Implications of irradiating the subventricular zone stem cell niche

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ABSTRACT

Radiation therapy is a standard treatment for brain tumor patients. However, it comes with side effects, such as neurological deficits. While likely multi-factorial, the effect may in part be associated with the impact of radiation on the neurogenic niches. In the adult mammalian brain, the neurogenic niches are localized in the subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus of the hippocampus, where the neural stem cells (NSCs) reside. Several reports showed that radiation produces a drastic decrease in the proliferative capacity of these regions, which is related to functional decline. In particular, radiation to the SVZ led to a reduced long-term olfactory memory and a reduced capacity to respond to brain damage in animal models, as well as compromised tumor outcomes in patients. By contrast, other studies in humans suggested that increased radiation dose to the SVZ may be associated with longer progression-free survival in patients with high-grade glioma. In this review, we summarize the cellular and functional effects of irradiating the SVZ niche. In particular, we review the pros and cons of using radiation during brain tumor treatment, discussing the complex relationship between radiation dose to the SVZ and both tumor control and toxicity.

Contents

1. Introduction

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Radiation therapy is critical in the treatment of brain tumors such as glioblastoma multiforme (Stupp et al., 2009; Stupp et al., 2005; Kumabe

et al., 2013; DeAngelis, 2005; Rusthoven et al., 2014; Chen et al., 2013). Modern techniques such as intensity-modulated radiation therapy allow focused delivery of radiation dose to the tumor while minimizing radiation dose to the adjacent critical structures. Nonetheless, adjacent healthy brain tissue also receives some radiation dose during treatment depending on the tumor location and geometry. Cellular and functional effects have been associated with radiation to the neurogenic niches (Achanta et al., 2009; Tada et al., 2000; Crossen et al., 1994; Monje et al., 2002; Capilla-Gonzalez et al., 2014; Padovani et al., 2012; Armstrong et al., 2013). The subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus (DG) of the hippocampus constitute the main neurogenic niches of the adult mammalian brain (Gates et al., 1995; Alvarez-Buylla et al., 2002; Doetsch et al., 1997; Seri et al., 2001; Eriksson et al., 1998; Quinones-Hinojosa et al., 2006). Cranial radiation is known to inhibit proliferation and neurogenesis in the hippocampus, which has been related to learning and memory deficits in rodents and humans (Achanta et al., 2009; Tada et al., 2000; Monje et al., 2002; Padovani et al., 2012; Armstrong et al., 2013; Redmond et al., 2013; Monje, 2008; Sato et al., 2013; Calabrese et al., 2009; Marazziti et al., 2012; Raber et al., 2004). Similarly, radiation of the rodent SVZ depletes precursor cells and decreases the production of new cells, affecting the consolidation and restitution of olfactory traces in the olfactory bulb (OB) (Balentova et al., 2013; Lazarini et al., 2009; Achanta et al., 2012), as well as the ability of the SVZ to respond to brain damage (Capilla-Gonzalez et al., 2014). Despite these negative effects, retrospective data suggest a potentially prolonged overall survival in patients with glioblastoma that received high dose of ipsilateral SVZ radiation(Chen et al., 2013; Gupta et al., 2012; Kast et al., 2013; Evers et al., 2010; Lee et al., 2013a; Lee et al., 2013b; Chen et al., 2015). In line with these reports, a prospective study of hypofractionated radiation therapy found improved survival in long term survivors with necrosis in the SVZ (Iuchi et al., 2014). In this review, we highlight the current knowledge regarding the cellular and functional effects of SVZ radiation, focusing in its implication on brain tumor therapy.

2. The adult subventricular zone: a source of neural stem cells

The SVZ is the main reservoir of neural stem cells (NSCs) in the adult mammalian brain (Doetsch et al., 1997; Quinones-Hinojosa et al., 2006; Sanai et al., 2004). It is widely accepted that NSCs correspond to a pool of astroglial cells capable of both self-renewal and differentiation into neurons, oligodendrocytes, or astrocytes (Sanai et al., 2004; Doetsch et al., 1999a; Ihrie et al., 2008). The SVZ is composed of different cell types that organize to construct a unique cytoarchitecture, which differs between rodents and humans (Fig. 1).

