Pathological changes in the central nervous system following exposure to ionizing radiation

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Short title An overview of radiation-induced CNS injury

Summary Experimental studies in animals provide relevant knowledge about pathogenesis of radiation-induced injury to the central nervous system. Radiation-induced injury can alter neuronal, glial cell population, brain vasculature and may lead to molecular, cellular and functional consequences. Regarding to its fundamental role in the formation of new memories, spatial navigation and adult neurogenesis, the majority of studies have focused on the hippocampus. Most recent findings in cranial radiotherapy revealed that hippocampal avoidance prevents radiation-induced cognitive impairment of patients with brain primary tumors and metastases. However, numerous preclinical studies have shown that this problem is more complex. Regarding the fact, that the radiation-induced cognitive impairment reflects hippocampal and non-hippocampal compartments, it is highly important to investigate molecular, cellular and functional changes in different brain regions and their integration at

clinically relevant doses and schedules. Here, we provide a literature review in order support the translation of preclinical findings to clinical practice and improve the physical and mental status of patients with brain tumors.

Key words Irradiation – Radiation-induced brain injury – Histopathological changes – Cognitive impairment – Interventional therapy

Introduction

Experience from preclinical studies provided valuable insight into pathogenic mechanisms related to radiation-induced injury. During the last decade, preclinical, animal studies indicated that interventional therapy could prevent, mitigate and ameliorate radiation-induced functional deficits. Implication of these recent preclinical findings to clinical therapy has the potential to improve the physical and mental status in patients with primary brain tumors and metastases (Reichman *et al.* 1986, Portnow *et al.* 2002, Monje *et al.* 2003, Jenrow *et al.* 2010).

Cognitive deficits, including progressive deficits in learning, memory and spatial information processing abilities represent a significant risk for patients undergoing radiotherapy of brain primary tumors and metastases. These symptoms occur in up to 90% of adult patients who survive more than 6 months after treatment and can be seen without clinical and radiographic evidence of any histological changes (e.g., demyelination, white matter necrosis) (Johannessen *et al.* 2003, Greene-Schloesser and Robbins 2012). Due to the advanced techniques used for conventional radiotherapy, the patients with brain tumor survive longer but they experience the late effects of radiotherapy. Regarding the fact, that the population of patients with late symptoms is growing rapidly, the current effort is focused on prevention/mitigation of functional consequences of radiation-induced brain injury (Jenrow *et al.* 2010, Gehring *et al.* 2012, Zhao and Robbins 2014, Rapp *et al.* 2015, Soria *et al.* 2019).

Based on the time of occurrence and clinical presentation, side effects of radiotherapy to the brain are discriminated into three types: (a) acute (during radiation up to first few weeks after irradiation), (b) subacute or early-delayed (1-6 months after irradiation) and (c) late (greater than 6 months to years after irradiation) (Greene-Schloesser and Robbins 2012). Acute effects are often characterized by drowsiness, headache, nausea, and vomiting as the result of increased intracranial pressure presumably caused by vasodilation, disruption of blood-brain barrier (BBB) and edema. Corticosteroids such as dexamethasone may improve these

symptoms; however, they are mostly transient and resolve spontaneously. The subacute type of radiation-induced brain injury related to encephalopathy characterizes somnolence, fatigue and deterioration of preexisting deficits that resolve within several months. Unlike previous symptoms, late radiation effects are often progressive and irreversible. Late radiation-induced changes include leukoencephalopathy syndrome, vascular lesions (i.e., teleangiectasias, endothelial thickening, hyalinization, fibrinoid deposition, thrombosis and occlusion of vessels), true radionecrosis, brain parenchyma calcifications and increasing white matter abnormalities (Muphy *et al.* 2015). The late effects include several neurocognitive deficits, such as decreased verbal and spatial memory, attention, novel problem-solving ability, ataxia and urinary loss. Moreover, cognitive dysfunction progresses to dementia in up to 2-5% patients with radiotherapy (Brandsma *et al.* 2008, Greene-Schloesser and Robbins 2012).

On the cellular level, irradiation triggers a cascade of the direct and indirect effects including activation of early response transcription factors, cascades of signal transduction, alteration of proliferative vascular and glial cells, neurogenesis and neural functions (Snyder *et al.* 2005). In this review, we present the previous and novel approaches used in the preclinical studies concerning with pathological mechanisms of the radiation-induced brain injury and perspective neuroprotective interventions.

Radiation-induced changes in the central nervous system

Apoptosis

Apoptosis is a distinct form of cell death, which is triggered among other insults by ionizing radiation. It has specific morphological and molecular features and implications for surrounding tissue. Acute (0.1-4 Gy) or chronic (0.5 Gy) irradiation led to disturbance in extracellular-signal-regulated kinase (ERK1/ERK2) and signaling pathways, increased level of reactive oxygen species (ROS) and Trp53 and p21 protein levels (Limoli *et al.* 2004).

As was reported in numerous preclinical studies, the influence of ionizing radiation on apoptosis is dose-dependent and occurs within hours after treatment (Shinohara *et al.* 1997, Peissner *et al.* 1999, Sasaki *et al.* 2000, Tada *et al.* 2000, Mizumatsu *et al.* 2003). Single irradiation with a dose of 2 Gy led to apoptosis of neuronal and glial population reside the subvetricular zone (SVZ) lining the brain lateral ventricles (LV), neocortex, piriform and entorhinal cortex, striatum, thalamus, amygdala, dentate gyrus (DG), olfactory bulb (OB), brainstem, cerebral and cerebellar white mater (Ferrer *at al.* 1995). Large scale doses of single irradiation (2-10 Gy) caused steep increase of apoptosis in the DG within 3 to 6 hours after treatment (Shinohara *et al.* 1997, Peissner *et al.* 1999, Tada *et al.* 2000) and reaching a maximum within 6 to 12 hrs after exposure (Sasaki *et al.* 2000; Mizumatsu *et al.* 2003). The level of apoptosis remained unchanged within 1 to 9 months after irradiation (Tada *et al.* 2000, Mizumatsu *et al.* 2003, Raber *et al.* 2004, Rola *et al.* 2004, Fan *et al.* 2007).

The most radiosensitive type of cells undergoing apoptosis are undifferentiated and/or proliferating cells. Results revealed that radiation-induced impairment of proliferating cells and immature neurons were time- and dose-dependent. Surviving stem cells have limited capability to repopulate and regenerate the injured self-renewing potential several months after irradiation (Tada *et al.* 2000, Kee *et al.* 2002, Fan *et al.* 2007). In our previous experiments, after fractionated irradiation with various total doses (20 Gy, 35 Gy, 40 Gy; dose per fraction: 5 or 8 Gy), we achieved a significant reduction or elimination of stem cells and immature neurons in neurogenic regions approximately 4 months after treatment (Bálentová *et al.* 2017, Bálentová *et al.* 2018, Bálentová *et al.* 2019).

Decline of neurogenesis in the DG was associated with impaired hippocampal-dependent learning and spatial memory (Raber *et al.* 2004, Rola *et al.* 2004, Greene-Schloesser *et al.* 2014). We also observed an early-delayed decrease in cognitive functions in

our experiment, in which rats were irradiated with a total dose of 20 Gy (divided into 4 fractions with a dose per fraction: 5 Gy) (Bálentová *et al.* 2018).

Within the context of the other neurogenic region, the SVZ, whole brain irradiation with a single (0.5-30 Gy) or fractionated doses (daily 1.5 Gy for 7 days) led to the peak of apoptosis 6 hrs after treatment with subsequent no additional apoptosis until 48 hrs after irradiation (Bellinzona *et al.* 1996, Shinohara *et al.* 1997). The proliferative response after apoptosis may represent the recruitment of relatively quiescent stem/precursor cells (Shinohara *et al.* 1997, Mizumatsu *et al.* 2003). These findings support the hypothesis that neural stem cells (NSCs) are radioresistant and can respond to a brain injury, recovering the neurogenic niche.

