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Review Article

Advances in the study of the molecular biological mechanisms of radiation-induced brain injury

Chen Gan[1,2*], Wen Li[1,2*], Jian Xu[1,2], Lulian Pang[1,2], Lingxue Tang[1,2], Sheng Yu[1,2], Anlong Li[1,2], Han Ge[1,2], Runze Huang[1,2], Huaidong Cheng[1,2,3]

[1]Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China; [2]Department of Oncology, Anhui Medical University, Hefei, Anhui, China; [3]Department of Oncology, Shenzhen Hospital of Southern Medical University, Shenzhen, Guangdong, China. [*]Equal contributors.

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Abstract: Radiation therapy is one of the most commonly used treatments for head and neck cancers, but it often leads to radiation-induced brain injury. Patients with radiation-induced brain injury have a poorer quality of life, and no effective treatments are available. The pathogenesis of this condition is unknown. This review summarizes the molecular biological mechanism of radiation-induced brain injury and provides research directions for future studies. The molecular mechanisms of radiation-induced brain injury are diverse and complex. Radiation-induced chronic neuroinflammation, destruction of the blood-brain barrier, oxidative stress, neuronal damage, and physiopathological responses caused by specific exosome secretion lead to radiation-induced brain injury.

Keywords: Brain injury, ionizing radiation, exosomes, neuroinflammation, blood-brain barrier

Introduction

Hundreds of thousands of patients worldwide receive radiotherapy each year for primary brain tumors and brain metastases originating from an extracranial tumor [1]. However, when the dose of radiotherapy exceeds the tolerance threshold of the central nervous system (CNS), it will damage the surrounding normal brain tissue and lead to radiation-induced brain injury (RIBI), which is mainly characterized by brain tissue edema and necrosis, demyelination, cognitive and memory impairment, and other dysfunctions. RIBI is divided into acute, early delayed (subacute), and late responses based on symptom onset time. Although acute and early delayed injuries can lead to serious clinical conditions, they are generally considered mostly reversible. However, late, delayed damage occurring 6 months to several years after brain radiotherapy is considered irreversible and progressive and is characterized by demyelination, vascular abnormalities, and eventual white matter necrosis. Fifty to ninety percent of these cancer survivors exhibit cognitive impairment after radiotherapy, which is often progressive and disabling [2]. Continued improvements in treatment have improved survival in patients with head and neck tumors and have increased the population of patients with delayed injury. The cognitive areas affected include learning, memory, processing speed, attention, and executive function [3]. Many studies have confirmed the existence of radiation-induced cognitive impairment (RICI) [4, 5]. Chang et al. found that the clinical symptoms of RICI ranged from mild cognitive impairment to severe dementia [6, 7]. The study of RICI is important because it can prevent and reduce the degree and incidence of cognitive impairment in patients with brain radiation. Several studies have shown that cognitive impairment reduces the quality of life of long-term survivors [8, 9]. In turn, cognitive impairment can lead to physical frailty through psychological distress [10], so improving patients' cognitive impairment is also important for promoting physical rehabilitation.

In previous studies, the main set of subjects presented with impairment and cognitive decline that occurred from 6 months to 1 year or more after irradiation [11]. These long-term sequelae are usually progressive and irrevers-

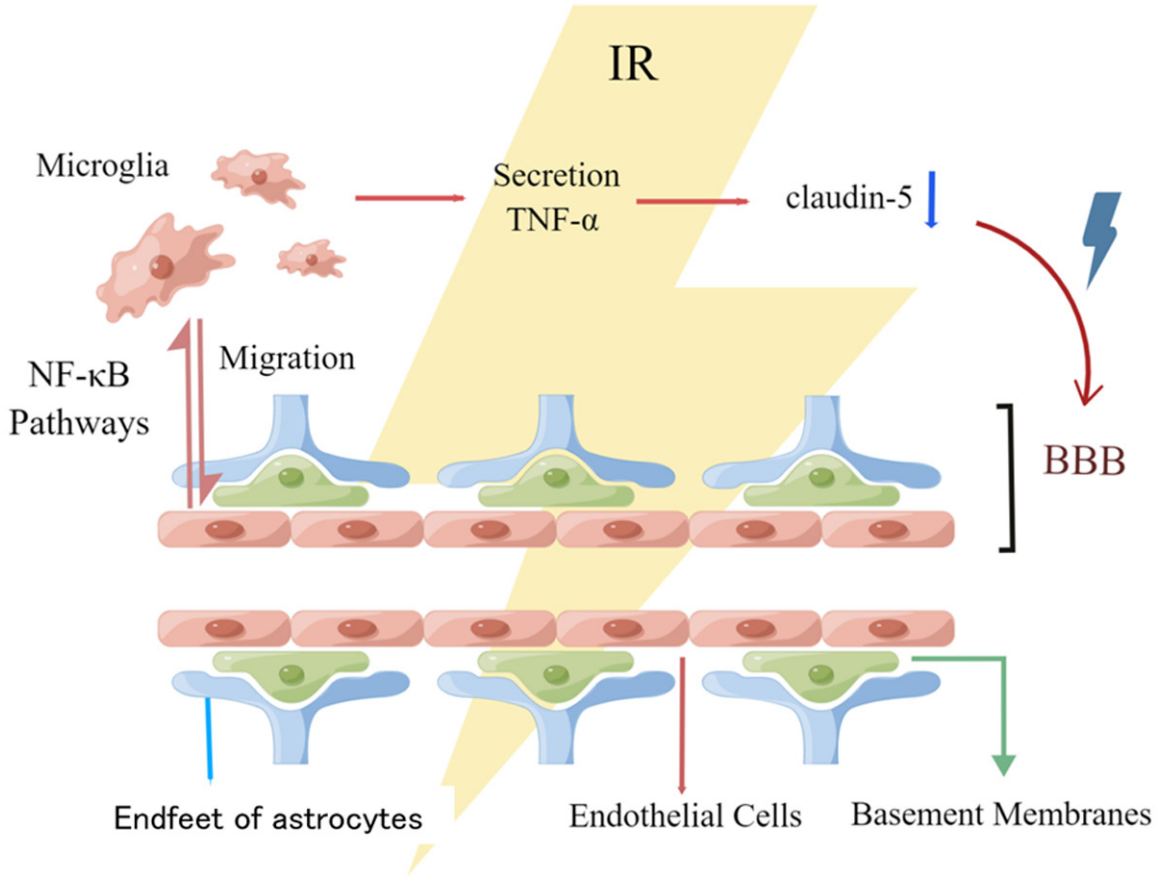

Figure 1. Composition of the BBB and the effect of IR on the BBB. The BBB consists of the basement membrane of ECs and the endfeet of astrocytes. Under IR, ECs activate microglia via the NF-κB pathway, which attracts microglia to migrate toward adjacent vessels. Microglial activation secretes TNF-α to downregulate claudin-5 expression, leading to early destruction of the BBB.

ible and include a wide range of clinical symptoms, such as neuropathy, encephalopathy, seizures, syncope, memory impairment, and ataxia, which seriously damage patients' quality of life [12, 13]. Up to 2-5% of radiotherapy patients can progress from cognitive impairment to dementia [14]. With the shift of the medical model to the biopsychosocial model, clinical treatment has begun to focus on how to meet patients' physical and psychological needs and improve their quality of life [15]. The exact mechanism of RICI is still unclear, and this paper summarizes the latest literature on RICI to provide ideas for related studies.

BBB disruption

Radiation-induced damage to the BBB is a dynamically changing process, and this disruption further exacerbates neuroinflammation in the brain. Damage to the BBB may be associated with radiation-induced release of various substances, such as high-mobility group box protein 1 (HMGB1) and TNF-α, as well as activation of the MAPK signaling pathway.