2.1. Rodent SVZ

The rodent SVZ contains four main cell types that are defined by their morphology, ultrastructure, and molecular markers (Doetsch et al., 1997). This region lines the ventricle cavity by a monolayer of ependymal multiciliated cells. Next to this ependymal layer, astrocyte-like NSCs extend an apical process ending in a primary cilium to directly contact the ventricle. This cilium has been suggested to play a signaling role in the regulation of NSC proliferation and differentiation (Tong et al., 2014; Ihrie et al., 2011; Mirzadeh et al., 2008). Astrocyte-like NSCs proliferate slowly to generate fast proliferating precursors that, in turn, give rise to neuroblasts (Doetsch et al., 1997; Doetsch et al., 1999b; Ponti et al., 2013) (Fig. 1A–B). Typically, neuroblasts in the SVZ form chains surrounded by non-neurogenic astrocytes and migrate tangentially through the rostral migratory stream (RMS) to the OB, where they differentiate into interneurons (Luskin et al., 1997; Lois et al., 1994; Kelsch et al., 2010; Carleton et al., 2003).

2.2. Human SVZ

The presence of astrocyte-like NSCs has also been described in the adult human SVZ (Sanai et al., 2004). The proliferative and neurogenic potential of this germinal zone is maintained during adulthood,
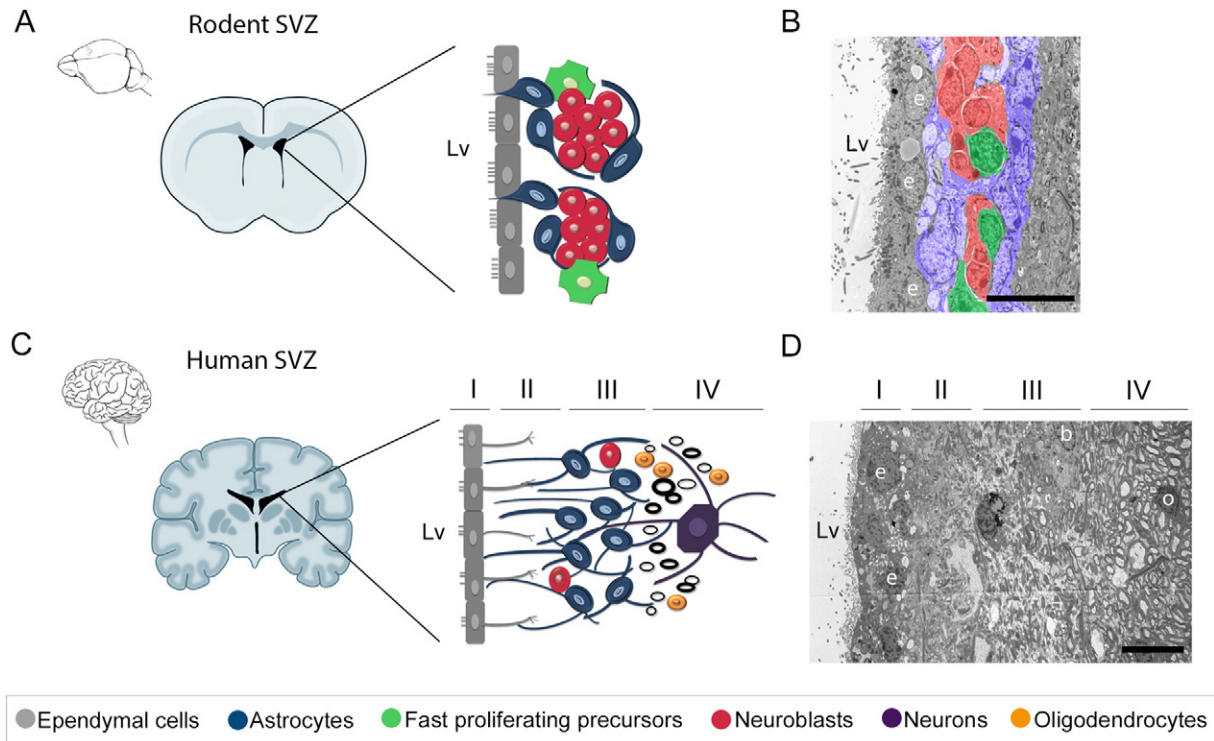
Fig. 1. Cell organization of the SVZ neurogenic niche. (A) Schematic representation of the SVZ in a coronal view of the mouse brain. The enlarged area depicts the cytoarchitecture of the neurogenic niche. (B) Electron microscopy image of the rodent SVZ. (C) Schematic representation of the SVZ in a coronal view of the human brain. The enlarged area depicts the four layers where the SVZ cells organize. (D) Electron microscopy image the human SVZ. b, astrocyte-like cell; e, ependymal cell; Lv, lateral ventricle; o, oligodendrocytes. Scale bar 10 μm.

