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Whole Brain Radiation-Induced Cognitive Impairment: Pathophysiological Mechanisms and Therapeutic Targets

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Abstract

Radiation therapy, the most commonly used for the treatment of brain tumors, has been shown to be of major significance in tumor control and survival rate of brain tumor patients. About 200,000 patients with brain tumor are treated with either partial large field or whole brain radiation every year in the United States. The use of radiation therapy for treatment of brain tumors, however, may lead to devastating functional deficits in brain several months to years after treatment. In particular, whole brain radiation therapy results in a significant reduction in learning and memory in brain tumor patients as long-term consequences of treatment. Although a number of *in vitro* and *in vivo* studies have demonstrated the pathogenesis of radiation-mediated brain injury, the cellular and molecular mechanisms by which radiation induces damage to normal tissue in brain remain largely unknown. Therefore, this review focuses on the pathophysiological mechanisms of whole brain radiation-induced cognitive impairment and the identification of novel therapeutic targets. Specifically, we review the current knowledge about the effects of whole brain radiation on pro-oxidative and pro-inflammatory pathways, matrix metalloproteinases (MMPs)/tissue inhibitors of metalloproteinases (TIMPs) system and extracellular matrix (ECM), and physiological angiogenesis in brain. These studies may provide a foundation for defining a new cellular and molecular basis related to the etiology of cognitive impairment that occurs among patients in response to whole brain radiation therapy. It may also lead to new opportunities for therapeutic interventions for brain tumor patients who are undergoing whole brain radiation therapy.

Key Words: Whole brain radiation, Cognitive impairment, Reactive oxygen species, Inflammation, Extracellular matrix, Physiological angiogenesis

BRAIN TUMORS AND RADIATION THERAPY

Brain tumors are one of the most aggressive and detrimental forms of cancer. Approximately 210,000 cases of primary and metastatic brain tumors are estimated to be diagnosed each year in the United States (American Brain Tumor Association, 2012; National Brain Tumor Society, 2012). Indeed, brain tumors are the most common of the solid tumors in children and the second leading cause of cancer-related deaths in children under the age of 20. Although the exact cause of brain tumors is still unknown, several risk factors such as certain genetic disorders, environmental factors, and electromagnetic fields have been identified (Chandana *et al.*, 2008). Treatment options for brain tumors are selected based on a number of different factors including tumor type, location and size of tumor, tumor grade, and age and general health of the patient. It is generally accepted that standard treatments for brain tumors include surgery, chemotherapy, and radiation therapy. Table 1 summarizes the advantages and disadvantages of standard therapeutic approaches for patients with brain tumors.

Surgery is usually the first step in treatment of patients with most benign and malignant brain tumors. It is generally recommended to remove as much tumor as possible when a tumor is accessible, provide a tumor tissue sample (biopsy) for an accurate diagnosis, remove at least part of the tumor to relieve intracranial pressure, and reduce the amount of tumor to be treated with chemotherapeutic drugs or radiation. Clinical data have shown that a near-total resection is important in improving survival in patients with high-grade gliomas (Simpson *et al.*, 1993; Hess, 1999). Even though surgical procedure serves as an initial treatment method and has curative effect for intracranial tumors that are located in the outer portion of

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Table 1. Standard therapeutic options for brain tumor treatment

Treatment	Pros	Cons	References
Surgery	• Reduction of elevated intracranial pressure by safely removing tumor for preserving neurological function • Complete cure of symptoms in case of relatively benign tumors or low-grade brain tumors	• Difficulty of achieving a complete resection without damaging crucial structures and normal brain function near tumor site • Presence of inoperable cases due to the inaccessible distribution • Infection, bleeding, blood clots, blood pressure instability, neurological deficits, coma, and death	Cohadon (1990), Simpson *et al.* (1993), Hess (1999), Castro et al. (2003), Rampling *et al.* (2004), Koo *et al.* (2006), Mut (2012)
Chemotherapy	• Availability of various drugs and drug combinations • Improvement and enhancement in efficacy by bioengineering and advanced nanotechnology	• Restricted application due to insufficient delivery of drugs across the blood-brain barrier • Development of multi-drug resistance by cancer cells as well as microvascular endothelial cells • Immunosuppression, fatigue, bruises and bleeding, nausea, vomiting, diarrhea, and hair loss	Graham and Cloughesy (2004), Rampling *et al.* (2004), Koo *et al.* (2006), Buckner *et al.* (2007)
Radiation therapy	• Ease of administration • Limited damage to surrounding healthy tissues/cells by localized treatment • Non-invasive approach • Treatment for inoperable and/or metastatic brain tumors	• Cognitive impairment (learning and memory loss) • Hormonal alteration (growth hormone deficiency) • Radiation-mediated necrosis (brain swelling) • Risk of secondary malignancy	Sheline *et al.* (1980), New (2001), Denham and Hauer-Jensen (2002), Stone *et al.* (2003), Béhin and Delattre (2004), Moulder and Cohen (2007)

the brain, it may not be efficient for all malignant brain tumors. Deeply-seated tumors within the brain that are not accessible or tumors locating near critical or sensitive areas in the brain that control language, movement, vision, or other important functions cannot be surgically removed because of the excessive risk of neurological damage during the operation. Both general and specific risks to brain tumor surgery depend greatly on the extent of the procedure and include infection, bleeding, formation of blood clots, blood pressure instability, temporary or permanent neurological deficits, coma, and death (Cohadon, 1990; American Brain Tumor Association, 2012).

Chemotherapy uses one or more type of drug(s) to kill cancer cells. Even though chemotherapy alone gives mild advantage to treat brain tumors, it usually provides an adjuvant outcome in combination with surgery and radiation therapy. In fact, the survival benefit in the patients with high-grade gliomas was observed when they were treated with a combination of chemotherapy and radiation therapy (Hegi *et al.*, 2005; Stupp *et al.*, 2005). Although there have been great improvements in the development of chemotherapeutic agents for the treatment of brain tumors, the clinical applications of currently available drugs for brain tumors are very limited due to significant side effects and insufficient delivery. The common clinical side effects of chemotherapy for brain tumors include suppression of the immune system, fatigue, bruises, bleeding, nausea, vomiting, diarrhea, and hair loss. In addition, the presence of blood-brain barrier (BBB) has been identified as a major obstacle for chemotherapeutic treatment of brain tumors. While many efforts have been made to administer chemotherapy to brain tumors that circumvent the BBB in order to improve delivery of drugs, chemotherapy might not be suggested as an effective treatment method for brain tumors (Buckner *et al.*, 2007; American Brain Tumor Association, 2012).

