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REVIEW

The Pathogenesis and Prevention Strategies of Radiation-Induced Brain Injury

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Abstract: Radiation-induced brain injury (RBI) encompasses the severe symptoms resulting from radiation-induced damage to the normal tissue surrounding tumors in patients undergoing radiotherapy for head and neck malignancies. The primary symptoms include skin erythema, pain, and may extend to headache, syncope, nausea, vomiting, memory impairment, alterations in mental status, visual disturbances, drowsiness, and other neurological abnormalities localized to the area of treatment. These side effects both limit the effectiveness of radiation therapy and reduce the patient's quality of life. During radiotherapy, while killing tumor cells, the radiation will damage the cerebral microvascular endothelial cells, cause cerebrovascular inflammatory response, destroy the blood-brain barrier, aggravate the cerebral oxidative stress response, and induce apoptosis of nerve cells. This review summarizes the mechanisms underlying the occurrence and progression of radiation-induced brain injury and discusses promising strategies for prevention and treatment that may be applicable to clinical patients suffering from this condition.

Keywords: radiation-induced brain injury, radiation protection agents, oxidative stress, apoptosis, cognitive function

Background

Radiation-induced brain injury (RBI) is the most serious complication of neurological impairment in patients with head and neck tumors who receive radiation therapy.[1] According to a 2021 Global Cancer Survey, cancer has become the leading cause of death worldwide in 2020. Among them, the overall incidence of head and neck tumors reached 9.5% (3.0% for thyroid cancer, 2.0% for lip and oral cancer, 1.6% for brain and nervous system cancer, 1.0% for laryngeal cancer, 0.7% for nasopharyngeal, oropharyngeal, and laryngopharyngeal cancers, and 0.3% for salivary gland cancers).[2] In China, the disease with the highest mortality rate is cancer, of which head and neck tumors rank sixth.[3] At present, with the optimization of clinical radiotherapy strategies, the side effects of radiotherapy have also been greatly reduced. However, numerous studies have shown that there is a persistent inflammatory response in the brain after radiation therapy, which is a major contributor to RBI.[4] Therefore, this article will review the mechanism of inflammation and its prevention and treatment strategies in the occurrence and development of RBI.

RBI Overview

Radiation-induced brain injury refers to a series of pathological changes related to healthy brain tissue damage in patients with head and neck tumors after radiotherapy, including a series of biochemical and cellular disorders such as capillary damage, blood-brain barrier disruption, abnormal autoimmune response, imbalance between oxidation and antioxidant balance, and inhibition of nerve cell development, as well as loss of endogenous neurogenesis, demyelination, and ablation of endogenous oligodendrocyte progenitor cells.[5] Combined with the state of chronic neuroinflammation, Xi and memory dysfunction, local neurological deficits, and progressive dementia can eventually occur.[6]

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Mechanism of Radiation-Induced Brain Injury

Ionizing Radiation Leads to Vascular Damage and Destruction of the Blood-Brain Barrier

The blood-brain barrier is a highly organized, multicellular structure that maintains immunochemical homeostasis in brain tissue by regulating molecular transendothelial transport between the parenchyma and systemic circulation, while also limiting the translocation of peripheral immune cells. It has been reported that, compared to brain parenchyma and vascular cells, low-dose radiation can induce damage and apoptosis in glial cells and vascular endothelial progenitor cells located in the ventricular zone.[5] In addition, a growing number of clinical and preclinical studies have shown that the effects of radiation on parenchymal cells and brain physiology are exacerbated by associated cerebral microvascular endothelial injury, resulting in cerebrovascular inflammation, disruption of the blood-brain barrier, and imbalance of metabolic homeostasis.[7–11] The vascular hypothesis is supported by a large body of data describing radiation-induced changes in vascular structure, including vasodilation, vascular lesions and endothelial progenitor cell depletion, senescence, and the appearance of abnormal endothelial cells, as well as activation of endothelial apoptosis and vascular inflammation.[12,13] Quantitative studies of the brains of irradiated animals have also shown that endothelial cell nuclei and vascular length decrease with time and dose increase.[14] The response of vascular tissue to radiation exhibits a two-phase pattern: the first is that the acute phase can occur within 24 hours of radiation, and the underlying mechanism is related to radiation-induced endothelial apoptosis. The second is the advanced stage, which takes several months to develop and is characterized by capillary collapse, basement membrane thickening, and loss of endothelial cell clonal activity.[15] Dimitrievich et al[16,17] have demonstrated that capillary sensitivity to a single X-ray dose of 200 to 2000 rad is significantly higher than that of larger vessels. Their study also showed that radiation injury was characterized by capillary destruction, extravasation of blood components, and pro-inflammatory changes. Evidence has been reported that the high vulnerability of the capillary layer to radiation is specifically due to the high radiation sensitivity of its endothelial cells, which are the major structural components of the capillary wall.[18] In radiation-induced brain diseases, the microvascular system is the primary tissue-blood interface in the central nervous system that maintains and controls nerve tissue homeostasis.[19] Extensive damage to parenchymal and/or stromal cells and progressive loss of their progenitor cells can lead to worsening of neuroinflammation and disruption of the blood-brain barrier (BBB), ultimately leading to white matter lesions.[20–24] The endothelial cells of the microvascular bed include specific cellular phenotypes and represent part of the blood-brain barrier, which tightly controls brain immunochemical homeostasis.[19] Thus, damage to the normal capillary endothelium by radiation can lead to disruption of the brain-blood barrier, which can lead to serious health consequences.