The BBB consists of endothelial cells (ECs), basement membranes, and the endfeet of astrocytes (shown in **Figure 1**). Due to its highly selective permeability, the BBB selects and controls the entry of most molecules from circulating blood into the CNS [16]. After radiation damage to the BBB, various inflammatory responses occur, such as infiltration into brain tissue by peripheral immune cells, reactive oxygen species (ROS) accumulation, and subsequent microglial activation [17]. Ionizing radiation (IR) damages ECs [18], alters EC permeability and is secondary to endothelial barrier damage [19], further exacerbating the inflammatory response.

The change in BBB permeability due to radiation is a dynamic process. Acute increases in BBB permeability were detected by BBB permeability tracers when the cranium received a single 20-60 dose of whole brain radiation therapy (WBRT) but recovered within a few weeks [20, 21]. A similar study found that BBB permeability peaked at 1-1.5 months [22], after which it recovered with time.

As shown in **Figure 1**, irradiated ECs can secrete cellular signals via the nuclear factor κB (NF-κB) pathway that activates microglia and induces microglia to migrate to adjacent vessels [23]. Microglia are activated by secreted tumor necrosis factor-α (TNF-α), which downregulates claudin-5 expression and leads to radiation-induced early BBB destruction [20]. In contrast, treatment with anti-TNF-α improves BBB permeability in X-ray-irradiated mice [24].

HMGB1 is a member of the highly conserved nonhistone DNA binding protein family and a master switch for neuroinflammation [25]. HMGB1 can disrupt junctions and increase endothelial permeability [26]. HMGB1 can enter the extracellular environment through two pathways: active secretion by activated macrophages and monocytes and passive release by necrotic or damaged cells [27]. Toll-like receptor 4 (TLR4) located on the microglial membrane binds to HMGB1 to promote microglial activation [28, 29]. EC membrane-expressed advanced glycation end product receptor (RAGE) binds to HMGB1 via the ROS pathway and ultimately activates NF-κB [30]. Activation of RAGE activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to increased endothelial permeability [31], which is the pathological basis for disrupting the integrity of EC barrier function [32]. Moreover, radiation was shown to promote the release of HMGB1 and activation of the MAPK signaling pathway through RAGE [33]. Activation of the MAPK signaling pathway increases the expression of NF-κB, matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) and inhibits the expression of the proteins ZO-1 and Claudin 5, which ultimately leads to damage to the endothelial barrier. Inhibition of HMGB1-RAGE signaling is a promising method for regulating inflammation and tumorigenesis [34, 35]. Animal experiments also confirmed that pregabalin inhibited microglial activation and inflammatory responses in a mouse model of RIBI and reduced neuronal apoptosis and loss in mice [36]. This study suggests that pregabalin attenuates NF-κB-mediated microglial inflammatory responses by inhibiting the intracellular to extracellular translocation of neuronal HMGB1. Mouse experiments also demonstrated that using the HMGB1 inhibitor glycyrrhizin reversed X-ray-induced depression-like behavior and neuronal damage [28]. Significant improvements in cognitive function were observed after the administration of AM251, a cannabinoid receptor inverse agonist, to mice with cognitive dysfunction (emotional and memory deficits) after brain radiotherapy and improved cell proliferation and survival in the hippocampus of irradiated mice [37]. This study found that AM251 inhibited HMGB1 expression in the hippocampus of irradiated mice and that inhibiting HMGB1 expression correlated with improved cognitive function in mice.

Inflammatory response

Multiple neuronal cell types and lineages exist in the brain, including astrocytes and neurons from neural stem progenitor cells (NSPCs) and intermediate and mature oligodendrocytes from proliferating oligodendrocyte precursor cells (OPCs). NSPCs and OPCs are highly proliferative, whereas neurons, astrocytes, and mature oligodendrocytes exist in a postmitotic state. Most cell proliferation occurs in the IR-sensitive ventricular-subventricular zone [38]. IR can trigger an immune response within the CNS, leading to chronic neuroinflammation [39], but changes in cognitive function may not occur until long after the injury. Neuroinflammation in the brain is mainly caused by the combined action of astrocytes, microglia, and peripheral immune cells after crossing the BBB. The role of microglia and astrocytes in neuroinflammation is shown in **Figure 2**.

Microglia

Microglia, the immune cells of the CNS, also play an important role in radiation-induced RIBI. Activated microglia can be transformed into both M1 and M2 forms and produce different inflammatory mediators, thereby mediating different physiological effects.

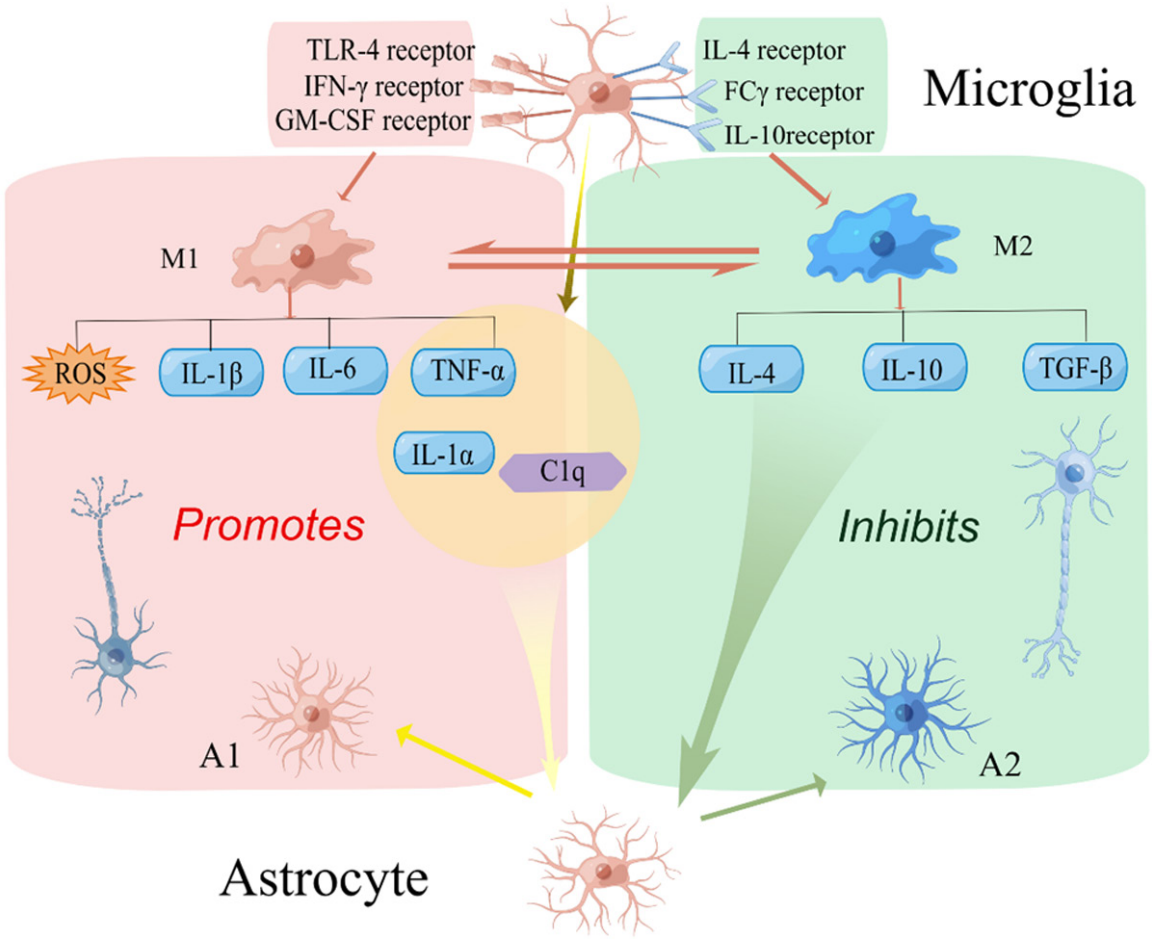

Figure 2. Role of microglia and astrocytes in neuroinflammation. 1. Microglia are activated by TLR-4, INF-γ, and GM-CSF and take on an M1 state with proinflammatory effects, producing corresponding inflammatory factors and ROS that damage neurons. 2. Microglia are activated by IL-4, IL-10, and FCγ and take on an M2 state with anti-inflammatory effects, producing corresponding inflammatory factors that protect neurons. 3. Microglia in the M1 and M2 states are interconvertible. 4. IL-1α, TNF-α and C1q secreted by microglia induce astrocyte activation in the proinflammatory A1 state, while IL-4 and IL-10 induce astrocyte activation in the anti-inflammatory A2 state.

Microglia are the intrinsic immune cells of the CNS and have an important role in immune surveillance and maintenance of brain homeostasis under physiological conditions. These cells are highly active in their presumed resting state and monitor the surrounding microenvironment through constant movement in all directions [40]. When microglia are activated, they shift from patrolling to protecting the injured site. Although activated microglia are critical for maintaining homeostasis of the brain microenvironment, continued activation in the late stages of RIBI can lead to chronic neuroinflammation and cognitive impairment [41, 42]. When the brain is exposed to IR, soluble factors that are initially present on the surface of neurons and inhibit microglial activation are disrupted [43]. As microglia activate, they move toward the site of injury and engulf apoptotic neurons and cellular debris, producing high levels of proinflammatory mediators [44]. In vivo evidence suggests that activated microglia localize near newly formed cells during brain inflammation and that neurogenic damage depends on the degree of microglial activation independent of the presence or absence of surrounding tissue damage. That is, there is a significant negative correlation between the number of microglia in the neurogenic area and the number of surviving new hippocampal neurons [45]. Other studies have demonstrated that selective inhibition of microglia-mediated neuroinflammation improves RICI [46].

The effect of microglial activation showed differences depending on age, and animal experi-

ments demonstrated that adult mouse brains exhibited sustained microglial activation after irradiation, while juvenile mice (3 weeks old) initially showed microglial activation after irradiation but recovered significantly after a week [47, 48]. A higher risk of radiation-induced chronic neurotoxicity has likewise been observed clinically in elderly patients [49]. The duration of irradiation is also another factor that affects microglial activation. After a single whole brain irradiation of 10 Gy for one week, only some microglia were activated. However, microglia responded consistently over two months of irradiation, exhibiting an activated state of cellular hypertrophy and the ability to engulf dead cells and damaged neurons [49].

Activated microglia can be divided into an M1 state [50], which promotes inflammation, and an M2 state, which inhibits inflammation; they produce different inflammatory mediators that determine whether they are neuroprotective or neurotoxic [51-53]. The production and conversion of microglia to the M1 phenotype and the production and secretion of the corresponding proinflammatory mediators require signaling through TLR-4 [54], the interferon-γ (IFN-γ) receptor complex [55], and the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor [56]. Microglia after high-dose radiation exposure exhibit an M1 state; they have an amoebic morphology with enhanced phagocytosis and release various proinflammatory mediators, such as interleukin 1β (IL-1β), IL-6, ROS, and TNF-α [41, 57]. Their release of the inflammatory factors TNF-α [58], IL-1β [59], and IL-6 [53] inhibits neural precursor production, neuronal differentiation, and survival specificity. Studies in rodents have shown that after a single high dose of irradiation, high levels of activated microglia and TNF-α are observed for at least 6 months [60]. This continuous activation of microglia releases proinflammatory factors that maintain the inflammatory state of the brain microenvironment, which in turn causes neuronal and progenitor cell death, resulting in a vicious cycle characterized by microglial activation, inflammatory factor release, and neuronal death [46]. In vitro assays have also confirmed that blocking neurotoxicity via IL-6 and TNF-α release restores neuroblastogenesis in vitro [53]. Previous studies have demonstrated that minocycline inhibits M1 microglial activation, ameliorating neuroinflammation and preventing further neuronal cell loss [61, 62]. However, minocycline has not been used successfully in patients. A recent randomized controlled trial found that 24 months of treatment with minocycline in a symptomatic Alzheimer's disease group did not delay the progression of cognitive impairment [63]. The transition of microglia from a resting state to a protective M2 phenotype is mediated by signaling through IL-4 receptors, FCγ receptors, or IL-10 receptors [64]. M2 microglia phagocytose dead cells and produce neurotrophic factors and inflammatory factors that promote hippocampal neurogenesis, such as IL-4, IL-10, and transforming growth factor-β (TGF-β) [65]. A recent study found that the supernatant of M2 microglia (containing 15-deoxy-Δ12,14-prostaglandin J2) promotes neurogenesis [66].

Microglia are highly dynamic cells capable of switching between M1 and M2 states. The transition of microglia from the M1 to the M2 state is thought to improve the brain's performance in restoring homeostasis after exposure to pathological stress [64]. One factor that may be critical for the microglial cell transition between activation states is suppressor of cytokine signaling 3 (SOCS3). Studies on LysMCre-SOCS3fl/fl mice have shown that when SOCS3 expression is lacking in myeloid cells, the polarization of microglia toward a proinflammatory state is enhanced, as shown by increased production and secretion of TNF-α, IL-1β, IL-6, CC-chemokine ligand 3 (CCL3), CCL4, and C-X-C motif chemokine ligand 11 (CXCL11) [67].

As previously described, microglia are activated and transformed into the M1 form by a combination of CSF mechanisms and colony-stimulating factor 1 receptor (CSF-1R) inhibitors, which can achieve temporary depletion of microglia [68]. In normal brains, CSF-1R inhibitor (CSF-1Ri) treatment depleted up to 99% of microglia and did not result in detectable changes in cognitive function [68, 69]. Complete repopulation was shown to occur within 14 days after inhibitor withdrawal, and the repopulated microglia were morphologically and functionally identical to microglia in the young brain [69]. Animal experiments have also confirmed that microglial depletion in the brain during or shortly after irradiation can prevent the loss of dendritic spines in hippocampal

neurons and the development of cognitive impairment at later time points [70-72]. Regarding the mechanism, subsequent studies found that WBRT-induced transcriptomic changes in microglia could be eliminated after microglial depletion and repopulation [73].

Intercellular cell adhesion molecule-1 (ICAM-1) is an important adhesion molecule that mediates the adhesion of leukocytes to ECs and then crosses the BBB into brain tissue. Irradiated microglia can produce ICAM-1 or release TNF-α and IL-6 to activate astrocytes to produce ICAM-1 [74]. The TAM (Tyro3, Axl, and Mer) tyrosinase receptors present on the surface of microglia, which receive kinases secreted by dendritic cells and macrophages, have a negative regulatory role in inhibiting the immune response of these cells. Loss of TAM receptors by microglia results in increased production of IL-6 and IL-1β, which, as paracrine factors, stimulate astrocytes to produce more IL-6 [75]. All of these processes can exacerbate intracranial nerve inflammation.

Astrocytes

Astrocytes also have an immune function and maintain brain homeostasis. Radiation-induced polarization of astrocytes can be induced by different cytokines into a neurotoxic A1 state or a neuroprotective A2 state. Dysregulation of the complement system, connexin (Cx), and alterations in Ca^{2+} signaling are all involved in astrocyte-mediated inflammation.

Astrocytes are one of the most common cells in the brain and were previously thought to be nonfunctional. Nevertheless, these cells have gradually been shown to have functions in immunity [76] and maintenance of brain homeostasis [77]. In a review, Michelle et al. noted that astrocytes achieve their protective effects on neurons through at least seven different mechanisms: 1) preventing glutamate toxicity, 2) preventing redox stress, 3) mediating mitochondrial repair mechanisms, 4) preventing glucose-induced metabolic stress, 5) preventing iron toxicity, 6) modulating immune responses in the brain, and 7) maintaining tissue homeostasis in the presence of DNA damage [78].

Radiation exposure to the cranium can lead to the reactive proliferation of astrocytes with significant morphological changes [79], including hypertrophy of cell protrusions, upregulation of intermediate filaments, and increased expression of glial fibrillary acidic protein (GFAP). As mentioned previously, the proinflammatory factors secreted by activated microglia stimulate astrocytes to secrete inflammatory factors. Therefore, in vitro experiments in which microglia and astrocytes were mixed and irradiated with 15 Gy revealed that proinflammatory factors such as PGE2, IL-6, and IL-1β secreted by microglia mediated phenotypic changes in astrocytes, e.g., the proliferation of reactive astrocytes [80]. Proliferating astrocytes release high levels of vascular endothelial growth factor (VEGF), and the expression of hypoxia-inducible factor-1a (HIF-1a), which stimulates astrocyte production of VEGF, increases BBB permeability after radiation-induced hypoxia at the site of injury. In addition, the accumulation of DNA damage due to IR may induce senescence-associated secretory phenotype (SASP) expression and senescence in astrocytes [81].

Similar to microglia, astrocyte polarization is followed by classification into A1 (neurotoxic) and A2 (neuroprotective) astrocytes. A1 astrocytes are mainly induced by IL-1α, TNF-α, and C1q secreted by microglia in models of neuroinflammation [82]. A2 astrocytes are induced mainly in ischemic and acute trauma models [83], and in vitro assays have found that IL-4 and IL-10 induce the production of A2-like astrocytes [84]. Low-dose radiation studies simulating space radiation also found that astrocytes exacerbate BBB permeability in the acute phase after irradiation but switch to a more protective phenotype in the subacute phase by reducing oxidative stress and the secretion of proinflammatory cytokines and chemokines [85]. Complement C3 is a typical marker of the type A1 astrocyte subtype. Animal studies have found that C3-deficient mice treated with cranial radiotherapy are superior to wild-type mice in learning and reversal of knowledge [86]. Dysregulation of the complement system leads to astrocyte expression that promotes inflammatory features and may contribute to the pathogenesis of autoimmune and neurodegenerative diseases. Recent studies have found elevated levels of the brain complement component proteins C1q (the proximal component of the complement cascade) and C3 (the downstream part of the complement

cascade, activated by C1q) after irradiation [87]. C1q is synthesized by microglia after irradiation, while astrocytes also express C1q in pathological conditions such as multiple sclerosis and temporal lobe epilepsy [82, 87]. The authors conducted further studies to demonstrate that the complement system is associated with the activation of microglia and astrocytes after radiotherapy and is a crucial mediator of radiation-induced cognitive decline. The results showed that the proximal complement factor C1q increases in abundance within 2 h after radiotherapy and colocalizes with activated microglia and astrocytes. Levels of the downstream complement component C3 increased significantly within 2 h after radiation, but it colocalized mainly with reactive astrocytes. This finding suggests that radiation activates microglia, causing them to produce C1q, which then activates astrocytes. A genetically engineered mouse model with C1q deletion specifically in microglia was then used to test this hypothesis. The results showed that mice lacking microglial C1q had lower levels of numerous inflammatory cytokines in response to radiation. The deletion of microglial C1q also prevented TLR4 upregulation in microglia, thus suggesting that C1q may act on microglia in addition to astrocytes. Whether C1q-directed therapy can be used clinically to avoid a radiation-induced cognitive decline will depend on whether these drugs successfully cross the BBB and do not reduce the efficacy of radiation therapy.

Cx is a transmembrane protein responsible for intercellular communication [88]. Several studies have found that altered levels of CX expression in astrocytes are associated with a variety of cognitive impairment diseases. For example, in mice model of AD, Cx43 and Cx30 expression is increased in astrocytes surrounding amyloid plaques in APP/PS1 mice [89], and a decrease in Cx43 and Cx30 expression in depression patients [90, 91]. Cx43 levels increase with disease progression in epilepsy patients [92, 93]; and at the genetic level, CX30 miRNA was upregulated in glioblast astrocytes and expressed in rat brain apoptotic neuronal cells [94]. However, most of the current studies on altered CXs expression in RIBI have focused on the alteration of CX43, and few studies on other CXs, so our review focuses on CX 43 expression alterations. Cx43, a member of the Cx family, plays a vital role in neuroinflammation, including promoting the assembly of gap junctions and increasing intercellular signal exchange [95-97], and is an important component of astrocyte gap junction channels. Regulation of Cx43 hemichannel opening prevents tissue damage due to excessive activation of the inflammatory response [98], and upregulation of Cx43 is essential for radiation-induced neuroinflammation [99]. Upregulation of Cx43 can lead to an increase in inflammatory factors such as TNFα, INF-γ, IL-6, and IL-1β, leading to the development of radiation-induced neuroinflammation. Previously, Cx43 was found to be a direct target gene of miR-206, and subsequent studies also confirmed that miR-206 [100] could alleviate irradiation-induced neurological damage by regulating Cx43 [101]. In contrast, overexpression of miR-374a also abrogated γ-ray-induced upregulation of Cx43 in astrocytes and reduced inflammatory factors released from astrocytes [99]. Therefore, the regulation of Cx43 is expected to be a new research direction and a potential therapeutic target for treating inflammation-related neuronal injury after radiotherapy.

Another vital assessment of astrocyte function is the generation and propagation of stimulus-induced intercellular Ca^{2+} transients and waves [102]. Preclinical studies have shown that neurodegeneration is associated with behaviorally relevant changes in astrocyte Ca^{2+} signaling [103]. Studies in transgenic animal models have confirmed the causal relationship between impaired astrocyte Ca^{2+} signaling and cognitive and behavioral impairment [104-106]. One study found persistent cognitive deficits in mice 12-15 months after whole-brain radiotherapy [107]. Further analysis revealed a constant attenuation of astrocyte Ca^{2+} signaling but did not reveal altered astrocyte-astroglia gap junction coupling. This finding suggests that altered Ca^{2+} signaling may contribute to the persistent impairment of cognitive function after whole-brain radiotherapy in mice.

Peripheral immune infiltration

After the brain is irradiated, monocytes and macrophages from the peripheral blood can enter the brain in different ways and participate in the inflammatory process in the brain. G-CSF may improve cognitive dysfunction after brain irradiation.

Despite the presence of innate immune cells in the brain, peripheral immune cells can migrate to the brain when the BBB is destroyed [108].