Radiation therapy has been commonly used as the standard treatment for brain tumors (Tsao *et al.*, 2005; Khuntia *et al.*, 2006; Kantor *et al.*, 2008). It employs controlled high energy rays such as x-ray and γ-ray to either kill cancer cells directly or interfere with their ability to grow. Radiation can be given by either external or internal means; external radiotherapy is a critical component to treat brain tumors in many patients (Buckner *et al.*, 2007). For example, stereotactic radiosurgery delivers a high dose of radiation during a single session from an external source, such as gamma knife and linear accelerator (LINAC), to treat brain tumors. Whole brain radiation therapy is another way of providing external radiation and is commonly used to treat various brain tumors by administering ionizing radiation to the entire brain. Whole brain radiation therapy may be given before, during, or after chemotherapy, or following partial or complete surgical removal of brain tumors. In addition, whole brain radiation therapy can be used to treat inoperable brain tumors and metastatic tu-

mors that have spread to the brain from other part of the body. Walker *et al.* (1979) suggested dose-dependent effects of radiation on malignant gliomas by demonstrating the relationship between increased radiation therapy dose and increased survival. Other clinical trials demonstrated that post-operative radiation therapy provides significant survival benefits compared with surgery alone or chemotherapy (Andersen, 1978; Walker *et al.*, 1978). Additionally, recent advances in neuroimaging technologies with three-dimensional computerized treatment planning system and three-dimensional conformal radiotherapy (3D-CRT) have markedly enhanced efficacy and safety of radiation therapy (Bucci *et al.*, 2005). Therefore, radiation therapy has been shown to be of major significance in tumor control and survival rate of brain tumor patients (Sheline *et al.*, 1980). According to the Central Brain Tumor Registry of the United States (CBTRUS), about 200,000 patients with brain tumors are treated with either partial large-field or whole brain radiation every year in the United States (Stone *et al.*, 2004; Moulder and Cohen, 2007).

RADIATION THERAPY AND BRAIN INJURY

The use of radiation therapy for treatment of brain tumors is limited by the risk of radiation-induced damage to the normal, healthy brain tissue that can subsequently lead to devastating functional deficits (Sheline *et al.*, 1980; New, 2001; Denham and Hauer-Jensen, 2002; Stone *et al.*, 2003; Béhin and Delattre, 2004; Moulder and Cohen, 2007). Radiation-induced brain injury is classified as acute, early delayed (subacute), and late delayed reactions based on the timing of onset of symptoms (Tofilon and Fike, 2000; Kim *et al.*, 2008; Ramanan *et al.*, 2010). Acute injury, occurring 48 hours to weeks after whole brain radiation therapy, is fairly mild to moderate in severity and is involved in fatigue, hair loss, skin erythema, headache, nausea, drowsiness, and emesis. Early delayed (subacute) injury is observed 1 to 6 months after whole brain radiation therapy and is associated with the clinical symptoms of fatigue, somnolence, short-term memory loss, and transient demyelination. Even though acute and early delayed injuries can lead to severe medical conditions, it is generally believed that most of the symptoms and signs of these injuries are reversible. On the other hand, late delayed injury, occurring 6 months to several years after whole brain radiation therapy, is considered irreversible and progressive and is characterized by demyelination, vascular abnormalities, and ultimate white matter necrosis (Schultheiss and Stephens, 1992).

Previous studies have demonstrated that late delayed injury is largely responsible for cognitive impairment (DeAngelis *et al.*, 1989; Roman and Sperduto, 1995; Akiyama *et al.*, 2001; Johannesen *et al.*, 2003; Bentzen, 2006; Shi *et al.*, 2006; Welzel *et al.*, 2008; Douw *et al.*, 2009; Warrington *et al.*, 2012). Indeed, progressive impairments in learning and memory were observed in 40-50% of brain tumor patients as long-term consequences of radiation therapy. Recent randomized, prospective human clinical trials also provide evidence that the addition of whole brain radiation to stereotactic radiosurgery may cause a significant reduction in learning and memory in patients with brain tumors (Chang *et al.*, 2009). Consistent with the human studies, a significant deterioration

Table 2. Types of radiation-induced brain injury

Type of injury	Test	Doses (Total/fractions)	Species	References
Cognitive impairment	• Morris water maze test	25 Gy/single	Rat	Akiyama *et al.* (2001)
		10, 20, and 40 Gy/single	Rat	Liu *et al.* (2010b)
		20 Gy/4 and 40 Gy/8	Rat	Zhou *et al.* (2011)
	• Auditory verbal learning test, Medical College of Georgia Complex figures test, Attentional performance test, Multiple-choice test of vocabulary knowledge	40 Gy/20 and 36 Gy/18	Human	Welzel *et al.* (2008)
	• Letter-digit substitution test, Concept-shifting test, Stroop color-word test, Visual verbal learning test, Memory comparison test, Categoric word fluency	56.6 ± 7.0 Gy/30.6 ± 3.9	Human	Douw *et al.* (2009)
	• Behavior tests (IntelliCage)	6 Gy/single	Mouse	Barlind *et al.* (2010)
	• Barnes maze test	36 Gy/8	Mouse	Warrington *et al.* (2012)
Growth hormone deficiency	• Insulin tolerance test, Growth hormone-releasing hormone-arginine stimulation test	53.5 ± 10.0 Gy (Biological effective dose)	Human	Darzy *et al.* (2005)
	• Growth hormone-releasing hormone-arginine stimulation test	59.4 Gy (50.1-60) /29.7	Human	Sara *et al.* (2011)
		55.1 ± 5.0 Gy/29.1 ± 1.5	Human	Quik *et al.* (2012)
Motor dysfunction	• Spontaneous motor activity test	6 Gy/single	Mouse	Manda *et al.* (2007)

