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REVIEW

Pathological Changes in the Central Nervous System Following Exposure to Ionizing Radiation

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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

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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 h after treatment (Shinohara *et al.* 1997, Peissner *et al.* 1999, Tada *et al.* 2000) and reaching a maximum within 6 to 12 h 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 h after treatment with subsequent no additional apoptosis until 48 h 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-inflammatory 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 h 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 h 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-aldosterone 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) environmental 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 Pio before, during, and for 4 or 54 weeks after fractionated irradiation with a total dose of 40 or 45 Gy (5 Gy/d, 2 d/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 RAAS, 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 h 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 dysfunctions 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 and 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.

Conclusions

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

There is no conflict of interest.

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