Ionizing Radiation Leads to Oxidative Stress

Early studies have shown that damage to the central nervous system is often associated with an inflammatory response. The mechanism of the inflammatory response in the brain differs from that of peripheral tissues, which may be related to stronger immunosuppression in this organ.[25] As effector cells of the innate immune system of the brain and the most important antigen-presenting cells in the cerebral cortex, microglia play a key role in the initiation, development, and recovery of neuroinflammation.[26]

Studies have found that when the body receives radiotherapy, ionizing radiation deposits energy into tissue cells, and at the same time damages mitochondria, it will decompose water to produce reactive oxygen species (ROS), and the reactive oxygen species produced induce a series of strong oxidative stress responses, The causes of neuroinflammation are complex and diverse. Measuring inflammatory response indicators can serve as a method to evaluate the degree of oxidative stress. Researchers detected the levels of inflammatory responses in vitro or in vivo after irradiation with different doses of radiation, and the results showed that: tumor necrosis factor- α (TNF-α), increased expression of proinflammatory factors such as interleukin-1β (IL-1β), cyclic oxygenase 2 (COX-2), activation of transcription factors (AP-1), nuclear factors NFκB, CREB, and mRNA levels of several chemokines (MCP1/CCL2, Gro/KC/CXCL1) are upregulated.[27–30] This, in turn, leads to further damage to cellular nucleic acids, proteins, and lipids, as well as extracellular matrix components, and local tissue damage promotes microglial activation.[25,31] Initial

acute radiation-induced microglial activation and neuroinflammatory responses, followed by persistent microglia secreting inflammatory cytokines and production of reactive oxygen species, have led to a cascade of chronic neuroinflammatory responses associated with hippocampal nerve development and cognitive impairment.[21,30,32] Studies have demonstrated that the transcriptional profile of irradiated microglia is very similar to that obtained by microglia during aging, which is the greatest risk factor for cognitive decline and neurodegenerative diseases. In recent years, more and more studies have shown that hippocampal neurogenesis is related to cognitive function. Although the mechanism is not fully understood, a link has been reported between sustained microglial activation and impaired hippocampal neurogenesis.[19,33]

Ionizing Radiation Causes Nerve Cell Death

In recent years, a large number of studies have shown that radiation-induced brain injury is not the result of damage to a single cell or structure, but is caused by the interaction of multiple types of cells, among which astrocytes, endothelial cells, microglia, neurons and oligodendrocytes are the main ones. More recently, preclinical studies have focused on the hippocampus, one of two sites in the brain for adult neurogenesis that plays an important role in learning and memory[9]. The hippocampus is made up of three regions, the dentate gyrus (DG), CA3 and CA1, which are involved in both rodent and human cognition. In addition, DG is one of two sites of adult neurogenesis in the mammalian brain. Neuronal stem cells (NSCs) in DGs are both self-renewing and giving rise to new neurons, astrocytes, and oligodendrocytes.[34,35] Endothelial cells and astrocytes have been shown to promote or modulate neurogenesis, creating a specific microenvironment conducive to this process. Additionally, a dose-dependent decrease in the number of neural stem cells (NSCs) has been observed, along with a reduction in the proliferation of surviving NSCs and a decrease in their differentiation into neurons.[31,36] Radiation has been demonstrated to induce apoptosis in central nervous system (CNS) cells, with this phenomenon being particularly pronounced during the neonatal and early postnatal periods. Additionally, it has been observed in the brains of young adult rats. Neurons and glial cells in the lateral ventricles (LV), olfactory bulb (OB), neocortex, piriform and entorhinal cortex, dentate gyrus (DG), striatum, thalamus, amygdala, brainstem, and subcompartmental zone (SVZ) of the cerebellar white matter were all subject to apoptosis after a single dose of 2 Gy.[37] A single high-dose (2–10 Gy) of rat whole-brain irradiation increases dramatically in hippocampal DG cell apoptosis within 3 to 6 hours and plateaus within 6 to 12 hours after radiation therapy.[38–40] The number of apoptotic cells remains unchanged for one to nine months after radiation therapy.[40–42]

