced neuroinflammation (61, 62). Furthermore, the ACEI and ARB also prevented the radiation-induced reduction in hippocampal and cortex Homer1a gene expression (E. Moore; personal communication), suggesting that RAS blockade may be targeting radiation-induced changes in synaptic plasticity and neuroinflammation.

The ability to translate these drug-based findings to the clinic is predicated by ensuring that their protective effect on the normal brain is selective and not observed in tumor cells. A growing body of evidence suggests that PPAR $\alpha$  and PPAR $\gamma$  agonists, as well as RAS blockers, do not protect tumor cells. In contrast, these drugs exhibit significant antitumor effects and can enhance anticancer therapies (63–65). Thus, they seem to be ideal drugs for translational clinical studies.

## Summary

Preclinical studies have provided valuable insights into the pathogenesis of radiation-induced brain injury, includ-

ing cognitive impairment. Although reductions in hippocampal neurogenesis and hippocampal-dependent cognitive function have been observed, other brain regions are clearly affected. Treatment using stem cell therapies suggests that the radiation-induced reduction in neurogenesis can be prevented. However, the use of stem cell–based therapies to prevent or ameliorate radiation-induced cognitive impairment will require a great deal more research before this treatment strategy can be translated to the bedside.

In contrast, preclinical studies using clinically prescribed PPAR $\alpha$  and PPAR $\gamma$  agonists and/or RAS blockers have shown that these drugs can prevent or ameliorate radiation-induced cognitive impairment independent of protection and restoration of neurogenesis. The translation of these exciting preclinical findings to the clinic offers the promise of significantly improving the QOL of brain tumor patients who receive radiation therapy.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** E. Moore, D. Greene-Schloesser, M.E. Robbins  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** E. Moore, D. Greene-Schloesser, M.E. Robbins  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** E. Moore, D. Greene-Schloesser, M.E. Robbins  
**Writing, review, and/or revision of the manuscript:** D. Greene-Schloesser, E. Moore, M.E. Robbins

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