Monocytes are important mediators of innate immune function because of their ability to differentiate into tissue macrophages. Based on the expression of specific cell surface antigens, monocytes can be divided into two distinct subpopulations, namely, "inflammatory" (Ly-6ChiCCR2CX3CR1+-) and "circulating" (Ly-6Cl° CCR2-CX3CR1) monocytes. The chemokine C-C motif chemokine receptor 2 (CCR2) is expressed in neurons and glial cells [109, 110]. Nevertheless, recent studies have suggested that CCR2 is mainly expressed in blood-derived monocytes and macrophages but not in resident cells in the CNS [111-113]. Mouse experiments identified CCR2 as a critical mediator of hippocampal neuronal dysfunction and hippocampal cognitive impairment after cranial irradiation (10 Gy), and CCR2 deficiency prevented hippocampal body-dependent spatial learning and memory impairment induced by cranial irradiation [114]. In a similar study, when CCR2-deficient mice were irradiated using low doses (2 Gy), CCR deficiency rescued hippocampal neural progenitor cell survival and stabilized neurogenesis after exposure to low doses of irradiation [115]. These results suggested that circulating Ly-6C(hi)CCR2(+) monocytes [circulating Ly-6C(hi)CCR2(+) monocytes] are preferentially recruited to the diseased brain and differentiate into microglia after cranial radiotherapy. Nevertheless, interestingly, this study found that microglial transplantation in CNS pathology was not associated with significant BBB disruption [116]. Similar studies have also found that cranial radiation alters the homeostatic balance of the brain, allowing the entry of CCR2+ macrophages from the peripheral circulation and increasing the sensitivity of the hippocampal formation to IR [117]. This study did not detect abnormal expression of multiple markers associated with BBB integrity. Thus, infiltration of peripheral CCR2+ macrophages may be mediated by inflammation-induced chemotactic signaling. Recent studies have confirmed that irradiated microglia can secrete CCL2 but can barely express CCR2 [48, 118]. In addition, CCL2 has been found to damage the integrity of the BBB in mice [110]. Thus, CCL secreted by microglia after cranial irradiation can cause peripheral immune involvement in the brain by damaging the BBB and inducing peripheral immune cells to enter the brain in multiple ways.

Macrophages are an essential component of inflammatory infiltration during RIBI. Previous studies have found that the number of macrophages in the brain following radiation usually increases in a radiation dose-dependent manner and promotes the secretion of inflammatory factors such as IL-1 and TNF-α by macrophages. Animal experiments have also shown a significant increase in macrophages after cranial irradiation [117, 119]. However, the source of the increased macrophages in the brain under the pathological setting of RIBI is still controversial. Because microglia and peripheral immune cells share multiple immune markers, such as CD11c, CD68, and MHC II [120], these cells are difficult to distinguish by conventional techniques. In contrast, using transgenic and bone marrow chimeric animals and experimental methods such as flow cytometry and two-photon imaging have allowed the identification and functional study of infiltrating immune cells. Using bone marrow chimeric mice, researchers demonstrated that bone marrow-derived cells (BMDCs) were explicitly recruited to the site of radiotherapy and differentiated into inflammatory cells and microglia. Moreover, more than 50% of microglia in the irradiated areas of the brain are not resident microglia but are recruited from the bone marrow after radiotherapy [121]. The aggregation effect is time- and dose-dependent and persists for up to 6 months after cranial irradiation of >15 Gy [122]. However, some studies have suggested that a significant increase in neutrophil infiltration was observed only 12 h after radiation exposure. No significant increase was observed for the remaining time [123].

G-CSF is an endogenous hematopoietic growth factor commonly used clinically to increase granulocytes in patients with granulocytopenia. Interestingly, one study found that G-CSF, as a neuronal ligand, stimulates neurogenesis [124] and positively affects performance in the radial maze of normal rats [125]. In contrast, similar results were obtained in a later mouse test, in which mice given G-CSF 7 days after whole-body irradiation showed improved progenitor cell proliferation throughout the brain, suggesting that bone marrow-derived G-CSFR-positive

cells are essential for brain repair after radiation injury. Behavioral tests also confirmed that G-CSF improved neurocognitive function after brain irradiation. Bone marrow-derived cells with monocyte/macrophage and microglia phenotypes were also found to be in the irradiated brain in the perivascular and parenchymal regions. These findings suggested that G-CSF restores radiation-induced white matter destruction [126].

Oxidative stress & DNA damage

Mitochondrial dysfunction and abnormal levels of mitochondrial translocator protein (18 kDa, TSPO) both lead to excess ROS and oxidative damage in the brain. Direct radiation damage to DNA and damage to mitochondrial DNA are mechanisms of neuroinflammation.

Basal levels of ROS in the brain are due to normal cellular function and metabolic activity. Although ROS production is a natural consequence of mitochondrial respiration, excess ROS produced by cranial brain injury beyond the capacity of biological cellular antioxidant mechanisms will lead to pathophysiological changes in the brain. Neuronal and glial cells are particularly susceptible to oxidative damage because the CNS is rich in polyunsaturated fatty acids, has a high oxygen consumption, and lacks antioxidant defenses [127]. Increased ROS activate the regulation of the NF-κB pathway, leading to neuroinflammation through NF-κB phosphorylation, activator protein-1 (AP-1), specificity protein-1 (SP-1), cAMP-responsive element-binding protein (CREB), and signal transducers and activators of transcription (STAT). CREB and STAT contribute to neuroinflammation [128]. Studies have demonstrated that a dose of 0.5 Gy increases ROS in microglial cell lines [129]. A dose of 2 Gy induces microglial activation in the hippocampus and modulates electron transport chain (ETC) enzyme activity in mitochondria [130]. Higher doses can lead to oxidative damage accompanied by mitochondrial fission and expression of fusion proteins in parallel with microglial activation [131].

IR can induce mitochondrial dysfunction, characterized mainly by reduced oxidative capacity and decreased ATP production, which is one of the main hallmarks of radiation-induced DNA damage and aging of neural tissue [132]. In vitro assays showed that after exposure of cells to 5 Gy irradiation, ROS levels increased significantly within the first few minutes and appeared to decrease at 30 min, and mitochondrial dysfunction was detected 12 h after irradiation. This change was manifested by a decrease in the activity of nicotinamide adenine dinucleotide (NADH) dehydrogenase, the primary regulator of ROS release from the ETC [133]. During brain development, mitochondrial dysfunction and excessive ROS production contribute to brain cell aging, cognitive impairment, and abnormal behavior [134]. In addition to the effect on the ETC, excess ROS interfere with Ca^{2+} homeostasis and induce Ca^{2+} overload, which can cause changes in mitochondrial potential and induce further ROS production [135]. During this process, mitochondria may experience potential membrane collapse, increased mitochondrial permeability, and rupture of the outer mitochondrial membrane [136]. The increase in mitochondrial membrane permeability eventually leads to the release of cytochrome c, which initiates apoptosis [137].

TSPO is an outer mitochondrial membrane protein with low basal expression in the central nervous system, mainly by ECs [138]. However, this protein is expressed in activated microglia during neurological injuries or other cranially active pathological processes and is therefore used as an indicator of microglial activation [139, 140]. Recent studies have found that neuronal activity also increases TSPO levels in the brain, suggesting that it may not be a reliable marker of microglial activation [141]. Similarly, the reduction in TSPO may not represent an improvement in neuroinflammation but may reflect “malnutrition, senescence, and death, or mitochondrial dysfunction in microglia” [142]. TSPO expression levels were positively correlated with the concentrations of several proinflammatory factors, including IL-6 [44, 140]. The ligands of TSPO can regulate TSPO expression and alter the activation status of microglia between M1 and M2 proinflammatory or anti-inflammatory states [143, 144]. TSPO may be involved in immunomodulatory functions by regulating mitochondrial energy and ROS production [139].

IR can cause DNA double-strand breaks (DSBs), leading to secondary genetic instability and oxidative stress, ultimately leading to brain EC

senescence and cell death [145]. High-energy LET rays damage DNA directly, while low-energy LETs damage DNA by promoting the breakdown of water molecules in biological tissues and generating free radicals. The latter pathway can include base damage and release, depolymerization, crosslinking, and strand breakage in various ways [146]. DNA damage can rapidly trigger the activation of transcription factors such as NF-κB, CREB, and AP-1. These transcription factors control intracellular ROS production and inflammatory factors, including IL-1β, TNF-α, cyclooxygenase 2 (COX-2), and monocyte chemoattractant protein-1 (MCP-1) [42, 147]. Unrepaired and misrepaired double-strand breaks (DSBs) may lead to genomic instability, cell death, or cellular senescence (an irreversible state of cell cycle arrest) [148, 149].

Activation of the poly ADP-ribose polymerase (PARP) family of proteins is one of the hallmarks of neuritis and the DNA damage response (DDR). The role of PARP proteins is to initiate base excision repair (BER) in response to single-strand breaks (SSBs) and DSBs. In mammalian cells, the PARPase family includes at least 17 members; however, only PARP1, PARP2, and PARP3 are involved in DNA damage repair activities. Most studies in the field of neuroinflammation have focused on PARP1, but most current PARP inhibitors (PARPis) are active against both PARP1 and PARP2. The best-known pathway by which PARP-1 promotes neuroinflammation is by regulating proinflammatory transcription factors such as NF-κB, AP-1, and nuclear factors that activate T cells [150]. NF-κB regulates the expression of several genes involved in immunity and inflammation. Under basal conditions, NF-κB is localized in the cytoplasm and, when activated, undergoes nuclear translocation, binds to DNA, and increases the transcription of inflammatory cytokines, chemokines, adhesion molecules, and inflammatory mediators, including inducible nitric oxide synthase (iNOS), ROS and TNF-α [151]. Following radiation-induced DNA damage, PARP binds to SSBs and recruits BER proteins to induce polyadenosine diphosphate ribosylation modification (PARylation) and initiate DNA repair. PARP-1 plays an important role in the upstream regulation of radiation-induced NF-κB activation, and the PARP-1 inhibitor AG1436 enhances radiation toxicity by inhibiting NF-κB activation [150]. DNA damage leads to activation of PARP-1, usually secondary to oxygen and nitrogen species (ROS/RNS), and elevated intracellular calcium, resulting in activation of ERK1/2-mediated phosphorylation [152, 153]. In addition, PARP-1 is involved in the microglial and astrocytic response to inflammation [153, 154], so PARP inhibition can reduce neuroinflammation, astrogliosis, and microglial activation. Based on the report that PARPis can be used as a radiosensitizer in preclinical studies in the glioma population [155, 156], if PARPis are used in the treatment of glioblastoma multiforme, tumor cell death can be enhanced by inhibiting DNA repair pathways. In addition, normal brain tissue can be protected from radiation-induced neuroinflammation by inhibiting glial activation and inflammatory mediators [157]. However, the feasibility and clinical effectiveness of this method need to be further explored.

IR can also directly alter mitochondrial DNA (mtDNA), most notably by common deletion mutations. Growing evidence has shown that radiation-induced mitochondrial damage is more common than nuclear damage [158] and may be related to mtDNA's lack of histone protection and efficient DNA repair system [159]. mtDNA is released into the cytoplasm after the mitochondrial membrane is damaged and ruptured [160]; mtDNA may induce the release of type I interferon and the expression of other interferon-driven genes [161, 162]. IR also indirectly causes mitochondrial dysfunction by producing ROS, triggering disruption of the ETC, and increasing antioxidant enzyme production through nuclear factor E2-related factor 2 (Nrf2) [163].

Neuronal injury

Direct damage to neurons by IR is another cause of RIBI. Age, Sonic hedgehog (Shh) signaling, Mg^{2+} in the hippocampus and differences in epigenetics are all factors that influence the outcome of radiation.

The hippocampus is in the medial temporal lobe of the brain. It consists of the dentate gyrus (DG) and the cornu ammonis (CA), which are the areas of the brain primarily responsible for memory formation. The hippocampus is critical for declarative memory (learning) acquisition, integration and retrieval and spatial

memory formation; complete or partial hippocampal damage may lead to spatial learning and memory impairment. In the adult mammalian brain, neural stem cells (NSCs) are mainly found in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal DG, and they represent a group of self-renewing cells that can differentiate into neurons in response to different stimuli [164]. The SGZ contains the neurogenic "niche", a specific microenvironment that allows neuronal development, including precursor cells, their direct descendants and immature neurons, immune cells (e.g., microglia and macrophages), ECs, and the extracellular matrix. The presence of neurogenesis in the adult hippocampus remains controversial. Nevertheless, it has been suggested that adult neurogenesis persists throughout a person's life but decreases slightly with age; however, the volume of the DG remains constant [165]. Animal experiments have confirmed that hippocampal irradiation results in a dose-dependent loss of NSCs and that surviving NSCs show reduced proliferation and neuronal differentiation [166]. Radiotherapy also increases N-methyl-D-aspartic acid receptor expression in the hippocampus, resulting in excitotoxicity and cognitive dysfunction [167].

Animal studies showed that rats receiving a single 30 Gy dose of WBRT for three months had learning and memory deficits, as well as a decrease in the number of neurons in the CA1 region of the hippocampus, an upregulation of caspase-3 expression in the hippocampal DG, and an increase in neuronal apoptosis [168]. A synaptic plasticity-based study found altered cognitive function and reduced expression of the synaptic plasticity marker vesicular glutamate transporters 1 (VGLUT1) in mice three months after cranial irradiation, suggesting that radiation impairs intrinsic excitability and synaptic plasticity in hippocampal CA1 pyramidal neurons [169]. Age is an essential factor affecting radiation outcomes. Although hippocampal neurogenesis was reduced in neonatal (10-day-old) and adult mice after IR, hippocampal apoptosis sensitivity was significantly higher in neonatal mice than in adult mice [130]. Dendritic spine density in the DG was reduced considerably in young rats at 1 and 3 months after cranial radiotherapy with 10 Gy, and depletion of the synapse-associated proteins PSD-95 and Drebrin coincided with alterations in dendritic spines [170]. This study hypothesized that the decrease in PSD-95 and Drabrin levels caused by IR affects the morphological structure of dendritic spines through effects that block functional connectivity pathways in the brain and lead to cognitive impairment. In addition, similar studies have found a more robust inflammatory response to low-dose IR (LDIR) in the hippocampus of young mice [171]. One study even irradiated embryonic mice prenatally. The mice exhibited several higher-order dysfunctions (e.g., reduced nocturnal activity, working memory deficits, delayed fading of threat-evoked response inhibition, and signs of aberrant behavior), and electrophysiological examination showed impaired hippocampal synaptic plasticity [172]. Therefore, hippocampal protection is a concern for all age groups and is especially important for individuals who are still growing.

Shh signaling is critical for forming neurogenic ecotopes in the SVZ and hippocampal DG subgranular zone and in the specification of cell types in the nervous system [173, 174]. Studies based on the constitutive Shh pathway have found that activation of the Shh pathway has an overall protective effect against hippocampal radiation damage [175]. This pathway regulates the neurogenic network, reduces hippocampal defects in stem cells and neuronal compartments, and attenuates radiation-induced astrogliosis [176]. In addition, radiation can damage hippocampal-prefrontal cortical pathways, which may also cause RICI [177].

Decreased Mg^{2+} content is one of the critical factors leading to secondary CNS injury, and early Mg^{2+} supplementation can alleviate CNS injury. Therefore, some studies found that RIBI could be alleviated by Mg^{2+} supplementation in a rat model of radioactive brain injury and suggested that the protective mechanism of Mg^{2+} on the hippocampus might be related to the c-Fos and NF-κB genes [178]. 5'-Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a crucial sensor of cellular energy homeostasis [179]. Mammalian hippocampal neurons express AMPK [180], and cellular metabolism can influence or regulate neurogenesis [181]. Animal experiments have found that a dose-dependent activation of AMPK can occur in the mouse brain for several hours after

irradiation [182]. Interestingly, however, adult Cre-lox mice lacking AMPK in the brain showed further loss of early neural progenitor cells and neuroblasts in the hippocampal region after undergoing radiotherapy but no loss of newborn neurons [182].