of memory function was observed in aged rats over a 7-month period post-radiation therapy (Lamproglou *et al.*, 1995). Yoneoka *et al.* (1999) found a similar, late onset of cognitive impairment in adult rats at 12 months following cranial irradiation. Additionally, a fractionated dose of γ-ray irradiation to rats resulted in a significant increase in working memory errors primarily at 6 and 9 months (Brown *et al.*, 2007). Moreover, it was found that a clinically relevant regimen of fractionated whole brain radiation led to significant impairments in spatial learning and reference memory in rats (Shi *et al.*, 2006). Furthermore, our most recent study demonstrated that a clinical fractionated series of whole brain radiation induces a transient deficit in contextual learning, disruption of working memory, and progressive impairment of special learning in mice (Warrington *et al.*, 2012). In addition to cognitive impairment, whole brain radiation causes other brain injuries including growth hormone deficiency and motor dysfunction (Table 2) (Darzy *et al.*, 2005; Manda *et al.*, 2007; Sara *et al.*, 2011; Quik *et al.*, 2012). Although there have been significant developments in understanding pathophysiological mechanisms as summarized in Table 3, limited information on the etiology of radiation-induced damage to normal brain tissue is currently available. In particular, the cellular and molecular mechanisms responsible for whole brain radiation therapy-mediated cognitive impairment remain largely unknown. At present, there are no successful treatments or effective preventive strategies for radiation-induced brain injury. Therefore, the present review specifically focuses on three pathophysiological mechanisms by which whole brain radiation induces cognitive impairments; (1) effects of radiation therapy on oxidative stress and inflammation in brain, (2) effects of radiation therapy on matrix metalloproteinases and extracellular matrix in brain, and (3) effects of radiation therapy on physiological angiogenesis in brain. It will help identify therapeutic targets for novel preventive and treatment approaches for brain tumor patients who suffer from significant side effects after whole brain radiation therapy.

Radiation therapy and inflammation in brain

The pro-oxidative and pro-inflammatory environments have been implicated in the pathophysiological process of brain injury and subsequent development of various neurodegenerative diseases (McGeer and McGeer, 1995; Dheen *et al.*, 2007). Indeed, oxidative stress can induce expression of pro-inflammatory mediators, such as cytokines, chemokines, and adhesion molecules, *via* redox-responsive transcription factor-mediated molecular signaling pathways. It is well known that expression of pro-inflammatory genes is up-regulated by increased oxidative stress through activation of a variety of transcription factors, such as activator protein-1 (AP-1), nuclear factor-κB (NF-κB), cAMP responsive element-binding protein (CREB), specificity protein-1 (SP-1), and signal transducers and activators of transcription (STATs) (Wung *et al.*, 1997; Verhasselt *et al.*, 1998; Lakshminarayanan *et al.*, 1998; Simon *et al.*, 1998; Bouloumie *et al.*, 1999; Grösch and Kaina, 1999; Park *et al.*, 2001; Lee *et al.*, 2001a; Lee *et al.*, 2001b; Lee *et al.*, 2001c; Lee *et al.*, 2001d; Flora *et al.*, 2002; Lee *et al.*, 2003; Lee *et al.*, 2010b).

Evidence suggests that oxidative stress-mediated overexpression of pro-inflammatory mediators is associated with brain microvascular endothelial cell dysfunction and BBB

Table 3. Pathophysiological mechanisms of whole brain radiation-induced cognitive impairment

Mechanisms of action	Biomarker	Doses (Total/fractions)	Species	References
Oxidative stress	• MDA	10 Gy (single)	M	Limoli *et al.* (2004)
	• ROS, NF-κB, PAI-1, NOX4	1-10Gy (single)	R	Collins-Underwood *et al.* (2008)
Inflammation	• COX-2, TNF-α, IL-1β, IL-6, iNOS, ICAM-1, MIP-2, MCP-1	5-35 Gy (single)	M	Kyrkanides *et al.* (2002)
	• TNF-α, IL-1β, MCP-1	10 Gy (single)	R	Lee *et al.* (2010b)
	• c-Jun, TNF-α, IL-1β, IL-6, COX-2	10 Gy (single)	M	Deng *et al.* (2012)
Extracellular matrix	• MMPs, TIMPs, Collagen type IV	10 Gy (single), 40 Gy/8	R, M	Lee *et al.* (2012)
	• EMMPRIN	GKS (Max. 75 Gy)	R	Wei *et al.* (2012)
Physiological angiogenesis	• VEGF, Ang-1, Ang-2, Tie-2	10 Gy (single)	R	Lee *et al.* (2011)
	• VEGF	GKS (Max. 75 Gy)	R	Wei *et al.* (2012)
Stem/progenitor cell death	• Caspase-3, p53, Nitrotyrosine, AIF	8 Gy (single)	R	Fukuda *et al.* (2005)
	• PARP, Annexin V, γ-HA2X	1-5 Gy (single)	H	Acharya *et al.* (2010)
Impaired neurogenesis	• NeuN, Tuj1, GFAP, NG2	10 Gy (single)	R	Monje *et al.* (2003)
	• Ki-67, DCX, NeuN, GFAP, NG2, CD68	2-10 Gy (single)	M	Rola *et al.* (2004)

MDA: Malondialdehyde, ROS: Reactive oxygen species, NF-κB: Nuclear factor-κB, PAI: Plasminogen activator inhibitor, NOX: NADPH oxidase, COX: Cyclooxygenase, TNF: Tumor necrosis factor, IL: Interleukin, iNOS: Inducible nitric oxide synthase, ICAM: Intercellular adhesion molecule, MIP: Monocyte inflammatory protein, MCP: Monocyte chemoattractant protein, MMP: Matrix metalloproteinase, TIMP: Tissue inhibitor of metalloproteinases, EMMPRIN: Extracellular matrix metalloproteinase inducer, VEGF: Vascular endothelial growth factor, Ang: Angiopoietin, Tie: Endothelial receptor tyrosine kinase, p53: Tumor suppressor protein 53, AIF: Apoptosis inducing factor, PARP: Poly (ADP-ribose) polymerase, γ-HA2X: Phosphorylated histone H2A, NeuN: Neuron-specific nuclear protein, Tuj1: Neuron-specific class III β-tubulin, GFAP: Glial fibrillary acidic protein, NG2: Chondroitin sulfate proteoglycan, DCX: Doublecortin, CD68: Cluster of differentiation 68, GKS: Gamma knife surgery, M: Mouse, R: Rat, H: Human.