Low doses of ionizing radiation can also adversely affect metabolic pathways that are not directly involved in regulating apoptosis, such as acute or chronic irradiation affecting the ERK1/ERK2 (extracellular signal-regulated kinase) signaling pathway, as well as changes in Trp53 phosphorylation and p21 protein levels, thereby affecting neuronal survival after irradiation.[43,44] At the same time, ionizing radiation can interfere with the expression of cell cycle regulatory proteins, leading to subsequent apoptosis, which is one of the main mechanisms by which ionizing radiation causes cell death within a few hours of irradiation.[45] In addition, it has been found that radiation irradiation can lead to down-regulation of the anti-apoptotic gene Bax and up-regulation of the pro-apoptotic gene Bcl-2 in the mitochondrial pathway, promotes the release of cytochrome C (Cytc), activate Caspase-mediated apoptosis, and induce the occurrence of neuronal apoptosis.[44,46]

Prevention and Treatment of RBI

A large amount of research has shown that the reduction in hippocampal neurogenesis is related to spatial memory and learning.[47,48] Researchers have conducted whole brain or local irradiation of rodent heads and subsequently found significant impairment in cognitive function in animal behavior tests such as Morris water maze (MWM), passive avoidance, Barnes maze, novel object recognition.[49–53] Currently, in order to prevent the occurrence of Radiation-induced brain injury (RBI), many methods for preventing and treating radiation damage induced by ionizing radiation have been developed. The main methods used in clinics include physical protection and medical protection. The main drugs for prevention/treatment are as follows (Table 1):

Table 1 Summary of Therapeutic Strategies and Mechanisms for Radiation-Induced Brain Injury

Treatment Strategies	Mechanism of Action
Anti-inflammatory drug therapy	Reduces reactive oxygen species (ROS) in the brain, enhances the inhibition of hydroxyl radicals, and reduces oxidative damage. Reduces the expression of pro-inflammatory factors and alleviates inflammation. Inhibition of neuronal apoptosis by regulating neuronal apoptosis-related pathway proteins.
Stem cell therapy	Rescue the normal function of nerve cells by restoring tissue damage caused by radiation.
Targeted drug therapy	Binding to the cell surface by specific small molecule antigens, thereby reducing the cytotoxicity of radiation-induced brain injury.

(1) Anti-inflammatory treatments encompass a range of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), steroidal drugs, COX inhibitors, and PPAR (peroxisome proliferator-activated receptor) agonists, all of which suppress inflammatory responses. Additionally, hydroxychloroquine, morphine, tetrahydrofuran, and methoxyquinoline are utilized, alongside dextrocorticoids and neuroprotective agents such as carbamazepine, which inhibits damaging oxygen free radicals. Furthermore, various vitamins and antioxidants, including vitamin E, vitamin C, and selenium, also play a role in anti-inflammatory treatment.[33,51,52] Clinically prescribed medications, including PPAR α and γ agonists, as well as RAS receptor blockers, prevent radiation-induced neuroinflammation and cognitive impairment. In addition, amifostine and hydrogen-rich water can attenuate damage caused by ionizing radiation by reducing inflammation and inhibiting oxidative stress through meso-oxygen and hydroxyl radicals.[53–57] Some scholars have utilized hydrogen-rich water to treat rats with radiation-induced brain injury. The results indicate that a specific dosage of hydrogen-rich water intervention can significantly reduce the inflammatory response in rat brain tissue and assist in the restoration of cognitive function. This effect may be mediated through signaling pathways related to factors such as PI3K and Akt.[58,59]