Inflammation and oxidative stress

Ionizing radiation influences the inflammatory/immune system and modulates immune cell populations (Kalm *et al.* 2009). Oxidative stress results from an inflammatory response and is defined as an imbalance between production of ROS and ability of organism to detoxify reactive products or to repair the resulting damage. Irradiation activates microglia and causes infiltration of the brain with immune cells, which produce ROS (Hwang *et al.* 2006). The most widely used method for evaluation of oxidative stress is measurement of inflammatory response to the increase of oxidative stress. Irradiation with various single doses (2-10 Gy) upon in vitro or in vivo conditions increased expression of pro-inflammatory molecules such as tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), intercellular adhesion molecule-1 (ICAM-1), cyclooxygenase 2 (COX-2) (Kyrkanides *et al.* 1999, Ramanan *et al.* 2008, Kalm *et al.* 2009, Lee *et al.* 2010), activation of transcription factors (AP-1, nuclear factor kappa B; NFκB, cAMP response element-binding protein; CREB) (Ramanan *et al.* 2008, Lee *et al.* 2010) and upregulation of mRNA levels of several chemokines (MCP1/CCL2, Gro/KC/CXCL1) (Lee *et al.* 2010). Single irradiation with doses ≥15 Gy resulted in acute

infiltration of neutrophils and a delayed increase in T cells, MHC (major histocompatibility complex) II-positive cells, and cluster of differentiation 11c (CD11c)-positive cells at least 1 year after the irradiation (Moravan *et al.* 2011). Preclinical data support the hypothesis, that oxidative stress might drive the progression of radiation-induced late injury (Robbins and Zhao 2004, Zhao *et al.* 2014). Administration of various anti-inflammmatory drugs prevents radiation-induced cognitive impairment (nonsteroidal and steroidal agents, COX inhibitors, etc.) (Reichman *et al.* 1986, Portnow *et al.* 2002, Monje *et al.* 2003).

Neurogenesis

Adult mammalian brain contains at least two discrete sources of NSCs. The first source is known as the subgranular zone (SGZ) and it is located in the DG of the hippocampal formation (Baptista and Andrade 2018). The second region is called the SVZ and it extent along the brain LV outer wall, the anterior SVZ (SVZa). The neuronal progeny of the SGZ travel to the granular cell layer (GCL) and the progeny of the SVZa traverse as tangentially oriented chains, migrate to the rostral migratory stream (RMS) en route the olfactory bulb (OB) (Doetsch *et al.* 1997, Kempermann 2002, Alvarez-Buylla and Lim 2004, Bohlen and Halbach 2011, Baptista and Andrade 2018). Except of the self-renewing capacity, the NSCs are capable to generate new neurons, astrocytes and oligodendrocytes (Carleton *et al.* 2003, Abrous *et al.* 2005, Lledo *et al.* 2006, Biswas *et al.* 2019, Urbach and Witte 2019).

According to high rate of cell proliferation in this region, the DG is more sensitive to therapeutic doses of radiation. Single whole brain irradiation (2-10 Gy) of young adult mice led to significant reduction of proliferating cells and immature neurons in the DG. The long-term impairment of SGZ neurogenesis was associated with hippocampal-dependent memory deficits (Monje *et al.* 2002, Raber *et al.* 2004, Rola *et al.* 2004). In contrast to young adults, older rodents did not shown sustained decrease of immature neurons, however they displayed cognitive dysfunction (Lamproglou *et al.* 1995, Schindler *et al.* 2008, Tang *et al*. 2019). In

addition to radiation-induced changes in the DG, single (5-30 Gy) and fractionated (daily 1.5 Gy) irradiation of rat brain have been shown to result in dose dependent increase of apoptosis and decrease in cellularity, which involved reduction of proliferating cells, NSCs and progenitors. However, the cellular response to fractionated irradiation differs from that of single treatment; the single dose response is rapid and the fractionated response is delayed and surpassed the radiation treatment (Shinohara *et al.* 1997, Gaber *et al.* 2003, Bálentová *et al.* 2017, Bálentová *et al.* 2019, Tang *et al.* 2019). The apparent resistance of cells after fractionated treatment may represent the recruitment of quiescent NSCs (Shinohara *et al.* 1997, Mizumatsu *et al.* 2003). During fractionated irradiation, the first dose per fraction affects preferentially proliferating cells, but the apoptosis occurs several hours later. The proliferative activity is then rebound and the next dose per fraction eliminate the cells that start to proliferate spontaneously or in response to the previous cell death (Shinohara *et al.* 1997). Systematic experimental applications showed, that there is a limit for a numbers of doses per fractions (Shinohara *et al.* 1997, Snyder *et al.* 2005). Criteria, which can alter the effect of radiation treatment, include the dose rate, energy, activity and intensity of the source, source - to-axis distance (SAD), shielding, etc. (https://www.nde-ed.org/EducationResources/CommunityCollege/RadiationSafety/theory/activity.htm).

Previous findings revealed, that local brain irradiation did not cause the same degree of cognitive impairment as the whole-brain irradiation (WBI). Clinical retrospective study of Peiffer *et al.* (2013), which used neuroanatomic target theory suggests, that the incidence and type of cognitive decline depends more on specific areas of interest than on the total dose received by the brain. This type of targeting, i.e. WBI is not predictive of cognitive outcomes.

Glial cells

Molecular studies have provided evidence that glial cells are essential for the survival of neurons by supplying trophic factors to the neurons (Jäkel and Dimou 2017). Thus, the

mechanism underlying the adverse brain effects of irradiation has been believed to mainly be the insufficient supply of nutrients and blood to neurons due to the impaired functions of irradiated glial cells (Kudo *et al.* 2014).

Regarding to radiation response of glia following irradiation, the myelin-producing oligodendrocytes did appear more radiosensitive than other glial cells. The key cell for production of mature oligodendrocytes is the oligodendrocyte type-2 astrocyte (O-2A) a progenitor cell that is able to differentiate into an oligodendrocyte or fibrous astrocyte (Tabata 2015). Radiation-induced loss of O-2A progenitor cells leads to failure of their reproducing capacity that ultimately results in demyelination and white matter necrosis (Li and Leung 2015). Single irradiation (1-30 Gy) of the rat cervical spinal cord examined 24 hrs after treatment revealed a significant increase of oligodendroglial apoptosis and concomitant decrease of O-2A cells and mature oligodendrocytes (Li *et al.* 1996, Atkinson *et al.* 2003). Radiation-induced oligodendroglial apoptosis was seen after WBI with doses of 10-22 Gy in the SVZ, SGZ of the DG, corpus callosum, subcortical and periventricular white matter (Sano *et al.* 1997, Chow *et al.* 2000, Sasaki *et al.* 2000, Kurita e*t al.* 2001). On the contrary, several studies reported the increased numbers of immature oligodendrocytes and this effect did not really reflect production of new oligodendrocytes but rather was a manifestation of radiation-induced inflammatory response (Sasaki *et al.* 2000, Mizumatsu *et al.* 2003). In contrast, fractionated irradiation of rats with a total dose of 45 Gy investigated a year later did not affect gross morphology, structural integrity of myelin and white matter necrosis, and these changes did not correspond to the observed cognitive impairment (Shi *et al.* 2009). Thus, the relationship between radiation damage of oligodendrocytes and late radiation-induced changes remains unclear.

Astrocytes are the most numerous and diverse neuroglial cells in the central nervous system (CNS) which exceed the neurons by more than five times. Except of their supportive

role, the astrocyte performs numerous functions, i.e. define the micro-architecture of the brain, maintain brain homeostasis, store and distribute energy substrates, control the development of neural cells and modulate the synaptic transmission (Jäkel and Dimou 2017). It has been suggested that descendants of the SVZ astrocytes represent a part of neurogenic lineage, or they might dedifferentiate into uncommitted precursors (Doetsch *et al.* 1997). In the adult RMS, the astrocytes ensheathe the chains of migrating neuronal precursors and provide important signals and guidance for migrating young neurons toward the OB (Kempermann 2002). Fractionated irradiation (with a total dose of 40 Gy) caused activation of astrocytes and microglial cells at least 6 months after treatment (Ciciarello *et al.* 1996, Yuan *et al.* 2006). The prominent molecular characteristics of activated astrocytes are upregulation of glial fibrillary acidic protein (GFAP), proliferation, secretion of a host of proinflammatory mediators (COX, ICAM-1) and altered expression of many genes (Liddelow and Barres 2017). Activated astrocytes and reactive astrogliosis accompany many pathological situations that affect the CNS, such as trauma, ischemic damage, neuroinflammation, or neurodegenerative disorders (i.e. Alzheimer's disease, Batten disease) (Pekny and Pekna 2014). The reactive astrogliosis is often associated with decline in cognitive functions. Radiation treatment of adult rats with either single (20-45 Gy) or fractionated doses (a total dose of 20 or 40 Gy) led to a significant reactive astrogliosis, disruption of BBB integrity and cognitive impairment up to 1 year after irradiation (Chiang *et al.* 1993, Wilson *et al.* 2009, Zhou *et al.* 2011). Although radiation-induced astrogliosis is not directly characteristic of inflammation, it is associated with or is a byproduct of brain inflammation. Irradiation of rat microglia-astrocytes mixed cultures and mouse microglia cultures showed initiation of reactive astrogliosis due to dose-dependent increase in mRNA levels for COX-2, IL1-β, interleukin 6 (IL-6), interleukin 18 (IL-18), TNF-α, and interferon-

gamma-inducible protein-10 (IP-10), which are associated with microglial activation (Hwang *et al.* 2006).