The effects of radiation on the hippocampus can also be realized epigenetically. Previous studies have found that two and 30 Gy whole brain irradiation significantly decreased histone H3 acetylation and elevated histone deacetylase 1 (HDAC1) levels in the rat hippocampus 7 and 30 days after radiation exposure [183]. This finding suggests that epigenetics is associated with irradiation-induced memory deficits and that alterations in chromatin structure may be a new possible molecular correlate of irradiation-induced cognitive deficits. Kang et al. found that the mRNA levels of HDAC1 were decreased in the hippocampus of mice one day after receiving 10 Gy cranial irradiation, and the mRNA levels of DNA (cytosine-5-)-methyltransferase 1 (DNMT1), HDAC1, and HDAC2 decreased 30 days after irradiation [184]. The results suggest that reduced epigenetic gene expression is associated with hippocampal dysfunction in mice exposed to cranial irradiation, with effects depending on the time after irradiation. In addition, elevated levels of microRNAs (miRNAs) related to epigenetic regulation (e.g., miR-34c, miR-488 [185], miR-132/miR-212, and miR-134 [186]) in the hippocampus have also been reported after exposure to low and moderate cranial doses of radiation. Interestingly, one study found that elevated miR-34a-5p induced in peripheral blood after total abdominal irradiation could target the 3' untranslated region (UTR) of brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus to mediate cognitive dysfunction [187]. Young male rats underwent a single dose of WBRT at 10 Gy for three months, after which hippocampal memory was significantly reduced, and severe neurogenic damage was observed. Further assays revealed that tyrosine kinase receptor A (TrkA) protein expression increased after one week of irradiation but decreased considerably during a 3-month period. The upregulation of TrkA expression improved irradiation-induced hippocampal precursor cell proliferation and promoted neurogenesis [188]. This study, therefore, suggests that TrkA-dependent signaling pathways may play a key role in radiotherapy-induced cognitive deficits and neurogenic damage.

In irradiation damage repair, one study found that DNA repair in the hippocampus was also delayed in the mouse brain after shallow irradiation doses [189]. Another study found reduced expression of genes involved in ATP synthesis (ND2, CytB, ATP50) in brain regions of irradiated rats and much slower repair of nuclear DNA in the hippocampus than in the cerebellum and cortex [190].

Exosomes and miRNAs

Radiation-induced exosomes mediate the development of RIBI, and a variety of miRNAs are involved.

Exosomes (30-100 nm) are membrane-bound extracellular vesicles (EVs) containing DNA, miRNA, mRNA, proteins, and lipids, which are gradually attracting attention as crucial pathological markers [191]. Exosomes differ from other EVs in that they pass through endosomal compartment biogenesis and carry tumor susceptibility gene 101 (TSG101) as a typical marker [192]. EVs play a vital role in intercellular communication, immune function, stem cell differentiation, neuronal function, tissue regeneration, and viral replication [193]. Host cell exosomes contain miRNAs, mRNAs, and proteins and can alter the physiology of the recipient cell through the transfer of genomic, proteomic, and lipid cargoes [193]. After delivering messages, exosomes are mostly depleted. Cells constantly produce large amounts of exosomes to maintain the communication system and continue impacting the organism. Because they can carry cancer-specific proteomic and transcriptomic biomarkers during tumor transformation, exosomes have become new drug delivery vehicles and key biomarkers for disease diagnosis [194].

IR stimulates the release of exosomes [195], and exosome-based mechanisms increase cancer cells' ability to survive radiation exposure [196]. In addition to the effects of radiation on the irradiated area, there are also non-targeted radiation effects, radiation-induced bystander effects (RIBEs), and remote isolation effects (RIAEs) [197]. As our understanding of exosomes has increased, new ideas for elucidating RIBEs and RIAEs have been reported.

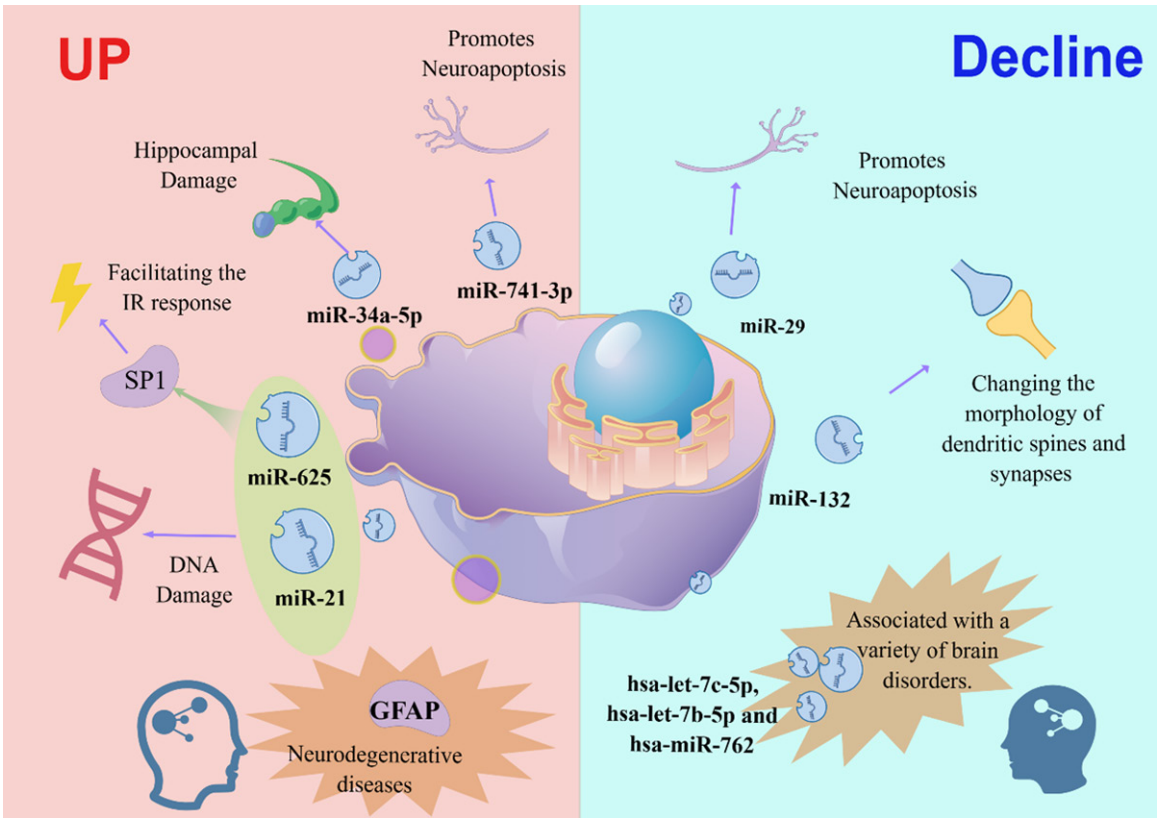

Figure 3. IR-induced changes in intracranial miR and EV levels and their effects (left is elevated, right is decreased). 1. miR-21 elevation leads to the DNA damage response (DDR), while miR-21 and miR-625 target SP1 to promote the response to acute low-dose IR. 2. miR-34a-5p elevation leads to hippocampal pathological changes, subgranular cone blade hypoplasia, and abnormal cell division. 3. miR-741-3p is significantly elevated in the RBI mouse model, and its inhibition improves neuronal apoptosis. 4. 3p levels rise significantly, and its inhibition ameliorates neuronal apoptosis. 4. Downregulation of miR-29 leads to a neuronal damaging effect. Downregulation of miR-132 leads to alterations in dendritic spines and synaptic morphology. IR induces an increase in GFAP, which has been shown to increase in various CNS diseases and neurodegenerative disorders. IR induces levels of hsa-let-7c-5p, hsa-let-7b-5p, and hsa-miR-762, which are associated with epileptic encephalopathy, frontotemporal dementia and/or amyotrophic lateral sclerosis, and mitochondrial complex IV.