(2) Neural stem cell transplantation: NSCs transplantation is considered to be an effective treatment strategy for various neurological diseases, characterized by a central nervous system (CNS) repair mechanism that restores tissue damage and salvages lost function. Cellular sources of NSCs include fetal and adult CNS-derived NSCs, neural progenitor cells, and a wide range of non-neural stem cells such as mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). Since the function of normal NSCs may be adversely affected by radiation, there is a strong rationale for improving cognition after cranial irradiation based on the strategy of transplanting neural stem cells.[60,61] Many preclinical studies have focused on xenografting human pluripotent NSCs (embryonic stem cells, ESC) into rodent hosts, and irradiation of rats two days after intrahippocampal transplantation of human NSCs has improved hippocampal-dependent cognitive impairment and preserved neurogenesis.[35,62,63] A recent study examined the transplantation of human embryonic stem cell-derived oligodendrocytes into the brains of mice after a regimen of four weeks of fractionated irradiation at clinically relevant doses. The behavioral test results indicated that the cognitive function of C57BL/6J adult female mice was fully restored ten weeks post-oligodendrocyte brain transplantation. However, the recovery of motor function was found to necessitate the simultaneous transplantation of the cerebellum.[64] Simultaneously, the research team optimized a protocol for deriving and selectively enriching late-stage oligodendrocyte progenitor cells from human embryonic stem cells (ESCs). They demonstrated that these cells have the capability to remyelinate the brain and improve behavioral deficits. The clinical impact of these studies can be substantial as the need to address quality of life in cancer survivors grows more pressing.[65]

(3) Targeted drug therapy: Radiotargeted therapy is an emerging technology that consists of specific small molecule antigens, such as nuclides or isoforms, that can bind to the cell surface, thereby reducing the cytotoxicity of Radiation-induced brain injury. Bevacizumab is a humanized monoclonal antibody that blocks vascular endothelial growth factor (VEGF) and competitively inhibits the binding of VEGF to endothelial cell surface receptors, reducing endothelial cell proliferation and neovascularization, and reducing vascular permeability by binding to VEGF.[66] In a randomized, single-blind, prospective clinical study comparing bevacizumab with conventional corticosteroid therapy for Radiation-induced brain injury (RBI), 62.1% of patients in the bevacizumab group

experienced significant improvement in symptoms of RBI, compared with 42.6% in the conventional hormone therapy group. Furthermore, bevacizumab was demonstrated to reduce symptoms of Radiation-induced brain injury and enhance overall outcomes.[67] In addition to therapeutic approaches, emerging studies have suggested the potential utility of plasma-based biomarkers in detecting early radiation-induced brain injury, offering a non-invasive tool for patient monitoring and risk stratification.[68]

Summary and Outlook

At present, a large number of scientific studies have been conducted on the mechanism of injury and the prevention and treatment of RBI, and there are some medical measures to prevent the occurrence of Radiation-induced brain injury, such as the use of goggles, Optimize radiotherapy regimens and the avoidance of excessive use of radioactive technology.[69] At the same time, many drugs can also reduce RBI in clinical practice, and these drugs can also improve oxygen metabolism, promote nerve cell regeneration, reduce inflammatory response and vascular inflammation, prevent brain cell damage, and promote further recovery of brain function and performance. In addition to drug therapy, there are a number of other treatments for Radiation-induced brain injury, including radiotargeted therapy, spinal deformity modification, and psychological support. Finally, psychoactive care can help patients better cope with Radiation-induced brain injury, rebuild self-confidence, reduce anxiety and depression, and urge patients to implement effective rehabilitation therapies. There is a growing interest in the prevention of radiation injury, especially cognitive impairment caused by radiotherapy for head and neck tumors.

In addition, in recent years, a large number of animal experimental studies have found that many drugs have radiation protection effects, which are expected to become new radiation protection agents, following amifostine, with the in-depth study of the role and mechanism of hydrogen-rich water, it is clearly found that hydrogen-rich water can significantly improve cognitive and learning and memory dysfunction after RBI, to reduce the occurrence of Radiation-induced brain injury, its mechanism of action may be closely related to inhibiting nerve cell apoptosis, promoting vascular structural integrity and nerve cell regeneration, and improving and reshaping synaptic plasticity. The translation of these promising preclinical discoveries into clinical practice offers hope for improving the quality of life of patients with brain tumors after radiotherapy. However, the overall mechanism of the RBI is complex and sophisticated, and so far, there are still many detailed regulatory mechanisms and integration mechanisms that we are not fully aware of. Therefore, a more in-depth and comprehensive discussion is still needed for RBI to provide more experimental basis and theoretical basis for the clinical treatment of Radiation-induced brain injury.

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