Microglial cells are the primary immune effector cells of the CNS and they constitute approximately 10-20% of the total population of glial cells. They act as the main inflammatory cell type in the brain involved in immune defense and the maintenance of brain homeostasis (Perry and Tealing 2013). Acute CNS injury, stroke, inflammatory and neurodegenerative diseases can activate microglia (Ladeby *et al.* 2005, Kawabori and Yenari 2015). Microglial activation is characterized by morphological transformation, induction of myeloid markers, free radicals, nitric oxide, increased expression of the proinflammatory genes, several surface molecules (ionized calcium binding adaptor molecule; Iba1, lectin binding sugar molecules, enzyme nucleoside diphosphatase; NDPase) and acquisition of phagocytic phenotype (Ladeby *et al.* 2005, Hwang *et al.* 2006, Lee *et al.* 2010). Single in vivo or in vitro irradiation led to up-regulation of mRNA and expression of proinflammatory mediators (ICAM, TNF-α, IL1-β, monocyte chemoattractant protein-1; MCP-1), apoptosis-related, stem cell-related, trophic and transcription factors (AP-1, CREB, NF-κB) (Lee *et al.* 2010). Radiation-induced activation of microglia did not seem to be associated with the acute decline of proliferative cells and immature neurons; they did appear too related to changes in neurogenesis (Mizumatsu *et al.* 2003). Rodent studies also detected the increase of activated microglia in the brain during the latent period before expression of late radiation-induced injury (Mildenberger *et al.* 1990, Chiang *et al.* 1997, Han *et al.* 2016).

Endothelial cells

Cranial irradiation has a fundamentally negative effect on the vasculature in the CNS. Radiation-induced vascular injury is a complex process and involves capillary and arterial damage with veins being less sensitive (Murphy *et al.* 2015).

A large amount of studies described radiation-induced structural changes of endothelium, characterized by apoptosis of endothelial cells, enlargement of cell nuclei, basement membrane thickening, adventitial fibrosis, increase in vessel permeability, telangiectasia, edema, thrombosis, hemorrhage and ischemic necrosis (Ljubimova *et al.* 1991, Schultheiss and Stephens 1992, Siegal and Pfeffer 1995, Yuan *et al.* 2003, Li *et al.* 2004, Brown *et al.* 2005, Yuan *et al.* 2006, Brown *et al.* 2007, Murphy *et al.* 2015). Radiation-induced injury may lead to the production of ROS under hypoxic conditions. Profound cerebral microvascular rarefaction reversed by systemic hypoxia been discovered in the hippocampus of mice 2 months after fractionated irradiation (Warrington *et al.* 2011). Moreover, systemic hypoxia is able to reverse radiation-induced impairment in the spatial learning and memory (Warrington *et al.* 2012). In contrast, tissue oxygen conditions may improve with hyperbaric oxygen treatment (HBO). Previous clinical studies described successful treatment of late CNS toxicity by prophylactic HBO (Chuba *et al.* 1997, Leber *et al.* 1998, Ohguri *et al.* 2007, Heyboer *et al.* 2017). In contrast, reoxygenation of hypoxic tissue may accelerate axonal injury (Stys 2004). Hypoxia is also a crucial stimulus for increase of vascular endothelial growth factor (VEGF) expression, known to modulate vascular permeability, inflammation and contributes to BBB breakdown (Proescholdt *et al.* 1999, Ramakrishnan *et al.* 2014). The model of radiation-induced myelopathy revealed, that BBB breakdown is associated with upregulation of VEGF expression in astrocytes without a concomitant endothelial proliferation (Tsao *et al.* 1999). Ionizing radiation induced the early endothelial cell apoptosis within 24 hrs after the single WBI or spinal cord irradiation (Schultheiss and Stephens 1992, Peña *et al.* 2000, Li *et al.* 2003, Li *et al.* 2004, Yang *et al.* 2017). Acid sphingomyelinase (ASM) pathway mediates the radiation-induced apoptosis of endothelial cells. Experiments made with knockout mice with inherited deficiency of ASM displayed mitigation of the endothelial cell apoptosis (Santana *et al.* 1996, Peña *et al.* 2000, Li *et al.* 2003). Inhibiting

ASM activity might provide a highly specific approach to reduce endothelial cell apoptosis (Kölzer *et al.* 2003, Kornhuber *et al.* 2010). Growth factors such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) and insulin-like growth factor-1 (IGF-1) were also tested a few years ago to mitigate endothelial cell apoptosis (Peña *et al.* 2000, Andratschke *et al.* 2004, Nieder *et al.* 2005).

Despite the fact, that vascular injury is recognized as a primary cause of radiation-induced changes, the pathophysiology of late injury is multifactorial (e.g., demyelination, microvascular changes, decline of neurogenesis, glial cells proliferation or decline) (Khunthia 2015).

Preclinical strategies for prevention/mitigation of radiation-induced changes

Potential preclinical and clinical interventions, needed for prevention, mitigation and amelioration of radiation-induced changes include: (a) reduction of apoptosis by e.g., inhibition of ASM activity (Kölzer *et al.* 2003, Kornhuber *et al.* 2010); (b) inhibition of VEGF (Gonzales *et al.* 2007); (c) inhibition of inflammatory response by nonsteroidal and steroidal agents, COX inhibitors, PPAR (peroxisomal proliferator-activated receptor) agonists (Reichman *et al.* 1986, Portnow *et al.* 2002, Monje *et al.* 2003, Zhao and Robbins 2014); (d) oxygen starvation or HBO (Chuba *et al.* 1997, Warrington *et al.* 2012, Heyboer *et al.* 2017); (e) administration of erythropoietin (EPO) (Knisely *et al.* 2004); (f) renin-angiotensin-aldosteron system (RAAS) blockers (Jenrow *et al.* 2010); (g) acetylcholinesterase (ACHE) inhibitors (Rapp *et al.* 2015); (h) *N*-methyl-D-aspartate (NMDA) receptor antagonists (Brown *et al.* 2013); (i) CNS stimulants (Gehring *et al.* 2012); (j) stem cell therapy (Acharya *et al.* 2011, Piao *et al.* 2015, Sato *et al.* 2018, Soria *et al.* 2019, Smith *et al.* 2020); (k) enviromental enrichment (Naylor *et al.* 2008, Wong-Goodrich *et al.* 2010, Riggs *et al.* 2017), etc.

Regarding the therapeutic potential of growth factors, earlier studies showed that they increase the long-term radiation tolerance of the spinal cord (Nieder *et al.* 2002, Andratschke

et al. 2004, Nieder *et al.* 2005). The VEGF pathway blocking with bevacizumab might be able to reduce radiation necrosis in patients with brain tumors (Gonzales *et al.* 2007). However, application of the right dose, timing and combination of various growth factors seem to be problematic for human radiotherapy.

Numerous experimental studies have suggested that EPO is an endogenous mediator of neuroprotection in various CNS disorders and injuries (e.g., ischemia, concussive brain injury, experimental autoimmune encephalomyelitis, and kainate-induced neurotoxicity) (Sakanaka *et al.* 1998, Brines *et al.* 2000, Gorio *et al.* 2002). However, EPO is not validating for post-radiation therapy because the potential adverse effect of EPO on tumor control need to be investigated (Henke *et al.* 2003).