although it is drastically decreased when compared to fetal and pediatric stages (Quinones-Hinojosa et al., 2006; Sanai et al., 2004; Sanai et al., 2011; Guerrero-Cazares et al., 2011). The human SVZ differs from that found in rodents since it organizes into four layers: I) Ependymal layer, which is composed by multiciliated ependymal cells; II) Hypocellular gap, composed by expansions of ependymal and astrocytic cells; III) Astrocytic ribbon, where astrocytes are located; and IV) Transitional zone to the parenchyma, rich in myelin and oligodendrocytes. There has been no description of fast proliferating precursors, but migrating neuron-like cells can occasionally be found at the layers II and III as individual cells (Quinones-Hinojosa et al., 2006; Sanai et al., 2004) (Fig. 1C–D). However, the existence of an adult human RMS remains highly controversial (Sanai et al., 2004; Sanai et al., 2007; Curtis et al., 2007; Wang et al., 2011; Kam et al., 2009). The group of Curtis et al. suggested that a pathway of migratory neuroblasts is present in the adult human brain and that this pathway organized around a remnant of the ventricular cavity that extends from the SVZ to the OB (Curtis et al., 2007; Kam et al., 2009). In contrast, other studies failed in identifying an open ventricular system connecting the SVZ with the OB (Sanai et al., 2007) and described the existence of neuroblasts that continuously appear, singly or in pairs, without forming chains in an RMS that is nearly extinct by adulthood (Sanai et al., 2004; Sanai et al., 2011; Sanai et al., 2007; Wang et al., 2011).

2.3. NSCs and their host microenvironment

In the SVZ, NSCs are immersed in a specialized niche where they establish cell–cell and cell–microenvironment interactions to regulate their proliferation and fate. The extracellular matrix (ECM) is a crucial component of the SVZ microenvironment that is composed by vessel basal lamina rich in laminin and collagen I, and other ECM molecules such as metalloproteinases, brevican, tenascin-C, growth factors, and a variety of proteoglycans (Kazanis et al., 2007; Kerever et al., 2007; Kazanis et al., 2010; Kazanis et al., 2011; Mercier et al., 2002; de Chevigny et al., 2006; Akita et al., 2008; von Holst et al., 2006; Bandtlow et al., 2000; Novak et al., 2000). These ECM molecules modulate NSC function and are determinant for basic psychological processes, such as neuroblasts migration (Capilla-Gonzalez et al., 2015a).

3. The functions of the SVZ niche in the brain

3.1. SVZ and olfaction

In rodents, SVZ neuroblasts that reach the OB are capable of reestablishing and re innervating the old or damaged population of olfactory neurons (Imayoshi et al., 2008; Belvindrah et al., 2009; Lledo et al., 2006; Petreanu et al., 2002; Lazarini et al., 2011). Consequently, SVZ neurogenesis disruption may result in an impairment of the olfactory function (Lazarini et al., 2009; Capilla-Gonzalez et al., 2012; Li et al., 2013; Sui et al., 2013). This phenomenon was observed in a study using N-ethyl-N-nitrosourea (ENU), an environmental toxic that affects proliferative cells. Adult mice exposed to this toxic showed a loss of astrocyte-like NSCs, fast proliferating precursors, and neuroblasts within the SVZ. Hence, ENU-exposure led to a decrease in the incorporation of SVZ-derived cells into the OB and subsequently impaired odor discrimination (Capilla-Gonzalez et al., 2012). Similarly, cranial radiation disrupts the SVZ neurogenic niche in mice and causes a reduction in the production of new OB neurons, which alters olfactory memory (Lazarini et al., 2009).

While the incorporation of SVZ-derived cells into the OB is required for normal olfactory function in rodents, the role of human neurogenesis in olfaction is uncertain (Capilla-Gonzalez et al., 2015b). In fact, neuroblast migration toward the OB is minimal or inexistent in the adult human brain (Sanai et al., 2004; Sanai et al., 2011; Sanai et al., 2007; Curtis et al., 2007; Wang et al., 2011; Kam et al., 2009). The cell turnover dynamics in the OB of the healthy human brain have

been established by measuring ^{14}C in genomic DNA (Bergmann et al., 2012). Results revealed that the postnatal production of new olfactory neurons is limited in humans, but there remains a continuous turnover of non-neuronal cells, such as oligodendrocytes (Bergmann et al., 2012), which may be related to the maintenance of the myelin tracts for the correct brain function (McKenzie et al., 2014). These findings are in line with those found in aged mice, where the migration of SVZ-derived neuroblasts into the OB is drastically decreased during aging yet the production of oligodendroglial cells is maintained (Capilla-Gonzalez et al., 2013). Another study in humans using ^{14}C dating approaches showed that new cells incorporate into the adult striatum, which likely derived from the adjacent SVZ (Ernst et al., 2014). The authors indicated that the newly generated cells mainly correspond to striatal interneurons and that they were absent in the striatum of patients with Huntington's disease, a neurodegenerative disease affecting striatal neurons (Ernst et al., 2014). Hence, apart from its role in maintaining the myelin, the human SVZ may play a key role in the prevention of neurodegenerative diseases, such as Huntington's disease, rather than in OB neurogenesis.

3.2. SVZ and tissue repair

Several research groups have reported the role of the SVZ neurogenesis in brain repair in animal models and humans (Thompson et al., 2008; Darsalia et al., 2005; Kaneko et al., 2009; Macas et al., 2006; Marti-Fabregas et al., 2010; Nait-Oumesmar et al., 2007). For example, following an induced cerebral ischemia in rodents, SVZ NSCs proliferate to produce new neuroblasts capable of migrating into the lesion site, where they differentiate into new neurons that replace the damaged cells (Jin et al., 2001; Liu et al., 2013; Zhang et al., 2014). It has been shown that the brain of patients that suffered an ischemic attack also showed an SVZ activation and new cells expressing neuronal markers were found into the lesion site (Macas et al., 2006; Marti-Fabregas et al., 2010; Liu et al., 2013; Jin et al., 2006). Similarly, the rodent SVZ activates in response to an experimental demyelination and newly generated cells migrate from the SVZ into the damaged tissue, where they differentiate into myelinating oligodendrocytes to contribute to brain repair (Capilla-Gonzalez et al., 2014; Nait-Oumesmar et al., 2007; Gonzalez-Perez et al., 2009; Picard-Riera et al., 2002; Jablonska et al., 2010). A similar response has been described in the human postmortem brains of individuals with multiple sclerosis lesions (Nait-Oumesmar et al., 2007). These SVZ responses to brain damage are in part mediated by cytokines, chemokines and their receptors (*e.g.* interferon gamma, tumor necrosis factor alpha, CXCL12/CXCR4) that are expressed from the injury site and in progenitor cells. These molecules initiate different cascades of intracellular signaling that mediate chemotactic cues to direct the migratory cells into the injury (Capilla-Gonzalez et al., 2015a; Imitola et al., 2004; Tran et al., 2004; Jaerve et al., 2012; Turbic et al., 2011). The SVZ role in tissue regeneration could be more relevant for humans than for rodents, since the OB neurogenesis is minimal in the human brain.

3.3. SVZ and tumorigenesis

Though the plasticity of the SVZ has quantifiable benefits for the adult brain, it comes with a potential limitation. NSCs residing in the SVZ possess remarkable similarities to brain tumor stem cells (BTSCs), a speculative subpopulation of cells within the brain tumor. BTSCs are likely responsible for tumor initiation and resistance to current therapies (Galli et al., 2004; Vescovi et al., 2006; Hemmati et al., 2003; Yan et al., 2013; Schonberg et al., 2013; Fomchenko et al., 2005; Guerrero-Cazares et al., 2009). Both NSCs and BTSCs have similar multi-potent and migratory capabilities, as well as share several cell markers, such as nestin, musashi, and CD133 (Galli et al., 2004; Hemmati et al., 2003; Quinones-Hinojosa et al., 2007; Singh et al., 2003). These similarities suggest that NSCs may also act as brain

tumor-initiating cells. Hypothetically, astrocyte-like NSCs transform into BTSCs that migrate from the SVZ to other brain regions where they contribute to tumor formation (Quinones-Hinojosa et al., 2007; Ignatova et al., 2002; Gil-Perotin et al., 2006; Jackson et al., 2006; Alcantara Llaguno et al., 2011) (Fig. 2). The expression of the platelet-derived growth factor (PDGF) receptor-α in the SVZ astrocytes has been related to their tumorigenic capacity. Following an exogenous stimulation by PDGF infusion, the production of neuroblasts is arrested and the proliferation of SVZ astrocytes increases, contributing to the generation of glioma-like masses (Jackson et al., 2006; Ozawa et al., 2010). A report using a nestin-ΔTK-IRES-GFP transgene that labels quiescent NSCs in a mouse model, also identified a subset of SVZ cells as a source of new cancer cells responsible for tumor growth. Interestingly, the chemical depletion of this subset of cells with ganciclovir and temozolomide impedes tumor development (Chen et al., 2012). Recently, a report studying brain tumor patients correlated contrast-enhancing glioblastoma recurrence with proximity to neurogenic regions, supporting the SVZ tumorigenic potential (Chen et al., 2015).

Given that the SVZ is implicated in multiple functions, factors that alter its germinal capacity merit evaluation. The remainder of this review will summarize the data related to the effects of irradiating the SVZ niche, particularly during brain tumor treatment.

4. Impact of radiation on the SVZ neurogenic niche

Radiation depletes the proliferative cells within the germinal niches in the adult rodent brain (Capilla-Gonzalez et al., 2014; Lazarini et al., 2009; Achanta et al., 2012; Panagiotakos et al., 2007; Fukuda et al., 2005; Tada et al., 1999; Fike et al., 2007; Ford et al., 2011). In the SVZ, astrocyte-like NSCs, fast proliferating precursors and neuroblasts are the main cell populations affected by radiation, while ependymal cells remain unaltered (Capilla-Gonzalez et al., 2014; Achanta et al., 2012) (Fig. 3). In particular, electron microscopy studies revealed that, 30 days after SVZ local radiation, the number of NSCs was reduced, fast proliferating precursors cells were practically non-existent, and

Fig. 2. Tumorigenic role of the SVZ niche. Schematic representation of a coronal hemisection of the rodent brain, depicting the SVZ role on tumor formation. NSCs within the SVZ are potent tumor-initiating cells. Hypothetically, SVZ cells are able to migrate to other brain regions to originate a tumor mass.

neuroblasts were scarce. These effects on the proliferative populations were further evaluated by examining the expression of Ki67, a marker of proliferative cells, which showed a notable decrease in the irradiated SVZ (Capilla-Gonzalez et al., 2014; Achanta et al., 2012). Additionally, in vitro assays revealed that NSCs remaining in the irradiated SVZ lack the ability to generate neurospheres, suggesting functional deficits in the population of NSCs (Achanta et al., 2012). It has been described that the impact of radiation on the NSC population leads to a decrease of neuroblasts that migrated from the SVZ to the OB (Lazarini et al., 2009; Achanta et al., 2012; Mandairon et al., 2003; Diaz et al., 2011). Studies with rodents that used a local radiation of the SVZ have shown that the expression of Doublecortin, a marker of immature neurons, was drastically reduced in the SVZ, RMS and OB, which indicated a disrupted neuroblasts migration towards the OB (Lazarini et al., 2009; Achanta et al., 2012). To confirm this result, authors injected retroviruses expressing green fluorescent protein into the SVZ to label NSCs and track the migratory pattern of newly generated neuroblasts. This assay revealed that, a week after retroviral injections, the SVZ neuroblasts failed to migrate through the RMS into the OB of irradiated mouse brains (Achanta et al., 2012). The decline in neuroblast migration has been associated with disorders involving olfaction. In particular, long-term olfactory memory was found to be sensitive to SVZ irradiation when animals were conducted in a task to remember different odorants after a month period (Lazarini et al., 2009).

A recent study has suggested that radiation may also compromise the role that NSCs play in tissue regeneration (Capilla-Gonzalez et al., 2014). In this work, authors used a mouse model that combined local SVZ radiation with a demyelination lesion in the striatum. In line with previous studies, authors first showed that the intact SVZ activates in response to the brain lesion. A month after demyelination, the SVZ increased proliferation and generated new cells that migrated into the lesion to differentiate into premature oligodendrocytes. However, when damage occurs in an irradiated brain, the SVZ has a less robust response than that found in non-irradiated animals (Capilla-Gonzalez et al., 2014). These results indicate that the ability of the SVZ to respond to brain damage decreases after radiation, which may be detrimental for an effective regenerative capacity. As previously mentioned, the radiation-related effect on tissue regeneration becomes more relevant for humans, where the role of the SVZ is correlated to the prevention or response to brain injuries, instead of OB neurogenesis (Bergmann et al., 2012; Ernst et al., 2014; Marti-Fabregas et al., 2010; Nait-Oumesmar et al., 2007; van den Berge et al., 2013). In this context, the healthspan of patients receiving radiotherapy, such as brain tumor patients, may be compromised. This compromise may be more evident in those patients who experience long-term survival.

It is known that radiation also alters the SVZ microenvironment. Using a computed tomography-guided localized radiation technique, a study demonstrated that the intact SVZ NSCs failed to migrate across the irradiated RMS, suggesting that the microenvironment becomes hostile for cell invasion after radiation (Achanta et al., 2012). Furthermore, radiation disrupts microvascular angiogenesis and induces local inflammation by increasing the number of active microglia (Panagiotakos et al., 2007; Monje et al., 2002; Kalm et al., 2009), which lead to an increase of pro-inflammatory cytokines, such as IL-1 beta and TNF-alpha, that influence neural progenitor cell function (Mizumatsu et al., 2003; Monje et al., 2003; Liu et al., 2010; Vallieres et al., 2002). Thus, radiation effects should be considered not only in the exposed NSCs but also in the microenvironment where these cells are immersed.

5. The use of radiation in the treatment of brain tumors: pros and cons

The first-line of treatment for the majority of primary malignant brain tumors is maximal safe resection followed by radiation therapy, with or without chemotherapy, based on numerous studies that
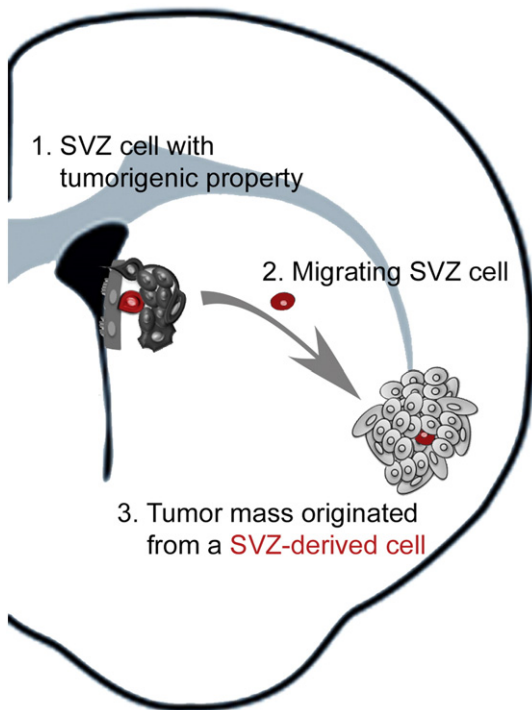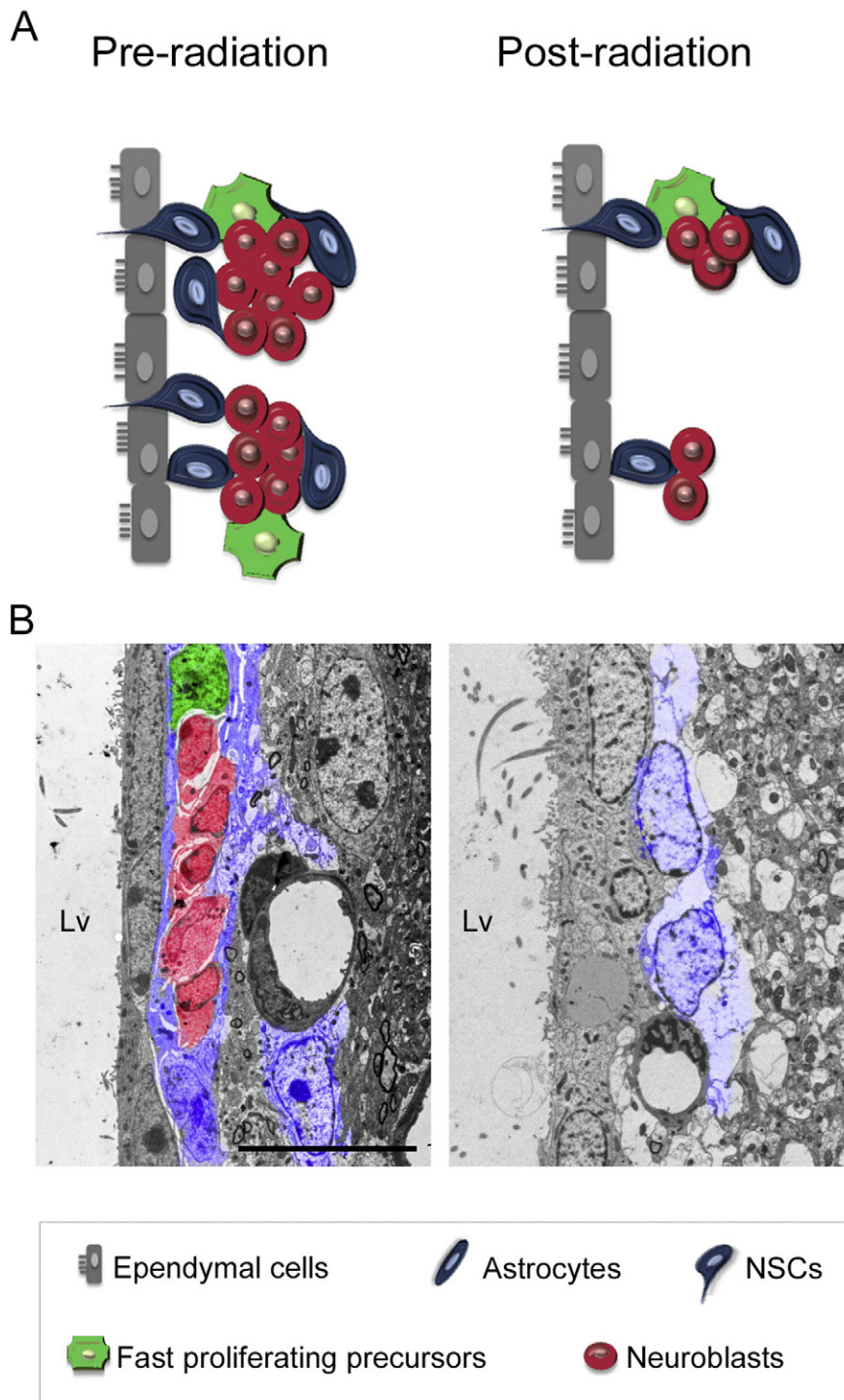
Fig. 3. Radiation disrupts the SVZ neurogenic niche. (A) Schematic representations of the rodent SVZ. In a pre-radiation condition the SVZ preserves its typical cell organization. Following radiation, the SVZ shows a notable depletion of fast proliferating precursors and neuroblasts. Some astrocytes remain after radiation and ependymal cells are not affected. (B) Electron microscopy images of the rodent SVZ pre- and post-radiation. Scale bar 10 μm.