Exosomes are essential in mediating RIBEs, where molecular signals from irradiated cells affect unirradiated cells [197] and propagate radiation effects. Recently, exosomes were even shown to convey genomic instability from irradiated cells to bystander cells [198].

MiRNAs (miRs) are a class of endogenous, non-coding, single-stranded RNAs approximately 21 nucleotides in length that are involved in regulating post-transcriptional gene expression [199, 200]. Previous studies have demonstrated that miRNAs can affect axonogenesis, synaptogenesis, and dendritic spine development [201] and participate in stress-induced immune responses in the brain [202], including cytokine production and inflammation [203]. MiRNA-mRNA gene regulatory networks have been shown to mediate reactions to IR [204, 205] and neuroinflammation [206]. As shown in **Figure 3**, the expression of multiple miRNAs appeared to be up- and downregulated by IR and had an impairing effect. MiR-21 is a well-described DDR miRNA that participates in RIBEs in a mediated manner [197]. Exposure of humans to low doses of radiation (7.72±4.73 mSv) also caused an increase in miR-21 and miR-625 expression levels, and miR-21 and miR-625 can contribute to the response to acute low-dose IR by targeting SP1 [207]. Downregulation of the hippocampal, frontal, and cerebellar miR-29 families was detected in mice 6 to 96 h after receiving 1 Gy irradiation, resulting in altered DNA methyltransferase 3 alpha gene expression and causing overall methylation of DNA [185]. Because miR-29 pro-

motes neuronal differentiation, dendritic growth, and axonal generation [208] and miR-29 downregulation has been observed to have a proapoptotic effect in C (AD) patients, it can lead to loss of newly generated neurons in the subventricular and subgranular regions [209]. Thus, IR-induced downregulation of miR-29 has a damaging effect on neurons. EC-secreted exosomes, including miR-132, have a role in maintaining cerebrovascular integrity [210]. Kempf et al. found that irradiation-induced decreases in miR-132 (24 h post-irradiation) may lead to rapid changes in the dendritic spine and synaptic morphology through abnormal cytoskeletal signaling and processing, resulting in neurocognitive side effects observed in patients treated with IR [186]. Interestingly, however, subsequent studies found that miR-132/miR-212 and miR-134 increased six months after irradiation [211]. This finding suggests that miR-132 is dynamically altered after irradiation, and whether this change is related to the dynamics of cognitive function in the later stages of radiotherapy is unclear. MiR-34a has been shown to negatively regulate the complexity of dendritic branches and nascent neurons [212]. Animal experiments found that 5 Gy γ-irradiation of newly born 3-day-old mice resulted in depression, hippocampal pathology, subgranular layer cone blade hypoplasia, abnormal and impaired cell division and DG neurogenesis in adult mice; upregulation of miR-34a-5p was observed in both animal and NSC models [213]. Inhibition of miR-741-3p levels in the hippocampus of mice with RIBI improved cognitive dysfunction and neuronal apoptosis six weeks after irradiation. The prominence and branching status of microglia was enhanced at the cellular level, and the number of GFAP-positive astrocytes was reduced. At the molecular level, the production of the proinflammatory cytokines IL-6 and TNF-α in the hippocampus and S100B in the serum was decreased [214].

Some studies have also demonstrated that miRNAs can regulate neuronal apoptosis after radiotherapy. MiR-124, together with miR-9, appears to inhibit the Brg- and Brahma (Brm)-related factor complex 53a (BAF53a), enabling neural progenitor cells to differentiate correctly into neurons [215]. Injection of human NSC-derived EVs into mice treated with 9 Gy cranial radiotherapy improved IR-induced cognitive dysfunction. Further analysis suggested that miR-124 alleviated the main component of radiation-induced cognitive dysfunction [216]. MiR-711 negatively regulates multiple prosurvival and DNA repair mechanisms following radiation, ultimately activating neuronal intrinsic apoptosis and senescence [217].

In addition, a fraction of IR-induced changes in miRNAs or EVs are altered in other neurodegenerative diseases, indicating that alterations in this fraction of miRNAs or EVs are also associated with altered cognitive function after radiotherapy. The expression levels of 13 exosomal miRNAs were decreased after exposure to high-energy radiation [218]. MirNet database analysis identified three subsets of miRNAs targeting the most of genes (hsa-let-7c-5p, hsa-let-7b-5p, and hsa-miR-762) that target the same subset of genes associated with epileptic encephalopathy (Amd1, CCNF, COX6B, PLXND1); mapping to the Gene Card-Human Disease Database identified associations with epileptic encephalopathy, frontotemporal dementia and/or amyotrophic lateral sclerosis, and mitochondrial complex IV deficiency [219]. In another study, microglia were cocultured with glioblastoma cells and subjected to radiotherapy, and the expression of circ_0012381 was found to increase after irradiation of glioblastoma cells. Circ_0012381 induced polarization of M2 microglia through miR-340-5p to increase ARG1 expression after entering microglia via exosomes [220]. GFAP is a marker of reactive astrocytes that can be activated in response to brain injury and can be contained by EVs. This molecule is increased in various CNS disorders and neurodegenerative diseases, such as AD [221]. A mouse study found that radiation-induced brain damage could be detected in EVs within 48 h after receiving 10 Gy of brain radiotherapy, as shown evidenced by increased HNE endocannabinoid and GFAP levels [222].

A recent study found that adipose-derived mesenchymal stem cells (MSCs) alleviated radiation-induced oxidative stress and inflammation in the hippocampus by suppressing radiation-induced microglial infiltration and promoting SIRT1 expression in the hippocampus [223]. In addition, MSCs have neuroprotective effects by decreasing M1 microglial and A1 astrocyte activation [224, 225]. MSCs cannot cross freely due to the presence of the BBB, but MSC-

derived exosomes can cross the BBB and exert potent and long-lasting neuroprotection and neurogenesis [226, 227]. A recent review by Hadi Yari discusses in detail the therapeutic benefits of MSC-derived exosome therapy for improving the pathological symptoms of acute and chronic neurodegenerative diseases [228]. Rats receiving EV or human NSC transplants after cranial radiotherapy showed improved dendritic complexity and spine density of neurons in the ipsilateral and contralateral hippocampus after irradiation [229]. Cellular experiments have also demonstrated that mouse adipose tissue-derived MSC- and NSC-secreted exosomes improve irradiated NSC survival and clonal activity [230]. In conclusion, MSCs and their derived exosomes offer new hope for ameliorating radiation-induced brain damage.

Conclusion

Radiotherapy is still one of the most important treatments for head and neck tumors, but toxic effects can occur. The molecular biological mechanisms that trigger radiation encephalopathy are complex and involve multiple pathophysiological responses. Chronic inflammation is present throughout RIBI, and future directions in the clinical treatment and prevention of RBI include inhibiting the activation of microglia and astrocytes, reducing oxidative stress and preventing the migration of peripheral immune cells into the brain, thereby reducing cognitive dysfunction. The study of exosome secretion due to radiotherapy has helped elucidate radiation encephalopathy, and the role of miRNAs, in particular, is increasingly appreciated. Identifying susceptible groups for RIBI and early identification and intervention are essential for improving cognitive function after radiotherapy in the corresponding groups. Therefore, future studies could modulate critical points in the inflammatory response from different pathways to differentially improve the pathological process of RIBI and delay disease progression.

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Disclosure of conflict of interest

None.

Address correspondence to: Huaidong Cheng, Department of Oncology, Anhui Medical University, Hefei, Anhui, China. E-mail: chd1975ay@126.com

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