Most novel potential therapeutic strategies have focused on anti-inflammatory agents and stem cell therapies. Rather than attempt to develop novel agents, recent studies have been focus on using drugs that have been used successfully for many years in clinical practice to treat other symptoms (Derosa 2010, McKeage and Keating 2011, Meguro *et al.* 2014, Storebø *et al.* 2018). The anti-inflammatory PPARα, δ and γ agonists are the nuclear receptors, belonging to the PPAR family of transcription factors, which regulate inflammatory signaling and provide neuroprotection in a variety of CNS diseases (Bright *et al.* 2008, Ramanan *et al.* 2010, Kvandová *et al.* 2016). For instance, the PPARγ agonist pioglitazone (Pio) has been prescribed for several years to treat diabetes (Derosa 2010). Administration of the PPARγ agonist pioglitazone (Pio) before, during, and for 4 or 54 weeks after fractionated irradiation with a total dose of 40 or 45 Gy (5 Gy/d, 2d/week for 4 or 4.5 weeks) substantially but not significantly reduced the radiation-induced cognitive impairment (Zhao and Robbins 2014). A clinical trial is after completion at Wake Forest Baptist Medical Center, Winston-Salem, NC, USA given to patients with brain tumors (https://clinicaltrials.gov/ct2/show/NCT01151670). A similar conceived study of Greene-Schloesser et al. (2014) showed that dietary

administration of the PPARα agonist, fenofibrate starting 7 days prior to radiation treatment and continuously until 30 weeks prevented the radiation-induced impairment in the perirhinal cortex, but did not protect inhibition of neurogenesis and activation of microglia. On the other hand, administration of fenofibrate before single irradiation of mice with inherited deficiency of PPARα receptor prevented inhibition of hippocampal neurogenesis by promoting the survival of newborn cells and decreased microglial activation (Ramanan *et al.* 2009). Inhibitors of the RAS, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs) have been used in the treatment of hypertension and have proved to be very effective in the experimental model of nephropathy (Moulder *et al.* 2003) and pneumopathy (Molteni *et al.* 2000). Later studies showed that chronic administration of ramipril beginning 24 hrs after single irradiation and continuously for 12 weeks may mitigate neurogenesis following 10 Gy but was not effective following 15 Gy (Jenrow *et al.* 2010). These preclinical outputs raise a question about a timing or dosage of ramipril administration and different radiobiological tissue response following single and fractionated irradiation. Recently, a phase I/II of clinical trial is developed to identify if ramipril can mitigate the radiation-induced cognitive impairment in brain tumor patients (https://clinicaltrials.gov/ct2/show/NCT03475186?term=ramipril&cond=brain&cntry=US&draw=2&rank=1).

Memantine, an NMDA receptor antagonist and donepezil, which is an ACHE inhibitor are drugs prescribed for the treatment of Alzheimer's disease (Meguro *et al.* 2014, Kishi *et al.* 2017). In a completed randomized clinical trial, the effect of memantine was studied in patients after radiotherapy for brain metastases. Patients treated with memantine had better cognitive function over time; specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed (Brown *et al.* 2013). Less promising results were achieved in another clinical study in which donepezil was

administered to patients treated with primary and secondary brain tumors. Treatment with donepezil did not significantly improve the overall cognitive composite score in patients (Rapp *et al.* 2015).

Interesting results were obtained in a small pilot study investigating the effects of methylphenidate. This psychostimulant drug is routinely prescribed to treat attention deficit hyperactivity disorder (Storebø *et al.* 2018). Following stimulant treatment of patients, there was evidence of a beneficial effect on test performance in speed of processing and executive function requiring divided attention (Gehring *et al.* 2012).

Transplantation of NSCs has been considered as an effective therapeutic strategy in a variety of neurological disorders characterized by the collapse of CNS repair mechanisms in restoring the tissue damage and rescuing the lost function. Cellular sources for NSCs include fetal and adult CNS-derived NSCs, neural progenitors and a wide range of non-neural stem cells such as mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) (Vishwakarma *et al.* 2014).

Numerous preclinical studies have been focused on xenogenic transplantation of human pluripotent MSCs or NSCs into the rodent host (Acharya *et al.* 2011, Piao *et al.* 2015, Sato *et al.* 2018, Soria *et al.* 2019). Recently published study by Soria et al. (2019) demonstrated, that intranasally delivered human MSCs promoted radiation-induced brain injury repair of cognitive dysfuncions and protect against neuronal loss 1 month following irradiation. Also, intrahippocampal transplantation of hNSCs or hNSCs-derived microvesicles after exposure to a single dose of 8 or 10 Gy reverses or prevents radiation-induced cognitive dysfunction following irradiation (Baulch *et al.* 2016, Sato *et al.* 2018). It also reduces the impact of radiation on dendritic complexity and spine density of neurons (Smith *et al.* 2020). Although stem cell therapy represents a good strategy for restoration of functional deficits, it has several major limitations: migration of the transplanted cells is

limited; the limited sources of donor cells and many ethical concerns and political restrictions (https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation).

Another promising non-pharmacological intervention to prevent/mitigate of radiation-induced changes represents an enriched environment. Stimulation of the brain by its physical and social surroundings has been shown to have a positive impact on the brain function not only in healthy animals but also in those with traumatic brain injury, stroke, epilepsy, Parkinson's disease an Huntington's disease. The functional improvement is partially determinate through the increase of neurogenesis (Spires *et al.* 2004; Bruel-Jungerman *et al.* 2005; Goldberg *et al.* 2012; Janssen *et al.* 2014, Maegele *et al.* 2015). In general, voluntary physical activity has been a very strong stimulus for adult hippocampal neurogenesis in rodents from birth to oldest age (Kannangara *et al.* 2011, Saraulli *et al.* 2017). Single exposure (a dose of 5-6 Gy) of juvenile mice brain combined with a voluntary running significantly restored level of neurogenesis and ameliorated radiation-induced cognitive changes (Naylor *et al.* 2008; Wong-Goodrich *et al.* 2010). Preclinical works indicates that the functional deficits observed in pediatric patients after radiation therapy are not irreversible and may be acceptable to treatment. Promising results have been achieved in some clinical trials that have used aerobic exercise to improve radiation-induced cognitive dysfunctions in children (Riggs *et al.* 2017). Pediatric patients treated for primary brain tumors and conducted exercise training improved cognitive performances and mitigate structural changes, i.e. decrease in hippocampal volume and increased white matter myelination.

Conclusion

Taking to account the most recent preclinical data, it is idealistic to suppose, that one therapeutic approach may prevent or mitigate every histopathological and functional consequences of radiation-induced brain injury. On the other hand, stem cell based therapies

and pharmaceutical treatment are very perspective and requires more preclinical research before they can be translate into clinical treatment.

Conflict of interest

The authors declared no conflict of interest in relation to article.

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References

ABROUS DN, KOEHL M, LE MOAL M: Adult neurogenesis: From precursors to network and physiology. *Physiol Rev* **85:** 523-569, 2005.

ACHARYA MM, CHRISTIE LA, LAN ML, GIEDZINSKI E, FIKE JR, ROSI S, LIMOLI CL: Human neural stem cell transplantation ameliorates radiation-induced cognitive dysfunction. *Cancer Res* **71:** 4834-4845, 2011.

ALVAREZ-BUYLLA A, LIM DA: For the long run: Maintaining germinal niches in the adult brain. *Neuron* **41:** 683-686, 2004.

ANDRATSCHKE N, NIEDER C, PRICE R, RIVERA B, TUCKER S, ANG K: Modulation of rodent spinal cord radiation tolerance by administration of platelet-derived growth factor. *Int J Radiat Oncol Biol Phys* **60:** 1257-1263, 2004.

ATKINSON S, LI YQ, WONG CS: Changes in oligodendrocytes and myelin gene expression after radiation in the rodent spinal cord. *Int J Radiat Oncol Biol Phys* **57:** 1093-1100, 2003.

BÁLENTOVÁ S, HAJTMANOVÁ E, FILOVÁ B, BORBÉLYOVÁ V, LEHOTSKÝ J, ADAMKOV M: Effects of fractionated whole-brain irradiation on cellular composition and cognitive function in the rat brain. *Int J Radiat Biol* **94 (3):** 238-247, 2018.

BÁLENTOVÁ S, HNILICOVÁ P, KALENSKÁ D, BARANOVIČOVÁ E, MURÍŇ P, BITTŠANSKÝ M, HAJTMANOVÁ E, LEHOTSKÝ J, ADAMKOV M: Metabolic and histopathological changes in the brain and plasma of rats exposed to fractionated whole-brain irradiation. *Brain Res* **1708:** 146-159, 2019.

BÁLENTOVÁ S, HNILICOVÁ P, KALENSKÁ D, MURÍŇ P, HAJTMANOVÁ E, LEHOTSKÝ J, ADAMKOV M: Effect of whole-brain irradiation on the specific

brain regions in a rat model: Metabolic and histopathological changes. *Neurotoxicology* **60**: 70-81, 2017.

BAPTISTA P, ANDRADE JP: Adult Hippocampal Neurogenesis: Regulation and Possible Functional and Clinical Correlates. *Front Neuroanat* **12:** 44, 2018.

BAULCH JE, ACHARYA MM, ALLEN BD, RU N, CHMIELEWSKI NN, MARTIROSIAN V, GIEDZINSKI E, SYAGE A, PARK AL, BENKE SN, PARIHAR V, LIMOLI CH: Cranial grafting of stem cell-derived microvesicles improves cognition and reduces neuropathology in the irradiated brain. *Proc Natl Acad Sci USA* **113(17):** 4836-4841, 2016.

BELLINZONA M, GOBBEL GT, SHINOHARA C, FIKE JR: Apoptosis is induced in the subependyma of young adult rats by ionizing radiation. *Neurosci Lett* **208:** 163-166, 1996.

BISWAS S, CHUNG SH, JIANG P, DEHGHAN S, DENG W: Development of glial restricted human neural stem cells for oligodendrocyte differentiation in vitro and in vivo. *Sci Rep* **9:** 9013, 2019.

BRANDSMA D, STALPERS L, TAAL W, SMINIA, VAN DEN BENT MJ: Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* **9:** 453-461, 2008.

BRIGHT JJ, KANAKASABAI S, CHEARWAE W, CHAKRABORTY S: PPAR regulation of inflammatory signaling in CNS diseases. *PPAR Res* **2008:** 658520, 2008.

BRINES ML, GHEZZI P, KEENAN S, AGNELLO D, DE LANEROLLE NC, CERAMI C, ITRI LM, CERAMI A: Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. *Proc Natl Acad Sci USA* **97:** 10526-10531, 2000.

BROWN WR, BLAIR RM, MOODY DM, THORE CR, AHMED S, ROBBINS ME, WHEELER KT: Capillary loss precedes the cognitive impairment induced by

fractionated whole-brain irradiation: A potential rat model of vascular dementia. *J Neurol Sci* **257:** 67-71, 2007.

BROWN PD, PUGH S, LAACK NN, WEFEL JS, KHUNTIA D, MEYERS CH, CHOUCAIR A, FOX S, SUH JH, ROBERGE D, KAVADI V, BENTZEN SM, MEHTA MP, WATKINS-BRUNER D, RADIATION THERAPY ONCOLOGY GROUP (RTOG): Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* **15(10):** 1429-1437, 2013.

BROWN WR, THORE CR, MOODY DM, ROBBINS ME, WHEELER KT: Vascular damage after fractionated whole-brain irradiation in rats. *Radiat Res* **164:** 662-668, 2005.

BRUEL-JUNGERMAN E, LAROCHE S, RAMPON C: New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. *Eur J Neurosci* **21:** 513-521, 2005.

CARLETON A, PETREANU LT, LANSFORD R, ALVAREZ-BUYLLA A, LLEDO PM: Becoming a new neuron in the adult olfactory bulb. *Nat Neurosci* **5:** 507-518, 2003.

CICCIARELLO R, D'AVELLA D, GAGLIARDI ME, ALBIERO F, VEGA J, ANGILERI FF, D'AQUINO A, TOMASELLO F: Time-related ultrastructural changes in an experimental model of whole brain irradiation. *Neurosurgery* **38:** 772-779, 1996.

ClinicalTrials.gov. U.S. National Institutes of Health, Bethesda, Maryland: https://clinicaltrials.gov/ct2/show/NCT01151670. Accessed 9 March 2016.

ClinicalTrials.gov. U.S. National Institutes of Health, Bethesda, Maryland: https://clinicaltrials.gov/ct2/show/NCT03475186?term=ramipril&cond=brain&cntry=US&draw=2&rank=1. Accessed 17 January 2020.

DEROSA G: Efficacy and tolerability of pioglitazone in patients with type2 diabetes mellitus: Comparison with other oral antihyperglycaemic agents. *Drugs* **70:** 1945-1961, 2010.

DOETSCH F, GARCÍA-VERDUGO JM, ALVAREZ-BUYLLA A: Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J Neurosci* **17:** 5046-5061, 1997.

FERRER I, MACAYA A, BLANCO R, OLIVÉ M, CINÓS C, MUNELL F, PLANAS AM: Evidence of internucleosomal DNA fragmentation and identification of dying cells in X-ray-induced cell death in the developing brain. *Int J Dev Neurosci* **13:** 21-28, 1995.

GABER MW, SABEK OM, FUKATSU K, WILCOX HG, KIANI MF, MERCHANT TE: The differences in ICAM-1 and TNF-α expression between high single fractions and fractionated irradiation in mouse brain. *Int J Radiat Biol* **79:** 359-366, 2003.

GEHRING K, PATWARDHAN SY, COLLINS R, GROVES MD, ETZEL CJ, MEYERS CA, WEFEL JS: A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol* **107(1):** 165-174, 2012.

GOLDBERG NR, FIELDS V, PFLIBSEN L, SALVATORE MF, MESHUL CK: Social enrichment attenuates nigrostriatal lesioning and reverses motor impairment in a progressive 1-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. *Neurobiol Dis* **45:** 1051-1067, 2012.

GONZALES J, KUMAR AJ, CONRAD CA, LEVIN VA: Effect of bevacizumab on radiation necrosis of the brain. *Int J Radiat Oncol Biol Phys* **67:** 323-326, 2007.

GORIO A, GOKMEN N, ERBAYRAKTAR S, YILMAZ O, MADASCHI L, CICHETTI C, DI GIULIO AM, VARDAR E, CERAMI A, BRINES M: Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological

recovery from experimental spinal cord trauma. *Proc Natl Acad Sci USA* **99:** 9450-9455, 2002.

GREENE-SCHLOESSER D, PAYNE V, PEIFFER AM, HSU FC, RIDDLE DR, ZHAO W, CHAN MD, METHENY-BARLOW L, ROBBINS ME: The peroxisomal proliferator-activated receptor (PPAR) α agonist, fenofibrate, prevents fractionated whole-brain irradiation-induced cognitive impairment. *Radiat Res* **181:** 33-44, 2014.

GREENE-SCHLOESSER D, ROBBINS ME: Radiation-induced cognitive impairment-from bench to bedside. *Neuro Oncol* **14** (Suppl 4): iv37-iv44, 2012.

HAN W, UMEKAWA T, ZHOU K, ZHANG XM, OHSHIMA M, DOMINGUEZ CA, HARRIS RA, ZHU C, BLOMGREN K: Cranial irradiation induces transient microglia accumulation, followed by long-lasting inflammation and loss of microglia. *Oncotarget* **7(50):** 82305-82323, 2016.

HENKE M, LASZIG R, RÜBE RC, SCHÄFER U, HAASE KD, SCHILCHER B, MOSE S, BEER KT, BURGER U, DOUGHERTY C, FROMMHOLD H: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* **362:** 1255-1260, 2003.

HEYBOER MIII, SHARMA D, SANTIAGO W, MCCULLOCH N: Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. *Adv Wound Care (New Rochelle)* **6(6):** 210-224, 2017.

HWANG SY, JUNG JS, KIM TH, LIM SJ, OH ES, KIM JY, JI KA, JOE EH, CHO KH, HAN IO: Ionizing radiation induces astrocyte gliosis through microglia activation. *Neurobiol Dis* **21:** 457-467, 2006.

CHIANG CS, HONG JH, STALDER A, SUN JR, WITHERS HR, MCBRIDE WH: Delayed molecular responses to brain irradiation. *Int J Radiat Biol* **72:** 45-53, 1997.

