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ABSTRACT.

Approximately 200,000 patients/year in the US 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 (≥6 months postirradiation) remain a significant risk, resulting in progressive cognitive impairment. These include functional deficits in memory, attention, and executive function that severely affect the patient's quality of life (QOL).

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 following irradiation. Clinically prescribed drugs, including PPAR α and γ 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 QOL of brain tumor patients who receive radiotherapy.

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 the part or all of the brain in smaller fractions (whole brain irradiation, fWBI). Improved anticancer therapies have resulted in increased long-term brain tumor patient survival [1], thus 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 >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 up to ~2-5% of long-term survivors that received fWBI, in which patients experience progressive 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); now it is recognized as one of the most important outcome measurements, second only to survival in clinical trials [9]. Successful long-term treatments or effective preventative 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) [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

two decades clearly demonstrate 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 due to dynamic 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) [13]. Two months following 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 below for details) prevent fWBI-induced cognitive impairment in preclinical models, without altering the reduction in vascular density and length (Brown, unpublished data). Additionally, 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) [18]; radiation-induced loss of O2A 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 h of single WBI doses of ≥3 Gy and total fWBI doses of ≥4.5 Gy [19]. Radiation-induced oligodendrocyte depletion may be a transient effect since there was no change 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 m after 40 Gy of fWBI 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 three regions, the dentate gyrus (DG), CA3, and CA1, which have been implicated in both rodent and human cognition. Additionally, the DG is one of two sites of adult neurogenesis in the mammalian brain. Neuronal stem cells (NSCs) in the DG are capable of both 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/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 which does not cause white matter necrosis or demyelination, only produced 3% of new hippocampal neurons as compared to unirradiated rats [27]. Unlike neurogenesis, gliogenesis appears to be preserved following 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 demonstrated.

In addition to the hippocampus, there are other domains in the brain that are 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 whole brain irradiation [29, 30]; leading to the hypothesis that there are specific brain regions that, following irradiation, can contribute to cognitive impairment. Peiffer et al [31] used dose-volume histogram analysis of two prospective clinical trials to demonstrate that it is not the dose to the whole brain, but rather the dose to specific regions, such as the temporal lobes as well as 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

Once considered a radioresistant population because they no longer could divide; there is a growing interest in radiation-induced changes in neuronal function, particularly synaptic plasticity. Irradiating the rodent brain elicits changes in, i] hippocampal long term potentiation (LTP) [32], ii] neuronal receptor expression of the immediate-early gene activity-regulated cytoskeleton-associated protein (Arc) [33], iii] N-methyl-D-aspartic acid (NMDA) receptor subunits [34], and iv] glutaminergic transmission [35]. Recently, Wu et al [36] noted that irradiating isolated rat brain slices with 2-10 Gy led to acute (30 min postirradiation) decreases in tyrosine phosphorylation and removal of excitatory NMDA receptors from the cell surface while simulataneously 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 demonstrated 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] (Moore, personal communication). Furthermore, these changes in Homer1a expression correlated with an increase in metabolic glutamate receptor 1 (Moore, personal communication). These exciting findings suggest new putative mechanisms/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, i] elevation of inflammatory cytokines in mouse brain up to 6 months postirradiation [38, 39], ii] a marked increase in the number of activated microglia in the neurogenic zone of the DG [27], iii] increased expression of the CCR2 receptor in the subgranular zone 9 months postirradiation [40], and iv] persistent microglial and astrocyte activation [41, 42] (Fig. 1A). These results provide a rationale for the use of anti-inflammatory-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 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 following WBI partially restores neurogenesis and hippocampal-dependent cognitive function [16, 47, 48]. Interestingly, these NSCs not only differentiate into neurons, but

also oligodendrocytes, astrocytes, and endothelial cells that can alter the hippocampal microenvironment [16]. However, these studies involve injecting NSCs into immunodeficient rats. Previous studies by Monje et al reported that inflammation impaired the neurogenic environment; thus the transplanted syngenic NSCs cannot produce neurons [27, 49]. Translating NSC transplantation to prevent/ameliorate radiation-induced cognitive impairment in patients will require considerable 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 i] peroxisomal proliferator-activated receptor (PPAR) α and γ agonists, and ii] blockers of the renin-angiotensin system (RAS) (Fig. 1B).

PPARα, δ, and γ are ligand-activated transcription factors that belong to the steroid/thyroid hormone superfamily of nuclear receptors [50], regulate inflammatory signaling, and are neuroprotective in a variety of CNS diseases [51, 52]. Dietary administration of the PPARγ agonist, pioglitazone (120 ppm), to young adult male rats starting 3 days prior to, 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]. Additionally, 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 the 1 year following fWBI may not be required [53]. A phase I/II trial of pioglitazone given to brain tumor patients before, during, and after fWBI is near completion (Chan, personal communication).

The PPARα 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]. Additionally, in a follow-up study using young adult male rats, dietary fenofibrate (0.2% w/w) administration starting one week prior to and continuously up to 30 weeks post 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 (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 (Greene-Schloesser personal communication).

Blockade of the Renin Angiotensin System (RAS) has proven to be one of the most effective approaches in the prevention/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 intra-organ 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 (20 mg/L drinking water), to young adult male rats 3 days prior to 40 Gy fWBI, during and for 28 or 54 weeks post-fWBI prevented the radiation-induced cognitive impairment observed 26 and 52 weeks postirradiation [60]. Giving L-158,809

before, during, and for only 5 weeks postirradiation similarly prevented the cognitive impairment observed 26 weeks postirradiation, indicating that continued RAS blockade may not be required [60]. Lee et al 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 ACEI or ARB appears effective at preventing radiation-induced cognitive impairment. Of note, RAS blockade did not prevent/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 (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 PPARα and PPARγ 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 appear to be ideal drugs for translational clinical studies.

SUMMARY

Preclinical studies have provided valuable insights into the pathogenesis of radiation-induced brain injury, including 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 suggest that the radiation-induced reduction in neurogenesis can be prevented. However, the use of stem cell-based therapies to prevent/ameliorate radiation-induced cognitive impairment will require considerable more research before they can be translated to the bedside. .

In contrast, preclinical studies using clinically prescribed PPARα and γ agonists and/or RAS blockers, have demonstrated that these drugs can prevent/ameliorate radiation-induced cognitive impairment independent of protection/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.

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, neuronal function, and elicits neuroinflammation. All of these pathways likely contribute to the development of radiation-induced cognitive impairment.

B. Potential therapeutic intervetions to prevent radiation-induced cognitive impairment. Preclinical models suggest that radiation-induced cognitive impairment can be prevented/ameliorated by targeting neurogenesis or inflammation. Neuronal stem cell transplants to the hippocampus can restore neurogenesis; improving cognitive function. PPAR agonists and RAS blockers prevent neuroinflammation and radiation-induced cogitive impairment independent of changes in neurogenesis.

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Figure 1: