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Radiation-induced brain injury: current concepts and therapeutic strategies targeting neuroinflammation

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Abstract

Continued improvements in cancer therapies have increased the number of long-term cancer survivors. Radiation therapy remains one of the primary treatment modalities with about 60% of newly diagnosed cancer patients receiving radiation during the course of their disease. While radiation therapy has dramatically improved patient survival in a number of cancer types, the late effects remain a significant factor affecting the quality of life particularly in pediatric patients. Radiation-induced brain injury can result in cognitive dysfunction, including hippocampal-related learning and memory dysfunction that can escalate to dementia. In this article, we review the current understanding of the mechanisms behind radiation-induced brain injury focusing on the role of neuroinflammation and reduced hippocampal neurogenesis. Approaches to prevent or ameliorate treatment-induced side effects are also discussed along with remaining challenges in the field.

Keywords

astrocytes | cognitive dysfunction | neurotoxicity | radiation-induced brain injury | senescence

Radiation therapy is widely used to effectively treat primary and metastatic brain tumors in adult and pediatric patients.[1,2] During standard approaches such as fractionated partial- and whole-brain radiation treatment (PBRT and WBRT, respectively), healthy brain tissue is inevitably exposed to radiation. As a result many patients experience side effects associated with damage to healthy brain tissue including hippocampal-related learning and memory dysfunction,[3] focal neurological deficits, increased intracranial pressure,[4] and rarely secondary epilepsy[5] and progressive dementia.[6] Cognitive domains affected include learning, processing speed, memory, executive function, and attention.[7] Despite the advent of modern radiotherapy techniques, radiation-induced brain injury remains an important complication where cognitive impairment can range from mild to severe and more rarely progressive and debilitating.[8–10]

The frequency of cognitive impairments following brain radiotherapy varies widely by study and is influenced by a number of factors including variability in time to assessment, definition of neurocognitive impairment, tumor type, patient age, baseline neurocognitive function, disease progression, radiotherapy modality (WBRT, PBRT, stereotactic), radiation dose, and the use of multimodal treatments including concurrent chemotherapy. Thus, determining the precise frequency of cognitive decline in the clinical setting remains challenging and it may be underestimated due to a number of factors including (1) a long-term follow-up is required to detect late posttreatment changes, (2) attrition bias favoring those with higher cognitive functioning and not counting those with lower cognitive functioning,[7] and (3) a paucity of clinical studies examining histological confirmed cases of radiation-induced injury.[11] Nevertheless, studies have sought to identify risk factors associated with more severe cognitive dysfunction after radiation and include advanced age,[12] smoking history,[7] WBRT rather than PBRT,[13,14] higher radiation dose,[15] and concurrent chemotherapy.[16,17]

Traditionally, radiation-induced brain injury is classified into acute, early-delayed, and late-delayed based on the time between the start of radiotherapy and the onset of side effects.[18–23] While acute and early-delayed injuries are generally transient

and occur days to months following treatment, late-delayed injury occurs at least 6 months after radiation is considered irreversible and progressive. Acute injury is characterized by edema, headaches, drowsiness and is rare with modern radiation therapy techniques and is generally improved by dexamethasone. The early-delayed reaction is characterized by transient demyelination, somnolence, attention deficits, and short-term memory loss. Late-delayed injury involves white matter necrosis, vascular abnormalities, and more permanent demyelination, gliosis, and lasting cognitive impairment.

Decades ago, oncologists recognized these secondary neurological dysfunctions and risk of therapy-induced cancers in their patients. Therefore, the National Cancer Institute established the Late Effects of Cancer Therapy Program so that patients could be followed up for decades following successful therapy of their primary cancer.[24] This initiative and historical patient cohort studies have led to improved therapies with fewer and less harmful delayed neurological and oncogenic effects.[25] Additionally, these studies led to the evaluation of remedial interventions to ameliorate these adverse effects.

The mechanism of radiation-induced injury that corresponds to the clinical findings are not completely understood; however, recognized neuropathological sequelae and several new hypotheses exist which are detailed in the sections that follow. Given the increasing population of long-term cancer survivors, it is critical to understand the causes of radiation-induced brain injury and to develop strategies to prevent them.