CHIANG CS, MCBRIDE WH, WITHERS HR: Radiation-induced astrocytic and microglial responses in mouse brain. *Radiother Oncol* **29:** 60-68, 1993.

CHOW BM, LI YQ, WONG CS: Radiation-induced apoptosis in the central nervous system is p53-dependent. *Cell Death Differ* **7:** 712-720, 2000.

CHUBA PJ, ARONIN P, BHAMBHANI K, EICHENHORN M, ZAMARANO L, CIANCI P, MUHLBAUER M, PORTER AT, FONTANESI J: Hyperbaric oxygen therapy for radiation-induced brain injury in children. *Cancer* **80:** 2005-2012, 1997.

ISSCR International Society for stem cell research: https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation. Accessed 20 January 2020.

JÄKEL S, DIMOU L: Glial cells and their function in the adult brain: A journey through the history of their ablation. *Front Cell Neurosci* **11:** 24, 2017.

JANSSEN H, ADA L, BERNHARDT J, MCELDUFF P, POLLACK M, NILSSON M, SPRATT NJ: An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomized controlled trial. *Disabil Rehabil* **36:** 255-262, 2014.

JENROW KA, BROWN SL, LIU J, KOLOZSVARY A, LAPANOWSKI K, KIM JH: Ramipril mitigates radiation-induced impairment of neurogenesis in the rat dentate gyrus. *Radiat Oncol* **5:** 11-12, 2010.

KALM M, FUKUDA A, FUKUDA H, OHRFELT A, LANNERING B, BJÖRK-ERIKSSON T, BLENNOW K, MÁRKY I, BLOMGREN K: Transient inflammation in neurogenic regions after irradiation of the developing brain. *Radiat Res* **171:** 66-76, 2009.

KANNANGARA TS, LUCERO MJ, GIL-MOHAPEL J, DRAPALA RJ, SIMPSON JM, CHRISTIE BR, VAN PRAAG H: Running reduces stress and enhances cell genesis in aged mice. *Neurobiol Aging* **32:** 2279-2286, 2011.

KAWABORI M, YENARI MA: The role of the microglia in acute CNS injury. *Metab Brain Dis* **30(2):** 381-392, 2015.

KEE N, SIVALINGAM S, BOONSTRA R, WOJTOWICZ JM: The utility of Ki-67 and BrdU as proliferative markers of adult neurogenesis. *J Neurosci* **115:** 97-105, 2002.

KEMPERMANN G: Why new neurons? Possible functions for adult hippocampal neurogenesis. *J Neurosci* **22:** 635-638, 2002.

KHUNTIA D: Contemporary review of the management of brain metastasis with radiation. *Adv Neurosci* **2015:** 1-13, 2015.

KISHI T, MATSUNAGA S, OYA K, NOMURA I, IKUTA T, IWATA N: Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. *J Alzheimers Dis* **60(2):** 401-425, 2017.

KNISELY JP, DE LOTBINIERE AC, DE LANEROLLE NC, BRINES ML: Randomized trial of erythropoietin as a central nervous system radioprotectant. *Int J Radiat Oncol Biol Phys* **60:** 343-344, 2004.

KÖLZER M, ARENZ C, FERLINZ K, WERTH N, SCHULZE H, KLINGENSTEIN R, SANDHOFF K: Phosphatidylinositol-3,5-Bisphosphate is a potent and selective inhibitor of acid sphingomyelinase. *Biol Chem* **384:** 1293-1298, 2003.

KORNHUBER J, TRIPAL P, REICHEL M, MÜHLE CH, RHEIN C, MUEHLBACHER M, GROEMER TW, GULBINS E: Functional Inhibitors of Acid Sphingomyelinase (FIASMAs): a novel pharmacological group of drugs with broad clinical applications. *Cell Physiol Biochem* **26(1):** 9-20, 2010.

KUDO S, SUZUKI Y, NODA SE, MIZUI T, SHIRAI K, OKAMOTO M, KAMINUMA T, YOSHIDA Y, SHIRAO T, NAKANO T: Comparison of radiosensitivities of neurons and glial cells derived from the same rat brain. *Exp Ther Med* **8:** 754-758.

KURITA H, KAWAHARA N, ASAI A, UEKI K, SHIN M, KIRINO T: Radiation-induced apoptosis of oligodendrocytes in the adult rat brain. *Neurol Res* **23:** 869-874, 2001.

KVANDOVÁ M, MAJZÚNOVÁ M, DOVINOVÁ I: The Role of PPARγ in Cardiovascular Diseases. *Physiol. Res* **65** (Suppl. 3): S343-S363, 2016.

KYRKANIDES S, OLSCHOWKA JA, WILIAMS JP, HANSEN JT, O'BANION MK: TNFα and IL-1β mediate intercellular adhesion molecule-1 induction via microglia-astrocyte interaction in CNS radiation injury. *J Neuroimmunol* **95:** 95-106, 1999.

LADEBY R, WIRENFELDT M, GARCIA-OVEJERO D, FENGER C, DISSING-OLESEN L, DALMAU I, FINSEN B: Microglial cell population dynamics in the injured adult central nervous system. *Brain Res Brain Res Rev* **48:** 196-206, 2005.

LAMPROGLOU I, CHEN QM, BOISSERIE G, MAZERON JJ, POISSON M, BAILLET F, LEPONCIN M, DELATTRE JY: Radiation-induced cognitive dysfunction: An experimental model in the old rat. *Int J Radiat Oncol Biol Phys* **31:** 65-70, 1995.

LEBER KA, EDER HG, KOVAC H, ANEGG U, PENDL G: Treatment of cerebral radionecrosis by hyperbaric oxygen therapy. *Stereotact Funct Neurosurg* **70:** 229-236, 1998.

LEE WH, SONNTAG WE, MITSCHELEN M, YAN H, LEE YW: Irradiation induces regionally specific alterations in pro-inflammatory environments in rat brain. *Int J Radiat Biol* **86:** 132-144, 2010.

LI N, LEUNG GKK: Oligodendrocyte Precursor Cells in Spinal Cord Injury: A Review and Update. *Biomed Res Int* **2015**: 235195, 2015.

LI YQ, GUO YP, JAY V, STEWART PA, WONG CS: Time course of radiation-induced apoptosis in the adult rat spinal cord. *Radiother Oncol* **39:** 35-42, 1996.

LI YQ, CHEN P, HAIMOVITZ-FRIEDMAN A, REILLY RM, WONG CS: Endothelial apoptosis initiates acute blood-brain barrier disruption after ionizing radiation. *Cancer Res* **63:** 5950-5956, 2003.

LI YQ, CHEN P, JAIN V, REILLY RM, WONG CS: Early radiation-induced endothelial cell loss and blood-spinal cord barrier breakdown in the rat spinal cord. *Radiat Res* **161:** 143-152, 2004.

LIMOLI CL, GIEDZINSKI E, ROLA R, OTSUKA S, PALMER TD, FIKE JR: Radiation response of neural precursor cells: Linking cellular sensitivity to cell cyle checkpoints, apoptosis and oxidative stress. *Radiat Res* **161:** 17-27, 2004.

LJUBIMOVA NV, LEVITMAN MK, PLOTNIKOVA ED, EIDUS L: Endothelial cell population dynamics in rat brain after local irradiation. *Br J Radiol* **64:** 934-940, 1991.

LLEDO PM, ALONSO M, GRUBB MS: Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci* **7:** 179-193, 2006.

MAEGELE M, BRAUN M, WAFASAIDE A, SCHÄFER N, LIPPERT-GRUENER M, KREIPKE C, RAFOLS J, SCHÄFER U, ANGELOV DN, STUERMER EK: Long-term effects of enriched environment on neurofunctional outcome and CNS lesion volume after traumatic brain injury in rats. *Physiol Res* **64(1):** 129-145, 2015.

MCKEAGE K, KEATING GM: Fenofibrate: A review of its use in dyslipidaemia. *Drugs* **71:** 1917-1946, 2011.

MEGURO K, KASAI M, AKANUMA K, MEGURO M, ISHII H, YAMAGUCHI S: Donepezil and life expectancy in Alzheimer's disease: a retrospective analysis in the Tajiri Project. *BMC Neurol* **14:** 83, 2014.

MILDENBERGER M, BEACH TG, MCGEER EG, LUDGATE CM: An animal model of prophylactic cranial irradiation: Histologic effects at acute, early and delayed stages. *Int J Radiat Oncol Biol Phys* **18:** 1051-1060, 1990.

MIZUMATSU S, MONJE LM, MORHARDT DR, ROLA R, PALMER TD, FIKE JR: Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res* **63:** 4021-4027, 2003.

MOLTENI A, MOULDER JE, COHEN EF, WARD WF, FISH BL, TAYLOR JM, WOLFE LF, BRIZIO-MOLTENI L, VENO P: Control of radiation-induced pneumopathy and lung fibrosis by angiotensin-converting enzyme inhibitors and an angiotensin II type 1 receptor blocker. *Int J Radiat Biol* **76:** 523-532, 2000.

MONJE ML, MIZUMATSU S, FIKE JR, PALMER TD: Irradiation induces neural precursor-cell dysfunction. *Nat Med* **8:** 955-962, 2002.

MONJE ML, TODA H, PALMER TD: Inflammatory blockade restores adult hippocampal neurogenesis. *Science* **302:** 1760-1765, 2003.

MORAVAN MJ, OLSCHOWKA JA, WILIAMS JP, O'BANION MK: Cranial irradiation leads to acute and persistent neuroinflammation with delayed increases in T-cell infiltration and CD11c expression in C57BL/6 mouse brain. *Radiat Res* **176:** 459-473, 2011.

MOULDER JE, FISH BL, COHEN EP: ACE inhibitors and AII receptor antagonists in the treatment and prevention of bone marrow transplant nephropathy. *Curr Pharm Des* **9:** 737-749, 2003.

NAYLOR AS, BULL C, NILSSON MK, ZHU C, BJÖRK-ERIKSSON T, ERIKSSON PS, BLOMGREN K, KUHN HG: From the cover: Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Proc Natl Acad Sci USA* **105:** 14632-14637, 2008.

NDT Resource Center https://www.ndeed.org/EducationResources/CommunityCollege/RadiationSafety/theory/activity.htm. Accessed 17 January 2020.

NIEDER C, ANDRATSCHKE N, PRICE RE, RIVERA B, ANG KK: Innovative prevention strategies for radiation necrosis of the central nervous system. *Anticancer Res* **22:** 1017-1023, 2002.

NIEDER C, PRICE RE, RIVERA B, ANDRATSCHKE N, KK: Effects of insulin-like growth factor-1 (IGF-1) and amifostine in spinal cord reirradiation. *Strahlenther Onkol* **181:** 691-695, 2005.

OHGURI T, IMADA H, KOHSKI K, KAKEDA S, OHNARI N, MORIOKA T, NAKANO K, KONDA N, KOROGI Y: Effect of prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys* **67:** 248-255, 2007.

PEIFFER AM, LEYRER CM, GREENE-SCHLOESSER DM, SHING E, KEARNS WT, HINSON WH, TATTER SB, IP EH, RAPP SR, ROBBINS ME, SHAW EG, CHAN MD: Neuroanatomical target theory as a predictive model for radiation-induced cognitive decline. *Neurology* **80:** 747-753, 2013.

PEISSNER W, KOCHER M, TREUER H, GILLARDON F: Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. *Mol Brain Res* **71:** 61-68, 1999.

PEKNY M, PEKNA M: Astrocyte reactivity and reactive astrogliosis: costs and benefits. *Physiol Rev* **94:** 1077-1098, 2014.

PEÑA LA, FUKS Z, KOLESNICK RN: Radiation-induced apoptosis of endothelial cells in the murine central nervous system: Protection by fibroblast growth factor and sphingomyelinase deficiency. *Cancer Res* **60:** 321-327, 2000.

PERRY VH, TEELING J: Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Semin Immunopathol* **35(5):** 601-612, 2013.

PIAO J, MAJOR T, AUYEUNG G, POLICARPIO E, MENON J, DROMS L, GUTIN P, URYU K, TCHIEU J, SOULET D, TABAR V: Human embryonic stem cell-derived oligodendrocyte progenitors remyelinate the brain and rescue behavioral deficits following radiation. *Cell Stem Cell* **16:** 198-210, 2015.

PORTNOW J, SULEMAN S, GROSSMAN SA, ELLER S, CARSON K: A cyclooxygenase-2 (COX-2) inhibitor compared with dexamethasone in a survival study of rats with intracerebral 9L gliosarcomas. *Neuro Oncol* **4:** 22-25, 2002.

PROESCHOLDT MA, HEISS JD, WALBRIDGE S, MÜHLHAUSER J, CAPOGROSSI MC, OLDFIELD EH, MERRILL MJ: Vascular endothelial growth factor (VEGF) modulates vascular permeability and inflammation in rat brain. *J Neuropathol Exp Neurol* **58:** 613-627, 1999.

RABER J, ROLA R, LEFEVOUR A, MORHARDT D, CURLEY J, MIZUMATSU S, VANDENBERG SR, FIKE JR: Radiation induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res* **162:** 39-47, 2004.

RAMAKRISHNAN S, ANAND V, ROY S: Vascular Endothelial growth factor signaling in hypoxia and Inflammation. *J Neuroimmune Pharmacol* **9(2):** 142-160, 2014.

RAMANAN S, KOOSHKI M, ZHAO W, HSU FC, RIDDLE DR, ROBBINS ME: The PPARα agonist fenofibrate preserves hippocampal neurogenesis and inhibits microglial activation after whole-brain irradiation. *Int J Radiat Oncol Biol Phys* **75:** 870-877, 2009.

RAMANAN S, KOOSHKI M, ZHAO W, HSU FC, ROBBINS ME: PPARα ligands inhibit radiation-induced microglial inflammatory responses by negatively regulating NF-Kb and AP-1 pathways. *Free Radic Biol Med* **45:** 1695-1704, 2008.

RAMANAN S, ZHAO W, RIDDLE DR, ROBBINS ME: Role of PPARs in radiation-induced brain injury. *PPAR Res* **2010:** 234975, 2010.

RAPP SR, CASE LD, PEIFFER A, RAPP SR, NAUGHTON MM, CHAN MD, STIEBER VW, MOORE JR DF, FALCHUK SC, PIEPHOFF JV, EDENFIELD WJ, GIGUERE JK, LOGHIN ME, SHAW EG: Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial. *J Clin Oncol* **33(15):** 1653-1659, 2015.

REICHMAN HR, FARELL CL, DEL MAESTRO RF: Effects of steroids and nonsteroid anti-inflammatory agents on vascular permeability in a rat glioma model. *J Neurosurg* **65:** 233-237, 1986.

RIGGS L, PISCIONE J, LAUGHLIN S, CUNNINGHAM T, TIMMONS BW, COURNEYA KS, BARTELS U, SKOCIC J, DE MEDEIROS C, LIU F, PERSADIE N, SCHEINEMANN K, SCANTLEBURY N, SZULC KU, BOUFFET E, MABBOTT DJ: Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. *Neuro Oncol* **19(3):** 440-450, 2017.

ROBBINS ME, ZHAO W: Chronic oxidative stress and radiation-induced late normal tissue injury: A review. *Int J Radiat Biol* **80:** 251-259, 2004.

ROLA R, RABER J, RIZK A, OTSUKA S, VANDENBERG SR, MORHARDT DR, FIKE JR: Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol* **188:** 316-330, 2004.

SAKANAKA M, WEN TC, MATSUDA S, MASUDA S, MORISHITA E, NAGAO M, SASAKI R: In vivo evidence that erythropoietin protects neurons from ischemic damage. *Proc Natl Acad Sci USA* **95:** 4635-4640, 1998.

SANO K, SATO M, TANAKA R: Radiation-induced apoptosis and injury of oligodendrocytes on neonatal rat brains. *Clin Neurol Neurosur* **99:** 117, 1997.

SANTANA P, PEÑA LA, HAIMOVITZ-FRIEDMAN A, MARTIN S, GREEN D, MCLOUGHLIN M, CORDON-CARDO C, SCHUCHMAN EH, FUKS Z, KOLESNICK R: Acid sphingomyelinase-deficient human lymphoblasts and mice are defective in radiation-induced apoptosis. *Cell* **86:** 189-199, 1996.

SARAULLI D, COSTANZI M, MASTRORILLI V, FARIOLI-VECCHIOLI S: The Long Run: Neuroprotective Effects of Physical Exercise on Adult Neurogenesis from Youth to Old Age. *Curr Neuropharmacol* **15(4):** 519-533, 2017.

SASAKI R, MATSUMOTO A, ITOH K, KAWABE T, OTA Y, YAMADA K, MARUTA T, SOEJIMA T, SUGIMURA K: Target cells of apoptosis in the adult murine dentate gyrus and O4 immunoreactivity after ionizing radiation. *Neurosci Lett* **279:** 57-60, 2000.

SATO Y, SHINJYO N, SATO M, NILSSON MKL, OSATO K, ZHU CH, PEKNA M, KUHN HG, BLOMGREN K: Grafting neural stem and progenitor cells into the hippocampus of juvenile, irradiated mice normalizes behavior deficits. *Front Neurol* **9:** 715, 2018.

SHI L, LINVILLE MC, IVERSEN E, MOLINA DP, YESTER J, WHEELER KT, ROBBINS ME, BRUNSO-BECHTOLD JK: Maintenance of white mater integrity in a rat model of radiation-induced cognitive impairment. *J Neurol Sci* **285:** 178-184, 2009.

SHINOHARA C, GOBBEL GT, LAMBORN KR, TADA E, FIKE JR: Apoptosis in the subependyma of young adult rats after single and fractionated doses of X-rays. *Cancer Res* **57:** 2694-2702, 1997.

SCHINDLER MK, FORBES ME, ROBBINS ME, RIDDLE DR: Aging-dependent changes in the radiation response of the adult rat brain. *Int J Radiat Oncol Biol Phys* **70:** 826-834, 2008.

SCHULTHEISS TE, STEPHENS LC: Permanent radiation myelopathy. *Br J Radiol* **65:** 737-753, 1992.

SIEGAL T, PFEFFER MR: Radiation-induced changes in the profile of spinal cord serotonin, prostaglandin synthesis, and vascular permeability. *Int J Radiat Oncol Biol Phys* **31:** 57-64, 1995.

SMITH SM, GIEDZINSKI E, ANGULO MC, LUI T, LU C, PARK AL, TANG S, MARTIROSIAN V, RU N, CHMIELEWSKI NN, LIANG Y, BAULCH JE, ACHARYA MM, LIMOLI CHL: Functional equivalence of stem cell and stem cell-derived extracellular vesicle transplantation to repair the irradiated brain. *Stem Cells Trans Med* **9(1):** 93-105, 2020.

SNYDER JS, HONG N, MCDONALD RJ, WOJTOWICZ JM: A role for adult hippocampal neurogenesis in spatial long-term memory. *Neuroscience* **130:** 843-852, 2005.

SORIA B, MARTIN-MONTALVO A, AGUILERA Y, MELLADO-DAMAS N, LÓPEZ-BEAS J, HERRERA-HERRERA I, LÓPEZ E, BARCIA JA, ALVAREZ-DOLADO M, HMADCHA A, CAPILLA-GONZÁLES V: Human mesenchymal stem cells prevent neurological complications of radiotherapy. *Front Cell Neurosci* **13:** 204, 2019.

SPIRES TL, GROTE HE, VARSHNEY NK, CORDERY PM, VAN DELLEN A, BLAKEMORE C, HANNAN AJ: Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J Neurosci* **24:** 2270-2276, 2004.

STOREBØ OJ, PEDERSEN N, RAMSTAD E, KIELSHOLM ML, NIELSEN SS, KROGH HB, MOREIRA-MAIA CR, MAGNUSSON FL, HOLMSKOV M, GERNER T, SKOOG M, ROSENDAL S, GROTH C, KIRSTEN DG, RASMUSSEN B, GAUCI D, ZWI M, KIRUBAKARAN R, HÅKONSEN SJ, AAGAARD L, SIMONSEN E, GLUUD CH: Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents-assessment of adverse events in non-randomised studies. *Cochrane Database Syst Rev* **5(5):** 2018.

STYS PK: White matter injury mechanisms. *Curr Mol Med* **4:** 113-130, 2004.

TABATA H: Diverse subtypes of astrocytes and their development during corticogenesis. *Front Neurosci* **9:** 114, 2015.

TADA E, PARENT JM, LOWENSTEIN DH, FIKE JR: X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. *Neurosience* **99:** 33-41, 2000.

TANG TT, ZAWASKI JA, KESLER SR, BEAMISH CHA, REDDICK WE, GLASS JO, CARNEY DH, SABEK OM, GROSSHANS DR, BABER MW: A Comprehensive Preclinical Assessment of Late-Term Imaging Markers of Radiation-Induced Brain Injury. *Neurooncol Adv* **1(1):** vdz012, 2019.

TSAO MN, LI YQ, LU G, XU Y, WONG CS: Upregulation of vascular endothelial growth factor is associated with radiation-induced blood-spinal cord barrier breakdown. *J Neuropathol Exp Neurol* **58:** 1051-1060, 1999.

URBACH A, WITTE OW: Divide or Commit – Revisiting the Role of Cell Cycle Regulators in Adult Hippocampal Neurogenesis. *Front Cell Dev Biol* **7:** 55, 2019.

VAN PRAAG H, CHRISTIE BR, SEJNOWSKI TJ, GAGE FH: Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* **96:** 13427-13431, 1999.

VISHWAKARMA SK, BARDIA A, TIWARI SK, PASPALA SAB, KHAN AA: Current concept in neural regeneration research: NSCs isolation, characterization and transplantation in various neurodegenerative diseases and stroke: A review. *J Adv Res* **5(3):** 277-294, 2014.

VON BOHLEN UND HALBACH O: Immunohistochemical markers for proliferative events, gliogenesis, and neurogenesis within the adult hippocampus. *Cell Tissue Res* **345 (1):** 1-19, 2011.

WARRINGTON JP, CSISZAR A, JOHNSON DA: Cerebral microvascular rarefaction induced by whole brain radiation is reversible by systemic hypoxia in mice. *Am J Physiol Heart Circ Physiol* **300:** 736-744, 2011.

WARRINGTON JP, CSISZAR A, MITSCHELEN M, LEE YW, SONNTAG WE: Whole brain radiation-induced impairments in learning and memory are time-sensitive and reversible by systemic hypoxia. *PLoS ONE* **7:** 30444, 2012.

WILSON CM, GABER MW, SABEK OM, ZAWASKI JA, MERCHANT TE: Radiation-induced astrogliosis and blood-brain barrier damage can be abrogated using anti-TNF treatment. *Int J Radiat Oncol Biol Phys* **74:** 934-941, 2009.

WONG-GOODRICH SJE, PFAU ML, FLORES CT, FRASER JA, WILIAMS CL, JONES LW: Voluntary running prevents progressive memory decline and increases adult hippocampal neurogenesis and growth factor expression after whole-brain irradiation. *Cancer Res* **70:** 9329-9338, 2010.

ZHAO W, DIZ DI, ROBBINS ME: Oxidative damage pathways in relation to normal tissue injury. *Br J Radiol* **80:** S23-31, 2014.

ZHOU H, LIU Z, LIU J, WANG J, ZHOU D, ZHAO Z, XIAO S, TAO E, SUO WZ: Fractionated radiation-induced acute encephalopathy in a young rat model: Cognitive dysfunction and histologic findings. *AJNR Am J Neuroradiol* **32:** 1795-1800, 2011.

YANG L, YANG J, LI G, LI Y, WU R, CHENG J, TANG Y: Patophysiological responses in rat and mouse models of radiation-induced brain injury. *Mol Neurobiol* **54(2):** 1022-1032, 2017.

YUAN H, GABER MW, BOYD K, WILSON CM, KIANI MF, MERCHANT TE: Effects of fractionated radiation on the brain vasculature in a murine model: Blood-brain barrier permeability, astrocyte proliferation, and ultrastructural changes. *Int J Radiat Oncol Biol Phys* **66:** 860-866, 2006.

YUAN H, GABER MW, MCCOLGAN T, NAIMARK MD, KIANI MF, MERCHANT TE: Radiation-induced permeability and leukocyte adhesion in the rat blood-brain barrier: Modulation with anti-ICAM-1 antibodies. *Brain Res* **969:** 59-69, 2003.