disruption leading to the initiation and progression of neurodegenerative diseases. For example, amyloid β (Aβ) peptides contribute to pathogenesis in Alzheimer's disease (AD) through pro-oxidative and pro-inflammatory mechanisms. Previous studies have shown that Aβ-induced oxidative stress in brain can lead to an inflammatory cascade via secretion of interferon-γ (IFN-γ) and interleukin-1β (IL-1β), as well as expression of CD40 in human brain microvascular endothelial cells (Suo *et al.*, 1998; Akiyama *et al.*, 2000). It was also demonstrated that Aβ increases the ability of monocytes/macrophages to infiltrate into brain tissue across the BBB (Fiala *et al.*, 1998; Giri *et al.*, 2002). Additionally, oxidative stress and inflammation in brain have been suggested to actively participate in the neurodegenerative process of Parkinson's disease (PD) (McGeer *et al.*, 2001; Schulz and Falkenburger, 2004). Degeneration of nigral dopaminergic neurons was observed in both an inflammation-mediated rat model and an *in vitro* cell culture model of PD (Liu and Hong, 2003). It was also found that cyclooxygenase-2 (COX-2) expression was induced specifically within the substantia nigra pars compacta (SNpc) dopaminergic neurons in human postmortem PD specimens and in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD during the destruction of the nigrostriatal pathway (Teismann *et al.*, 2003). Furthermore, treatment with antioxidant compounds or non-steroidal anti-inflammatory drugs (NSAIDs) exhibited beneficial effects such as delaying the onset or slowing the progression of neurodegenerative diseases including AD and PD (McGeer and McGeer, 1995; Akiyama *et al.*, 2000). These findings provide compelling evidence that oxidative stress-mediated inflammatory responses in brain play a significant role in the pathogenesis of neurological disorders.

Recent evidence has identified oxidative stress and inflammation as important pathways leading to radiation-induced brain injury (Hong *et al.*, 1995; Olschowka *et al.*, 1997; Chiang *et al.*, 1997; Kim *et al.*, 2002; Denham and Hauer-Jensen, 2002; Gaber *et al.*, 2003; Baluna *et al.*, 2006). For example, a marked elevation of COX-1/-2 activity and subsequent production of prostaglandin E_2 (PGE_2) synthesis in brain following ionizing radiation augments central nervous system (CNS) inflammation through up-regulation of a variety of pro-inflammatory mediators including tumor necrosis factor-α (TNF-α), IL-1β, IL-6, inducible nitric oxide synthase (iNOS), intercellular adhesion molecule-1 (ICAM-1), and matrix metalloproteinase-9 (MMP-9) (Kyrkanides *et al.*, 2002; Moore *et al.*, 2005). Enhanced expression of adhesion molecules, such as ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, was also observed in irradiated brains (Hong *et al.*, 1995; Olschowka *et al.*, 1997; Gaber *et al.*, 2003; Baluna *et al.*, 2006).

Radiation has been reported to up-regulate expression of pro-inflammatory cytokines and chemokines in brain. A rapid induction of gene expressions of the pro-inflammatory cytokines, such as TNF-α and IL-1β, in response to radiation has been implicated in radiotherapy-associated damages to the brain (Hong *et al.*, 1995; Gaber *et al.*, 2003). Moreover, a significant and marked up-regulation of mRNA and protein expression of pro-inflammatory mediators, including TNF-α, IL-1β, and monocyte chemoattractant protein-1 (MCP-1), was observed in hippocampal and cortical regions isolated from irradiated brains. Interestingly, cytokine expression was regionally specific since TNF-α levels were significantly elevated in cortex compared to hippocampus and IL-1β levels were elevated in hippocampus compared to cortical samples. A series of electrophoretic mobility shift assays (EMSA) also demonstrated that whole brain radiation significantly increased activation of pro-oxidative and pro-inflammatory transcription factors including AP-1, NF-κB, and CREB. (Raju *et al.*, 2000; Lee *et al.*, 2010b). Furthermore, both *in vitro* and *in vivo* studies showed that whole brain radiation-induced pro-inflammatory environments in the brain may be, at least in part, mediated through activation of microglia, suggesting the potential contribution of specific type of cells to the overexpression of pro-inflammatory mediators in the brain after radiation (Lee *et al.*, 2010b; Conner *et al.*, 2011). These data provide robust evidence indicating that oxidative stress-mediated inflammation is one of the major consequences of whole brain radiation and plays a pivotal role in subsequent radiation-induced tissue injury to normal brain. These studies may contribute to a deeper understanding of the pathophysiological mechanisms responsible for radiation-induced brain injury at the cellular and molecular levels. More importantly, it may provide a foundation for the development of novel strategies for prevention and treatment of radiation-induced brain injury specifically targeted against pro-oxidative and pro-inflammatory pathways.

In contrast, acute immune responses in cancer patients undergoing radiation therapy may have positive effects. Sepah and Bower (2009) detected higher levels of pro-inflammatory cytokines, such as IL-1β and IL-6, in early-stage breast and prostate cancer patients after radiation treatment, suggesting that the acute inflammatory responses may facilitate normal tissue repair processes. It is well known that aging is an important prognostic factor in determining the response of brain tumors to radiation therapy (Flowers, 2000; Schindler *et al.*, 2008). Clinical studies have shown that the use of radiation therapy for treatment of malignant gliomas resulted in significantly lower survival rates for patients older than 70 years of age compared with those for patients aged 70 and younger (Peschel *et al.*, 1993; Villà *et al.*, 1998). In addition, patients aged 50 or under survived longer than patients over 50 after radiation therapy due to inherent differences in the sensitivity of clonogenic cells to radiation (Rosenblum *et al.*, 1982). These studies clearly indicate that aging exerts a profound effect on the efficacy of radiation therapy for treatment of brain tumors. Although it is generally believed that the immune responses and the effectiveness of radiation therapy decline with age, the association among aging, inflammation, and radiation therapy remains to be further investigated. Our recent data demonstrated that radiation-induced acute inflammatory responses, such as overexpression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6), adhesion molecules (e.g., ICAM-1, VCAM-1, and E-selectin), chemokine (e.g., MCP-1), and matrix metalloproteinases (e.g., MMP-9), were significantly impaired in aged brain (Lee *et al.*, 2010a). The impaired response to whole brain radiation with age appears to reveal a generalized attenuation of the cellular response to damage and a reduced capacity of aging tissues to induce essential repair systems necessary for cellular maintenance. Additionally, these data contribute to a better understanding of age-dependent changes in radiation-mediated immune and inflammatory responses in brain and may lead to the development of effective treatment strategies for brain tumor patients who are undergoing radiation therapy.