Mechanisms of Radiation-Induced Brain Injury

Over the past 20 years, research into the late effects of radiation revealed that it arises from dynamic interactions between multiple cell types and not simply delayed mitotic death of vascular and parenchymal cells of the target organ. It is now known that the cellular response to radiation injury in the brain involves multiple cell types including astrocytes, microglia, oligodendrocytes, endothelial cells, and neurons that initiate and respond to inflammatory cascades and contribute to progressive neurological damage.[18,26] Animal models have greatly aided research into the potential mechanism of radiation-induced brain injury and have shed light on the roles of neuroinflammation. In terms of factors leading to a neuroinflammatory cascade, multiple processes are thought to occur concomitantly including damage to the neurovascular unit leading to blood–brain barrier (BBB) damage, neural progenitor cell (NPC) death, inhibition of neurogenesis in the hippocampus, and direct activation of glia resulting in the senescence-associated secretory

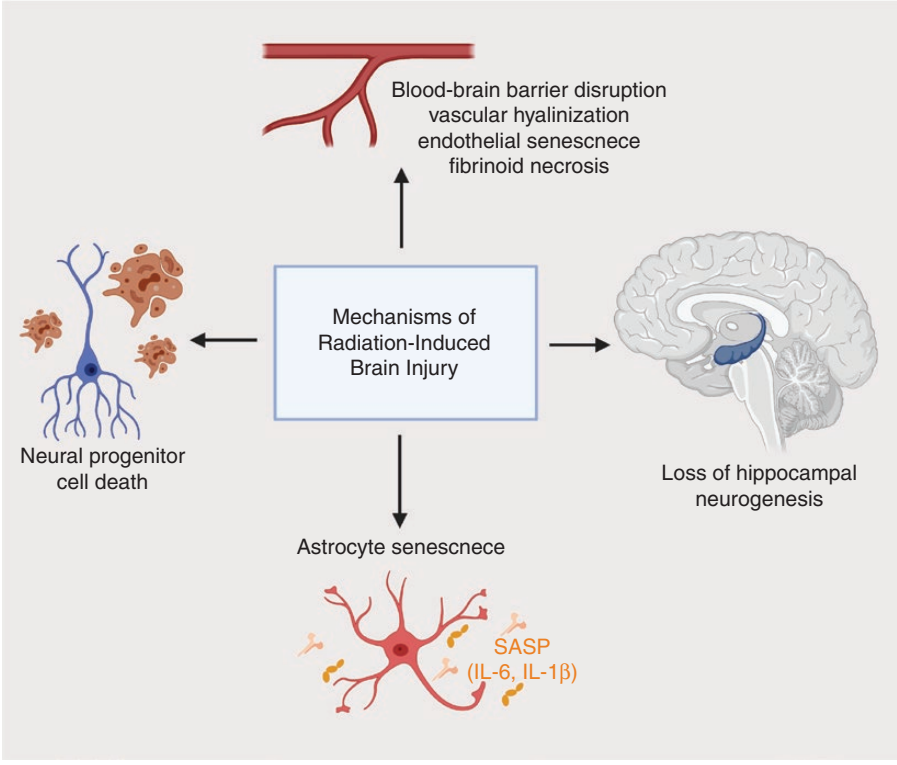

Figure 1. Mechanisms of radiation-induced brain injury. Vascular changes including blood-brain barrier disruption, vascular hyalinization, endothelial senescence, and fibrinoid necrosis. Other proposed mechanisms include loss of hippocampal neurogenesis, astrocyte senescence resulting in the release of senescence-associated secretory phenotype (SASP) cytokines, and neural progenitor cell death that result in cognitive decline following brain irradiation.

phenotype (SASP) (Figure 1). Evidence for each of these mechanisms is detailed in the sections below.

BBB Disruption

The BBB functions to restrict the passage of most soluble molecules found in the systemic circulation into the CNS. Therefore, disruption BBB results in a pathway for systemic immune and inflammatory cells to enter the brain and propel neuroinflammation. The BBB is composed of endothelial cells, pericytes, and astrocyte end-feet that form tight junctions and aid endothelial vesicular transport. In the acute setting, radiation results in the destabilization of the plasma membrane of vascular endothelial cells of the BBB[27] and changes in endothelial morphology are observed including basal lamina thickening, cytoplasmic vacuolization, and cell swelling.[28] Additionally, decreased endothelial cell density is apparent[29] as cells undergo apoptosis within the first 24 h following radiation.[30] Finally, studies have demonstrated a direct link between endothelial cell apoptosis and an increase in BBB permeability, which is significantly reduced in acid sphingomyelinase (ASMase) knockout mice, suggesting that endothelial cell apoptosis is mediated by the ASMase pathway.[27]

In terms of mechanisms of late endothelial damage, inadequate repair of damaged endothelial cells and BBB disruption contribute to tissue hypoxia and the upregulation of hypoxia-responsive genes. Gene expression changes that were persistent for weeks following radiation include induction of vascular endothelial growth factor (VEGF), which is thought to be triggered by hypoxia,[31] leading to a further increase in BBB permeability. Upregulation of tumor necrosis factor alpha, IL-1β, and NF-kB contributes to an inflammatory microenvironment and in turn upregulates intercellular adhesion molecule 1 (ICAM-1). Increased ICAM-1 is associated with BBB disruption in multiple injury and disease models.[32,33] While ICAM-1 is predominantly expressed by vascular endothelium following radiation, astrocytes also expressed the protein, and it is hypothesized that it mediates the release of proinflammatory cytokines in glia contributing to the toxic microenvironment of the irradiated CNS.[34]

Loss of Hippocampal Neurogenesis

The hippocampus is essential for learning and memory function. Adult neurogenesis occurs primarily in the dentate gyrus and subgranular zone (SGZ) of the hippocampus[35] and the subventricular zone (SVZ) of the lateral ventricles.[36] Radiation impairs neurogenesis in these areas and suppresses the differentiation of NPCs into mature neurons in animal models.[37–39] In one study, mice exhibiting reduced neurogenesis following 10 Gray (Gy) of intracranial radiation also had reduced cognitive performance on the maze test.[38] Further evidence supporting the role of NPC loss in cognitive dysfunction following radiation comes from studies showing that cognitive function can be partially rescued by neural stem cell transplantation to replace the lost hippocampal NPCs following the whole-brain irradiation in mice.[40]

Numerous studies seek to elucidate the mechanism by which radiation depletes NPCs in the hippocampus. One of the major hypotheses is that radiation induces inflammation and microvascular damage to the hippocampal SGZ and SVZ thereby altering the progenitor cell microenvironment in a manner that suppresses differentiation to the neuronal phenotype. Dysregulated signaling of hippocampal neurons, including downregulation of hippocampal glutamate receptor 1 and protein kinase C-gamma via Homer1a, is known to reduce long-term potentiation, working memory, and synaptic plasticity.[41] Furthermore changes to hippocampal neuron signaling may cause NPCs in this region to preference glial rather than neuronal differentiation.[42,43] Several clinical trials suggest that the findings from animal models are also applicable to humans. In an prospective observational study, Gondi et al.[44] enrolled adults with benign or low-grade brain tumors treated with fractionated stereotactic radiotherapy and correlated hippocampal dose-volume histogram data with cognitive impairment. The study concluded that bilateral hippocampal doses greater than 7.3 Gy are associated with long-term cognitive impairment and thus serves as a rationale for hippocampal avoidance strategies. In a phase II trial (RTOG 0933), Gondi et al.[3] enrolled patients with brain metastases treated with intensity-modulated radiotherapy (IMRT), which allowed avoidance of the hippocampus. Cognitive function was assessed using the Hopkins Verbal Learning Test before and at 2-month intervals following treatment up to 6 months. The patients receiving hippocampal avoidance radiotherapy were compared to historical controls of patients receiving whole-brain radiation without hippocampal avoidance. The historical control demonstrated a 30% mean relative decline in cognitive function from baseline in 4 months, while hippocampal avoidance resulted in a 7% mean relative decline in cognitive function. These results demonstrate that cognitive function is preserved with hippocampal avoidance.

Radiation-Induced Senescence and the SASP

Following radiation exposure cells adopt one of many cellular responses including DNA damage, which occurs either as a direct response to radiation or a secondary effect of free radicals and reactive oxygen species (ROS). If DNA double-strand breaks are not repaired cells undergo one of several fates: apoptosis, cellular senescence, mutation, or genomic instability. Multiple pathways are responsible for inducing cellular senescence in irradiated cells.[45] Although senescent cells do not replicate, they may avoid clearance and persist in tissues while continuing to produce inflammatory factors that contribute to tissue injury.[46] Therefore, radiation-induced cellular senescence is an important mediator of tissue dysfunction promoting chronic inflammation and contributing to radiation-induced side effects have been observed in multiple organs including the brain, lung, and heart.[47,48]

In the CNS, it has long been known that glia play many supportive roles for neurons, endothelial cells, and the neurovascular unit. Astrocytes protect against oxidative injury[49] and maintain the function of the BBB.[50] In response to various exogenous injuries astrocytes release a host of

proinflammatory cytokines. In animal models, endothelial cell senescence has also been observed in response to brain radiation and is thought to be a consequence of proinflammatory cytokine release from activated astrocytes,[51,52] which in turn release further proinflammatory molecules, upregulate adhesion molecules, and increase ROS production.[48,53] Recently, the role of IL-6 as a key proinflammatory cytokine in the SASP[54] was demonstrated in response to radiation in astrocytes.[55] Induction of senescence in response to radiation has previously been demonstrated in a variety of other cell types including fibroblasts,[56] endothelial cells,[57] and chondrocytes.[58] Clinically, pulmonary[59] and myocardial fibrosis[60] are considered a response to radiation therapy involving cellular senescence.

Recently our group has demonstrated that p53 isoforms, Δ133p53α and p53β, regulate cellular senescence in a variety of cell types including human fibroblasts,[61] CD8+ T cells,[62] and astrocytes.[55,63] Decreased Δ133p53α and increased p53β expression exists in senescent cells undergoing replicative as well as radiation-induced senescence. Furthermore, overexpression of Δ133p53α extends the replicative lifespan of cells by dominant negative inhibition of senescence inducing p53 target genes including: p21, miR-34a, PAI-1, and IGFBP7 as demonstrated in human fibroblasts.[61] Restored expression of Δ133p53α also rescues astrocytes from senescence in the setting of replicative and radiation-induced senescence.[55,63] Furthermore, senescent astrocytes are characterized by their expression of the SASP proinflammatory cytokines including IL-6 and IL-1β. Restored expression of Δ133p53α in near-senescent astrocytes reduces expression of these cytokines and increases expression of neuroprotective factors, Nerve growth factor (NGF) and Insulin-like growth factor 1 (IGF-1). When senescent astrocytes are co-cultured with neurons, neuronal apoptosis is observed. However, upon overexpression of Δ133p53α in the astrocyte population following radiation or replicative senescence, there is a reduction in neuronal apoptosis indicating that overexpression of Δ133p53α is neuroprotective. Thus, p53 isoforms, Δ133p53α and p53β, are important regulators of cellular senescence that can be manipulated for potential therapeutic effect (Figure 2).

Histopathological Changes in the CNS After Radiation

The histopathological changes in the brain after radiation therapy are variable from person to person and dependent on multiple factors including brain location treated, age, diagnosis, and dose/technique of the therapy. These have been described as acute, early delayed, and late delayed.[64,65] Treatment-induced necrosis of the neoplasm is desirable, while necrosis of surrounding tissues is an ongoing and serious clinical challenge.[66] Recognition of radiation-induced tissue necrosis is a diagnostic challenge for the radiologist, as there is a lack of optimal advanced MRI modality or imaging biomarkers. In addition, other non-radiation therapies such as glucocorticoids,

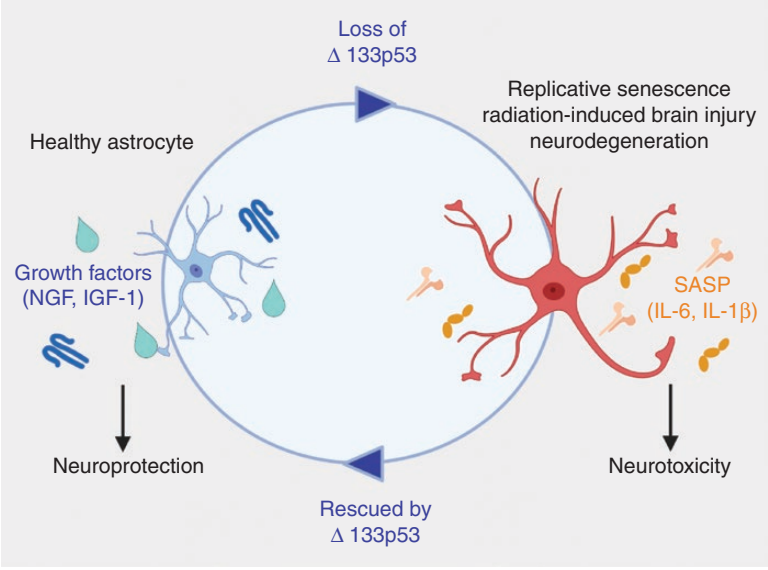

Figure 2. Schematic of Δ133p53α regulation of astrocyte-mediated neuroprotection and neurotoxicity. The transition from healthy to senescent astrocytes is evidenced in the setting of replicative senescence, radiation-induced brain injury, and neurodegenerative disease accompanied by the loss of Δ133p53α. In the senescent state, astrocytes release SASP cytokines and result in neurotoxicity. Senescent astrocytes can be rescued to a healthy astrocyte phenotype by overexpression of Δ133p53α which results in neuroprotection.

antiangiogenics, or immune/targeted therapies can make radiographic interpretations difficult.

If a decision is made to re-biopsy or resect an area suspicious for recurrence of tumor in the radiation field the pathologist is then tasked with interpretation of the tissue for tumor and/or treatment-related changes. No established histopathological classification system has been established for this, and the experience and training of the pathologist are key to obtaining an accurate diagnosis. In some cases, only necrotic tissue is present for the pathologist to evaluate. When viable, non-neoplastic tissue is present the following changes can be (at least in part) attributed to radiation therapy: astrogliosis, vascular changes, tissue rarefaction, chronic inflammation, and glial/neuronal cytomorphologic atypia.[67,68] The vascular changes seem to predominate and can range from thrombosis, hemorrhage, hyalinization, to fibrinoid necrosis which can further exacerbate the hypoxic/ischemic necrosis in the area. Distinguishing residual and recurrent glial tumor cells within these areas can also be very difficult. Immunohistochemical studies for mIDH1, GFAP, KI67, and p53 may help to highlight actively proliferating tumor cells in some cases, as proliferating cells are not as prominent from radiation change. Judging whether necrosis is related to disease progression or from radiation therapy can be crucial to subsequent treatment decisions and prognosis.

Approaches to Targeting the Neuroinflammatory Microenvironment

Enhancing neuronal survival, promoting hippocampal neurogenesis, and dampening the neurotoxic microenvironment are all strategies that have been proposed to ameliorate cognitive dysfunction in patients receiving brain irradiation. Drugs that are routinely used in other neurological conditions have recently been repurposed to treat or prevent radiation-induced brain injury and several clinical trials are ongoing. Studies elucidating the role of the neurotoxic microenvironment have led to a series of approaches to dampen inflammation and reverse NPC loss.

Lithium

As a pretreatment option, lithium increases NPC proliferation and rescues radiation-induced cell cycle arrest in animal models.[69] Both in vivo and in vitro studies have shown that lithium induces neurogenesis, which is otherwise decreased following radiation.[70,71] In lithium-treated animals, hippocampal neurons were protected from radiation-induced apoptosis and performed better on learning and memory tests.[71] One mechanism by which lithium reduces neuronal apoptosis may be due to a reduction in ROS via the glutathione pathway.[72]

Memantine

Glutamate *N*-methyl-D-aspartate (NMDA) receptors are involved in learning and memory and NMDA receptor agonist, memantine, is used to treat moderate to severe vascular dementia and Alzheimer's disease. As the same cognitive domains are also involved in radiation-induced brain injury, memantine has been investigated in several phase III trials. In one study (RTOG 0614),[73] patients receiving memantine had delayed time to cognitive decline and reduced the rate of memory decline, executive function, and processing speed compared to the control group. The follow-up study, NRG CC001,[73] a phase II/III trial that evaluated the combined neuroprotective effects of hippocampal avoidance (discussed in the section to follow) in addition to memantine during WBRT for brain metastases. Patients receiving WBRT for brain metastases were randomized to receive placebo or memantine within 3 days of initiating radiotherapy for 24 weeks and then cognitive function tests were performed. Patient receiving memantine had a significant delay in cognitive decline (hazard ratio 0.78, 95% confidence interval 0.62–0.99, $P = .01$), superior executive function at 8 and 16 weeks ($P = .0137$), and superior processing speed ($P = .0149$) at 24 weeks. While there was an improvement in recall in the memantine arm, it was not statistically significant ($P = .059$). This study is limited by a small number of patients ($n = 149$) who were analyzable by 24 weeks due to significant patient loss, which amounted to only a 35% statistical power.

Antioxidants

During radiation, the production of ROS leads to DNA, protein, and lipid membrane damage. Neurons are particularly susceptible to ROS due to their enhanced unsaturated fatty acid contents and higher levels of lipid peroxidation in response to radiation. Several preclinical studies have demonstrated some effect of antioxidant drugs or agents in reducing radiation-induced brain injury. For instance, the flavonoid quercetin has been shown to have neuroprotective properties and was investigated in an animal model exposed to 20 Gy of whole-brain irradiation and found to protect against some histopathological features of brain injury and neuroinflammation.[74] Specifically, astrocyte hypertrophy decreased along with vascular dilatation and endothelial damage. Proinflammatory cytokine release and neuronal survival were not evaluated.

Renin–Angiotensin System Blockage

Preclinical studies demonstrate that renin–angiotensin system (RAS) blockage may ameliorate late-delayed radiation induced organ injury, including kidney, lung, and brain.[75] Animal studies have shown that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers effectively reduce inflammatory pathway cascades including NF-kB and AP-1 in the brain. Furthermore, these RAS blockers prevent cognitive impairment in rodent models if they are administered before, during, or after fractionated whole-brain irradiation.[76] The angiotensin-converting enzyme inhibitor, ramipril, was administered to rats 2 weeks after 30 Gy radiation exposure and was associated with decreased optic neuropathy 6 months following irradiation.[76] It is hypothesized that RAS blockers

may attenuate radiation-induced brain injury by decreasing Ang II activity and also increasing the generation of anti-inflammatory peptide, Ang-(1–7). In one study primary rat astrocytes pretreated with Ang-(1–7) had decreased expression of cytokines IL-6 and IL-1β.[77] It is uncertain whether the acute changes in cytokine release in vitro will translate to late-delayed cognitive changes in vivo. A phase II trial (NCT03475186) is currently underway for ramipril in patients with brain tumors. Another drug affecting the RAS pathway under investigation for radiation-induced brain injury is angiotensin type 1 receptor antagonist. In murine models, administration of the drug before, during, and after fractionated whole-brain irradiation prevented or reduced cognitive impairment at 26 and 52 weeks after irradiation.[78]

Small Molecule Compounds Targeting p53 Isoform, Δ133p53α

As the SASP adopted by healthy neighboring cells plays an important role in chronic inflammation and cellular damage in a number of target organs, one approach is to target cells which release IL-6 and other damaging proinflammatory factors. Recently, we have shown that SASP can be diminished through the overexpression of p53 isoform, Δ133p53α.[55] Small molecule compounds that increase expression of Δ133p53α could therefore be used to prevent or ameliorate tissue damage due to radiation.

Exercise

It has long been known that hippocampal neurogenesis and memory are enhanced by exercise. Several studies have examined whether exercise ameliorates cognitive decline following brain radiation in animal models. Results of these studies produced conflicting findings with some showing that exercise improved[79,80] or had no effect[81] on behavioral deficits following radiation. Few studies investigate the mechanism by which exercise may modulate cognition post-irradiation. Wong-Goodrich et al.[82] investigated whether voluntary wheel running improved spatial learning and memory and whether this might be due to increased hippocampal neurogenesis in mice exposed to exercise after WBRT.[83] The WBRT group had significantly decreased spatial learning ability and this was rescued by wheel running up to 4 months following radiation exposure. These mice also had restored hippocampal neurogenesis and increased brain-derived neurotrophic factor (BDNF), IGF-1, and VEGF. To determine the mechanism, another study demonstrates that DNA 5-hydroxymethylation modification (5 hmC) and ten-eleven translocation (Tet) proteins decrease in the hippocampus post-radiation and that forced running increased levels of these factors along BDNF while increasing neurogenesis and improving cognitive dysfunction.[84] Tet inhibitor, SC1, was found to partially reverse such changes demonstrating that these effects may be Tet-dependent. The authors propose that Tet-mediated 5 hmC modification could represent a diagnostic biomarker of radiation-induced brain injury, although this has yet to be investigated in human studies.