Since the induction of both pro-oxidative and pro-inflamma-

Table 4. Therapeutic targets against whole brain radiation-induced cognitive impairment

Target pathway	Therapeutics	Mechanisms of action	References
Oxidative stress	• α-Tocopherol, α-lipoic acid, melatonin, bitter leaf extract	Antioxidant properties	Chan *et al.* (2004), Erol *et al.* (2004), Manda *et al.* (2007), Owoeye *et al.* (2011)
	• Cu(II), Mn(IV), V(IV) 2-methyl-aminopyridine complexes	SOD mimetic activities	Abou-Seif *et al.* (2003)
	• EUK-207, EUK-451	SOD/catalase mimetic activities	Vorotnikova *et al.* (2010)
Inflammation	• Indomethacin	NSAIDs	Monje *et al.* (2003)
	• Ramipril	Anti-inflammatory ACE inhibitor	Jenrow *et al.* (2010), Kim *et al.* (2004)
	• Pioglitazone	Anti-inflammatory PPARγ agonist	Zhao *et al.* (2007)
	• Fenofibrate	Anti-inflammatory PPARα agonist	Ramanan *et al.* (2009)
	• L-165041	Anti-inflammatory PPARδ agonist	Schnegg *et al.* (2012)
	• Atorvastatin	Anti-inflammatory statins	Jenrow *et al.* (2011)
	• Tamoxifen	Anti-inflammatory activity	Liu *et al.* (2010a)
Physiological angiogenesis	• Hypoxia	Recovery of vessel rarefaction	Warrington *et al.* (2012)
	• Gammaphos	Prevention of endothelial cell loss	Lyubimova and Hopewell (2004)
	• Bevacizumab	Reduction of capillary leakage	Gonzalez *et al.* (2007)
Neurogenesis	• Human embryonic stem cells	Delivery of stem/precursor cells	Acharya *et al.* (2009)
	• Human neural stem cells	Replacement of neural stem cells	Acharya *et al.* (2011)

SOD: Superoxide dismutase, NSAIDs: Non-steroidal anti-inflammatory drugs, ACE: Angiotensin-converting enzyme, PPAR: Peroxisomal proliferator-activated receptor.

tory pathways in brain plays crucial roles in the pathophysiological mechanisms of radiation-mediated brain injury, therapies selectively targeting these pathways have shown great potentials in protecting the brain from damages (Table 4). Indeed, a variety of therapeutics with antioxidant activity has been identified as radioprotectors against brain injury. Human clinical study revealed significant improvements in global cognitive ability, memory, and executive function among patients with nasopharyngeal carcinoma who received α-tocopherol, the most biologically active form of vitamin E and a fat-soluble antioxidant, for 1 year after radiation therapy (Chan *et al.*, 2004). Pre-treatment with α-lipoic acid, a widely available over-the-counter nutritional supplement in the United States, prior to whole body x-ray irradiation resulted in a significant neuroprotection by attenuating oxidative stress in cerebellum and recovering cognitive dysfunction in irradiated mice (Manda *et al.*, 2007). Additionally, radioprotective actions of melatonin (N-acetyl-5-methoxytryptamine), a naturally occurring hormone with powerful antioxidant property, have demonstrated the potential clinical use for prevention of oxidative stress-mediated brain damage induced by ionizing radiation (Erol *et al.*, 2004; Undeger *et al.*, 2004; Shirazi *et al.*, 2007). Recent study also showed that pre-administration of the methanol extract of *Vernonia amygdalina* leaf, a well-known for its antioxidant activity, significantly mitigated the radiation-induced gross morphometry changes in rat brain, such as reduction of the relative weight of the whole brain, relative weight of the cerebellum, the maximum width, rostrocaudal dimension, and dorsoventral extent of the cerebellum (Owoeye *et al.*, 2011). In addition to antioxidants, anti-inflammatory approaches have been employed as therapeutic strategies to radiation-induced brain injury. Monje *et al.* (2003) showed that inflammatory blockade with indomethacin, one of the most common NSAIDs, restored the imapired neurogenesis caused by cranial irradiation. Administration of another anti-inflammatory drug pioglitazone, a peroxisomal proliferator-activated receptor (PPAR) agonist, prior to, during, and up to 4- or 54-weeks after fractionated whole brain radaition significantly recovered the radiation-induced cognitive impairment in rats (Zhao *et al.*, 2007; Ramanan *et al.*, 2010). Moreover, treatment of rats with ramipril, one of the angiotensin-converting enzyme (ACE) inhibitors with anti-inflammatory activity, significantly ameriolated radiation-induced brain damage (Kim *et al.*, 2004; Ryu *et al.*, 2007; Jenrow *et al.*, 2010). Furthermore, chronic administration of atorvastatin, a member of drug class known as statins which have also shown to possess antioxidant and anti-inflammatory properties (Kim *et al.*, 2008), and ramipril exhibited combined protective effects against radiation-induced impairment of hippocampal neurogenesis in rats (Jenrow *et al.*, 2011). These studies provide compelling evidence that pharmacological strategies designed to selectively target oxidative stress- and inflammation-dependent pathways in brain could reduce radiation-induced damages to normal brain tissue.

Radiation therapy and extracellular matrix in brain

The BBB is a complex neuroprotective system consisting of brain microvascular endothelial cells, astrocytes, pericytes, and basement membrane (Rubin and Staddon, 1999). It provides a highly selective barrier that tightly regulates the exchange of materials and cells between the circulation and brain tissue (Abbott *et al.*, 2006). Under physiological conditions, the BBB restricts and controls the movement of various chemical substances and macromolecules to maintain the brain homeostasis that is essential for the normal operation

of the nervous system (Banerjee and Bhat, 2007). In some cases, however, the BBB becomes disrupted or modified as a consequence of various pathological insults (Banerjee and Bhat, 2007). Indeed, alteration or disruption of the BBB is commonly found in patients with neurological disorders, such as stroke, traumatic brain injury (TBI), AD, PD, and HIV-1 dementia (Staddon *et al.*, 1995; Rubin and Staddon, 1999; Toborek *et al.*, 2005; Banerjee and Bhat, 2007).

Studies have shown that alterations in the BBB may be responsible for injury to the normal brain tissue after radiation therapy (Diserbo *et al.*, 2002; Nordal and Wong, 2005). For example, radiation mediates disruption of the BBB by damaging the structural and functional integrity of the microvasculature in brain (Baker and Krochak, 1989; Rubin *et al.*, 1994). In addition, Delattre *et al.* (1989) demonstrated that cranial irradiation (CRT) markedly increased regional capillary permeability and capillaries of normal brain tissue are more sensitive to the acute effects of CRT than capillaries found in brain tumors. It was also found that BBB permeability was significantly increased in rat brain after whole brain and whole body irradiation (d'Avella *et al.*, 1992; Diserbo *et al.*, 2002). Furthermore, evidence from other *in vivo* studies has revealed a rapid increase in BBB breakdown in response to interstitial brachytherapy (Fike *et al.*, 1985; Groothuis *et al.*, 1987; Bernstein *et al.*, 1990). The cellular and molecular mechanisms by which radiation induces BBB disruption, however, remain unsolved.

The extracellular matrix (ECM) is a complex of various proteins and proteoglycans, including collagens, laminin, fibronectin, and tenascin (Paulsson, 1992). Besides acting as a physical barrier to the passage of macromolecules and cells, ECM separates adjacent tissues, provides mechanical support for cell attachment, and serves as a substratum for cell migration and a medium of communication between cells (Rutka *et al.*, 1988; Paulsson, 1992; Tilling *et al.*, 2002). In particular, since ECM proteins are major molecular constituents of the basement membrane and maintain the integrity of the BBB, degradation and consequent rearrangement of ECM are critically involved in the breakdown of the BBB. For example, the injection of bacterial collagenase to rat brain resulted in degradation of ECM, disruption of basement membrane, and an increase in BBB permeability (Rosenberg *et al.*, 1993). In addition, an increased degradation of collagen type IV was found to be significantly associated with BBB disruption in a rat model of bacterial meningitis (Sellner and Leib, 2006) and a mouse model of herpessimplex virus (HSV) encephalitis (Sellner *et al.*, 2006). Tilling *et al.* (1998) also reported that ECM constituents such as collagen type IV, fibronectin, and laminin significantly increased the transcellular electrical resistance of primary brain microvascular endothelial cells in an *in vitro* model of BBB, indicating that these proteins play an important role in enhancing barrier properties.

The matrix metalloproteinases (MMPs) are a large family of ECM-degrading enzymes and have been implicated in the pathophysiological processes of neurodegenerative diseases by causing BBB disruption (Mun-Bryce and Rosenberg, 1998; Romanic *et al.*, 1998; Strup-Perrot *et al.*, 2005). Indeed, in a variety of physiological and pathological conditions, MMPs become activated and play a key role in degradation of the ECM proteins (Planas *et al.*, 2001; Kim and Joh, 2012). Depending on substrate specificity and structural differences, MMPs are subdivided into gelatinases (MMP-2 and -9), collagenases (MMP-1, -8, -13, and -18), stromelysins (MMP-3, -10, and -11), matrilysins (MMP-7 and -26), metalloelastase (MMP-12), and membrane-type (MT) MMPs (MMP-14, -15, -16, -17, -24, and -25) (Romanic *et al.*, 1998; Visse and Nagase, 2003; Strup-Perrot *et al.*, 2005). In particular, the gelatinases MMP-2 and MMP-9, the most commonly investigated MMPs in the CNS, are able to degrade ECM components including collagen type IV which is essential for maintaining BBB integrity (Kim and Joh, 2012). The enzymatic activity of MMPs is regulated by tissue inhibitors of metalloproteinases (TIMPs), the endogenous inhibitors with a higher affinity for specific MMPs (Aoudjit *et al.*, 1999; Lukes *et al.*, 1999). For example, TIMP-1 inhibits MMP-9 activity by forming a specific complex with MMP-9, whereas MMP-2 is bound by TIMP-2 (Aoudjit *et al.*, 1999; Wang *et al.*, 2000; Giannelli *et al.*, 2002; Sellner and Leib, 2006). Therefore, a favorable balance of MMPs/TIMPs system plays a pivotal role in maintaining normal homeostasis in the CNS which is essential for preventing neurological disorders (Gardner and Ghorpade, 2003; Kim and Joh, 2012).

Evidence from *in vivo* and *in vitro* studies has demonstrated that MMPs and TIMPs are associated with radiation-induced damage to various tissues. For example, the overexpression of MMP-2 and MMP-9 was observed in lung after thoracic irradiation (Yang *et al.*, 2006; Yang *et al.*, 2007). Araya *et al.* (2001) have reported that radiation causes a significant elevation of MMP-2 production but no effect on TIMP-2 in human airway epithelial cells after irradiation, indicating the balance between MMP-2 and TIMP-2 was in favor of MMP-2 promoting proteolysis. Additionally, the use of pelvic radiation therapy for prostate cancer patients resulted in significant increases in MMP-2 and MMP-9 activity in rectal mucosa (Hovdenak *et al.*, 2002). It was also found that abdominal irradiation led to a significant elevation in MMP-2 and MMP-14 levels in rat ileum (Strup-Perrot *et al.*, 2005). Moreover, radiation-mediated upregulation of MMP-2 expression has been observed in various cell types, including astrocytes, endothelial cells, and epithelial cells (Sawaya *et al.*, 1994; Nirmala *et al.*, 2000; Zhao *et al.*, 2004). Furthermore, recent study provides evidence that whole brain radiation differentially regulates MMPs/TIMPs system in brain and an imbalance between MMP-2 activity and TIMP-2 expression may have an important role in the pathogenesis of radiation-induced brain injury by degrading ECM components of the BBB basement membrane (Lee *et al.*, 2012). These findings may contribute to defining a novel cellular and molecular basis for radiation-induced BBB disruption and subsequent brain injury that will lead to new opportunities for preventive and therapeutic interventions for brain tumor patients who are undergoing radiotherapy. Further studies, however, are necessary to elucidate the exact mechanistic links among MMPs/TIMPs system, ECM degradation, and BBB disruption in brain after whole brain radiation therapy.

Based on previous studies related to the pivotal role of ECM in normal homeostasis in brain, strategies aimed at blocking ECM degradation or modulating MMPs/TIMPs system in brain may be attractive for preventing and/or attenuating radiation-induced brain injury. One potential experimental approach is to administer a series of pharmacological agents that selectively inhibit MMPs by different mechanisms of action, including minocycline, simvastatin, AG3340, DPC-A37668, GM6001, PD166793, and Ro-31-9790 (Barnett *et al.*, 2007; Garcia-Alloza *et al.*, 2009; Krishnamurthy *et al.*, 2009), to animal models of whole brain radiation therapy which can lead

to identification of novel drugs for prevention and/or treatment for radiation-induced brain injury. However, there are no reports demonstrating therapeutic approaches targeting ECM or MMPs/TIMPs system in irradiated brain.

Radiation therapy and physiological angiogenesis in brain

Angiogenesis is the process of developing new blood vessels from pre-existing vessels. It has been known to play critical roles not only in many physiological processes such as embryonic development and wound healing, but also in the development of a number of pathological conditions including progression of tumors. These events are characterized by the dynamic, temporally and spatially coordinated interactions among endothelial cells, angiogenic factors, and ECM proteins (Miller *et al.*, 1994; Hanahan, 1997). One of the most important and extensively studied angiogenic factors is vascular endothelial growth factor (VEGF) which has a potent and specific activity for the vascular endothelium (Ferrara, 1999; Ribatti, 2005; Tammela *et al.*, 2005). VEGF and its receptors serve to initiate endothelial cell proliferation, endothelial cell migration, and production of new capillary sprouts, which promote vasculogenesis and angiogenesis (Breier *et al.*, 1992; Plate, 1999; Ferrara *et al.*, 2003). VEGF is also considered as a survival factor for endothelial cells by protecting them from apoptosis (Ferrara, 1999; Alavi *et al.*, 2003). In addition to VEGF, angiopoietins are a second family of vascular regulatory molecules that are also specific for the vascular endothelium involving in both physiological and pathological blood vessel generation (Davis *et al.*, 1996). Although angiopoietin-1 (Ang-1) is not directly associated with endothelial cell proliferation (Davis *et al.*, 1996), it mediates interactions between the endothelium and the surrounding matrix, which leads to stimulation of EC migration (Witzenbichler *et al.*, 1998), sprouting (Koblizek *et al.*, 1998), and tubule formation (Hayes *et al.*, 1999). Indeed, Ang-1 is necessary for subsequent vascular remodeling as well as vessel maturation and stabilization, while VEGF plays an active role during the early stages of vessel development (Sato *et al.*, 1995). All angiopoietin families, such as Ang-1, -2, -3, and -4, bind to the endothelial receptor tyrosine kinase (Tie-2) which is typically expressed by vascular endothelial cells (Peters *et al.*, 2004). The balance of Ang-1/Tie-2 system has been known to be necessary for vessel maturation and stabilization (Sato *et al.*, 1995). Ang-2 serves as a functional antagonist of Ang-1. By blocking Tie-2 signaling, Ang-2 leads to a loosening of tight vascular structure (Maisonpierre *et al.*, 1997; Mandriota and Pepper, 1998; Yancopoulos *et al.*, 2000). This loosening of cell-matrix and cell-cell interactions allows the endothelial cells to become more sensitive and responsive toward the other angiogenic factors such as VEGF. For example, in the absence of the activating signal from VEGF, Ang-2 promotes endothelial cell death and subsequently leads to rarefaction of vessels. In the presence of high expression levels of VEGF, however, the process of physiological angiogenesis is facilitated by Ang-2 (Mandriota and Pepper, 1998; Yancopoulos *et al.*, 2000). These studies suggest that a dynamic interplay among angiogenic factors, such as Ang-1, Ang-2, Tie-2, and VEGF, plays a key role in regulating various aspects of physiological angiogenesis (Fig. 1).

It is widely believed that radiation-mediated injury to normal tissues including brain is a consequence of acute and late damages to the microvascular endothelium (Dimitrievich *et al.*, 1984; Baker and Krochak, 1989; Ljubimova *et al.*, 1991; Roth *et al.*, 1999; Nguyen *et al.*, 2000). Several studies have identified microvascular networks as the most sensitive part in response to the radiation therapy and demonstrated the critical role of microvasculature in the pathogenesis of radiation-induced damages to normal tissues. For example, an increased permeability and an irregular proliferation of endothelial cells of microvasculature were observed in irradiated normal tissues (Baker and Krochak, 1989). Results from early and late effects of ionizing radiation on the normal tissue microvascular networks showed adverse alterations in the structure and function of microvasculatures such as significant decreases in vessel diameter and capillary surface area, a significant increase in vessel hematocrit, and a significant reduction of blood flow in locally irradiated hamster cremaster muscles (Roth *et al.*, 1999; Nguyen *et al.*, 2000). A number of previous studeis also suggest that radiation-induced early and persistent damages to the microvasculature may be responsible for cerebral vessel rarefaction leading to brain injury including cognitive impairments. Brown *et al.* (2005) revealed that fractionated whole brain radiation, a clinically relevant regimen of radiation therapy for brain tumor patients, substantially decreased both vessel density and length in rat brains at 10 weeks post-irradiation. A significant decrease in vessel density in rat brain with cognitive impairment was also observed from 10 weeks to 52 weeks after fractionated whole brain radiation, suggesting a potential role for loss of cerebral capillary in radiation-induced dementia (Brown *et al.*, 2007). Recent studies further confirmed the whole brain radiation-induced cerebral microvascular rarefaction and cognitive impairments (Warrington *et al.*, 2011; Warrington *et al.*, 2012). It was also found that a single exposure of rat brain strongly decreased cerebral blood flow (CBF) at 12 and 18 months after radiation (Keyeux *et al.*, 1997).

Recent evidence has demonstrated that the reduction of the number of endothelial cells may be responsible for the radiation-induced decrease in vessel density in brain. For example, the local irradiation of the rat brain caused a progressive and dose-related depletion in endothelial cells in the choroid plexus (Calvo *et al.*, 1987). A dose-dependent decrease in endothelial cell number was also observed in rat brain within 24 hours and maintained for up to 1 month after irradiation (Ljubimova *et al.*, 1991). In addition, Lyubimova and Hopewell

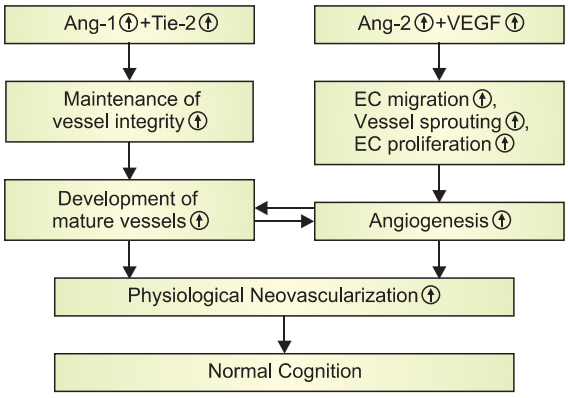

Fig. 1. Dynamic interaction among Ang-1, Ang-2, Tie-2, and VEGF in the regulation of physiological angiogenesis and cognition.

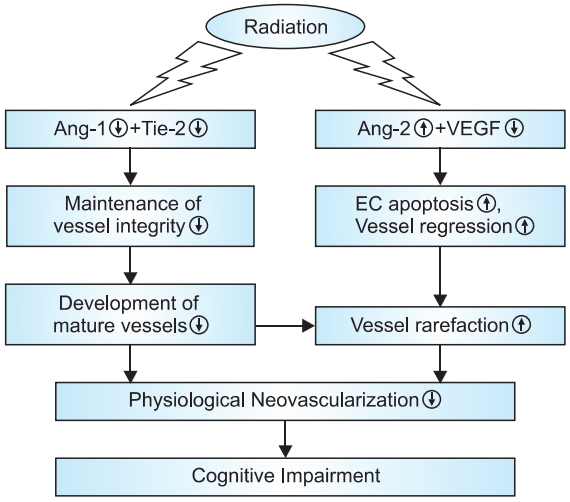

Fig. 2. Effects of whole brain radiation on physiological angiogenesis and cognition.

(2004) observed the time-dependent changes in endothelial cell number in rat brain for up to 65 weeks after irradiation. The initial marked loss of endothelial cells and the subsequent slow decline in endothelial cell density were detected at 24 hours and between 26 and 52 weeks after irradiation, respectively. These studies clearly indicate that cerebrovascular endothelial cells are the primary target cell population in the radiation-induced brain injury. Moreover, a radiation-mediated dose- and time-dependent induction of apoptosis of endothelial cells was observed in mouse central nervous system including spinal cord sections and multiple regions of the brain (medulla, pons, and hippocampus), suggesting that radiation-induced loss of endothelial cells in brain is mediated by apoptotic cell death (Peña *et al.*, 2000). Results from our recent study further confirmed that whole brain radiation significantly reduced endothelial cell density in brain by increasing endothelial cell apoptosis and decreasing endothelial cell proliferation (Lee *et al.*, 2011). A significant decrease in mRNA and protein expression of Ang-1, Tie-2, and VEGF was also detected in irradiated rat brains compared with sham-irradiated controls, while whole brain radiation significantly up-regulated Ang-2 mRNA and protein expression (Lee *et al.*, 2011). This study provides evidence for the first time that radiation-mediated differential regulation of various angiogenic factors may be responsible for attenuating physiological angiogenesis resulting in vessel rarefaction in irradiated brain (Fig. 2).

Although more detailed mechanisms of radiation-induced vessel rarefaction in brain remain to be further investigated, recovering cerebrovascular rarefaction by facilitating physiological angiogenesis in brain sounds a reasonable approach as therapeutic intervention strategy for treatment of radiation-induced brain injury (Table 4). Warrington *et al.* (2011) assessed the effects of hypoxia as a potential mechanism to reverse the radiation-induced microvascular rarefaction and found out that chronic systemic hypoxia was capable of completely restoring cerebrovascular density in irradiated animal brain. More importantly, treatment of animals with systemic hypoxia completely reversed whole brain radiation-induced impairments in learning and memory (Warrington *et al.*, 2012). In addition, the radioprotective drug gammaphos (S-2[3-amino propylamino] ethylphosphorothioate) exerted protective effects on cerebrovascular system though effective prevention of endothelial cell loss in brain (Plotnikova *et al.*, 1984; Plotnikova *et al.*, 1988; Lyubimova and Hopewell, 2004). It was also found that less than 10% of animals receiving gammaphos showed brain injury such as necrosis, while approximately 50% of the animals that had not received gammaphos exhibited brain injury by 65 weeks after irradiation (Lyubimova and Hopewell, 2004).

CONCLUSIONS

Whole brain radiation therapy continues to be a main treatment modality in the therapeutic management of brain tumors. The clinical use of radiotherapy, however, has been limited by the risk of radiation-mediated damages to normal brain tissue that can eventually cause serious brain injury including cognitive impairment. At present, the cellular and molecular mechanisms related to the etiology of cognitive impairment that occurs among brain tumor patients in response to whole brain radiation therapy remain largely unknown. In this review, we described three pathophysiological mechanisms that whole brain radiation leads to cognitive impairment by (1) triggering induction of pro-oxidative and pro-inflammatory environments in brain, (2) causing imbalance MMPs/TIMPs system and degradation of ECM in brain, and (3) alerting physiological angiogenesis through differential regulation of angiogenic factors in brain. These findings may contribute to defining a cellular and molecular basis for radiation-induced cognitive impairment. It will also help identify therapeutic targets for novel preventive and/or treatment strategies for brain tumor patients who suffer from significant clinical side effects after whole brain radiation therapy.

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