Human studies examining the effects of exercise on radiation-induced brain injury are limited. Gehring et al. examined a cognitive rehabilitation program in patients with glioma among these patients 61% had received prior radiation therapy and 39% had not.[85] However, the study stratified in minimization for the effect of irradiation, so it is uncertain what effect exercise had on radiation-induced cognitive changes. Nevertheless, the authors concluded that there was a moderate improvement in attention and verbal memory in the 6-month follow-up after the exercise program, so those with previous radiotherapy did benefit. A subgroup analysis comparing whether patients receiving radiation differed from those that did not in terms of improvement in cognitive function would be required to determine the magnitude of the effect of exercise on radiation-induced injury.

Peroxisomal Proliferator-Activated Receptor Agonists

Peroxisomal proliferator-activated receptors (PPARs) are a nuclear hormone receptor family that can activate neuroprotective and anti-inflammatory pathways in the CNS.[86,87] PPAR agonists inhibit proinflammatory cytokine release in both microglia and astrocytes[88] and enhance neuroprotection in animal models of neurodegenerative diseases and stroke.[89] In animal models, the use of PPAR agonists has decreased late cognitive effects of radiation. Two such agents that have been used in animal models are pioglitazone, a PPARγ agonist, and fenofibrate, a PPARα agonist. PPARγ was administered 3 days before, during, and for 4 weeks after 40 Gy fractionated whole-brain irradiation and prevented the radiation-induced decline in cognitive function.[90] Additionally, in a study administering fenofibrate to mice receiving 10 Gy of whole-brain irradiation, animals receiving the drug had an increased number of hippocampal neurons and less microglial activation.[91] Administration of PPARγ agonist during whole-brain irradiation raises the issue of whether the approach enhances tumor cell survival against radiation. However, multiple studies demonstrated that in fact antiproliferative signaling pathways and tumor cell cytotoxicity are preserved in both in vitro studies using a variety of cancer cell lines as well as animal models and clinical trials.[92] In a phase I trial (NCT01151670) the repurposed antidiabetic drug, pioglitazone, was found to be well tolerated by brain tumor patients undergoing radiotherapy and established a safe dose to be applied to future efficacy trials.[93]

Hippocampal Avoidance Strategies

The hippocampus plays an essential role in memory formation. NPCs of the dentate gyrus of the hippocampus are highly susceptible to radiation injury. Decreased hippocampal neurogenesis is thought to contribute to a decline in memory function following brain radiotherapy.[42] In animal studies, the extent of radiation-induced damage to NPCs predicts the duration of neurogenic and cognitive dysfunction suggesting that this group of cells plays a key role.[37,94] Hence strategies to avoid damage to the hippocampus have emerged as a strategy to reduce

radiation-induced brain injury. Current strategies to avoid hippocampal radiation are detailed below.

Stereotactic Conformal Radiotherapy

High-precision conformal techniques have been proposed for brain tumor radiotherapy due to superior dosimetric delivery, long-term tumor control, and the potential for reduced radiation-induced cognitive dysfunction. In a prospective randomized trial comparing stereotactic conformal radiotherapy (SCRT) to conventional radiotherapy, SCRT demonstrated improved functional outcomes in several neurocognitive domains evaluated longitudinally over 5 years.[95] Mean full-scale or global intelligence quotient (IQ) and performance IQ scores were significantly higher in the group that received SCRT. Mean full-scale IQ scores of patients in the SCRT group were either stable or improved over 5 years while those receiving conventional radiotherapy initially improved but then gradually declined. Neurocognitive domains of performance quotient and memory were particularly enhanced in the SCRT group over the conventional group. Thus, SCRT may represent a superior modality to preserve cognitive functioning in patients vulnerable to radiation-induced brain injury.

Intensity-Modulated Radiotherapy

A phase II trial (NRG/RTOG 0933) demonstrated enhanced memory preservation following WBRT with hippocampal avoidance using IMRT.[3] This study is discussed in detail in the prior section on hippocampal neurogenesis. A phase III trial (NRG-CC001) enrolling 518 patients with brain metastases compared WBRT (30 Gy in 10 fractions) and memantine with or without hippocampal avoidance. In terms of radiation dose, a per protocol dose to 100% of the hippocampus did not exceed 9 Gy and maximal hippocampal dose did not exceed 16 Gy. The primary endpoint was time to neurocognitive function failure as defined by a decrease in one of the neurocognitive tests (Hopkins Verbal Learning Test—Revised, Controlled Oral Word Association, or Trial Making Test). The primary outcome measure was time to neurocognitive function decline, which was significantly longer with hippocampal avoidance while achieving similar intracranial tumor control and survival.

Proton Beam Therapy

Previous studies have shown that increased radiation dose to the temporal lobes is associated with worse neurocognitive outcome and this is particularly severe in adult survivors of childhood brain tumors.[13,96] In a recent study,[97] 3 different treatment modalities were compared to determine if one might have a superior radiation dose sparing to normal tissues. The three modalities compared were: (1) double scattering proton therapy (DSPT), (2) proton beam therapy (PBT) via pencil beam scanning using a temporal lobe sparing field configuration, and (3) volumetric modulated arch therapy (VMAT), which is conventional photon radiotherapy with a temporal lobe sparing field configuration. These modalities were compared in 10 children with craniopharyngioma. The aim was to reduce the dose to the temporal lobe and hippocampus, while delivering the same dose to the tumors consistent with the DSPT plans. PBT consistently had the lowest volume fractions of temporal lobes across all investigated dose levels, leading to better estimated memory outcomes.

Another recent study[98] followed up 62 brain tumor patients treated with PBT and assessed neurocognition and quality of life at baseline and every 3 months following therapy. They found that the neurocognitive parameters tested remained largely stable during recurrence-free follow-up for an average of 22.5 months. Larger clinical studies are underway, including NCT02824731 and NCT03180502, and will be important for validating these findings and also allowing direct comparison to patients treated with photon radiotherapy.

Future Directions

Cognitive dysfunction following radiotherapy is a challenging and multifaceted adverse effect that limits treatment options for many patients while impairing quality of life for those who receive this treatment. An increased understanding of the mechanisms behind radiation-induced brain injury, including disruption of the BBB, decreased hippocampal neurogenesis, and increased neurotoxic SASP, has enhanced our ability to target the neuroinflammatory microenvironment. While currently no standard of care has been established, several preclinical studies demonstrate promising pharmacological approaches to ameliorate brain injury and several key clinical trials are currently underway. Advancing our understanding of radiation-induced brain injury remains challenging for several reasons, including the mechanistic uncertainty behind the molecular and cellular changes that occur after radiation to the brain. Furthermore, it is difficult to evaluate and quantify the severity of cognitive dysfunction in affected patients. In terms of the use of brain imaging, the severity of cognitive dysfunction is inconsistently correlated to brain imaging studies[99,100] and currently no biomarkers exist that predict poor outcome following therapy.

Beyond the adverse effects of radiation, other main cancer treatment modalities, including chemotherapy and immunotherapies, have also demonstrated therapy-related cognitive decline that is thought to be related to similar neuroinflammatory effects. For instance, cytokine release syndrome has been reported following CAR T-cell therapy and associated with release of SASP proinflammatory cytokines.[101] As combination therapy (including surgery, chemo and/or immunotherapy, and radiation therapy) is the standard of practice for treating CNS neoplasms, a better understanding of the pathophysiologic mechanisms surrounding cellular/tissue injury and long-term sequelae is essential. Hence, further research into prevention or amelioration of the neurotoxic microenvironment in the setting of radiation could present a promising approach applicable to a range of anticancer treatments. Translation of the preclinical findings to patient treatments presents the opportunity to significantly improve quality of life and dose limitation barriers for patients with brain tumors receiving radiation.

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