demonstrate a survival benefit with the addition of radiation (Stupp et al., 2009; Stupp et al., 2005; Roth et al., 1960; Walker et al., 1978; Gaspar et al., 1997). Radiation therapy causes damage to the genetic material of cells and consequently most of these cells die after attempting mitosis (Jackson et al., 2009). This halts progression and recurrence of tumors (Fig. 4). While modern radiation techniques such as intensity-modulated radiation therapy allow for focused treatment, adjacent normal structures continue to receive radiation dose which may lead to functional impairment, such as neurocognitive

sequelae (Padovani et al., 2012; Armstrong et al., 2013; Redmond et al., 2013; Panagiotakos et al., 2007; Blomstrand et al., 2012; Gondi et al., 2014). The current theory is that these side effects may in part be related to the radiation dose that the neurogenic niches receive. In this context, several studies have shown that it is possible to reduce radiation dose to the NSCs by defining them as objects at risk during radiation therapy planning (Blomstrand et al., 2012; Gondi et al., 2014; Wan et al., 2013; Oehler et al., 2013; Redmond et al., 2011; Barani et al., 2007; van Kesteren et al., 2012; Gondi et al., 2010). A retrospective study of
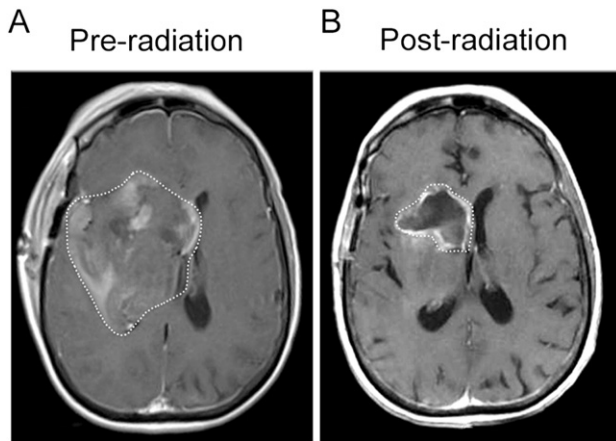
Fig. 4. Radiation is a frequent tool in the treatment of brain tumor patients. (A) MRI of a brain tumor patient before being treated. (B) MRI after brain tumor resection and four-week post-radiation (60 Gy dose).

pediatric patients with medulloblastoma suggested a potential benefit of reducing radiation dose to the neurogenic niches. Specifically, the mean dose to the hippocampus and SVZ was limited to 42.3% without compromising the whole-brain target volume using intensity-modulated proton therapy. The neurogenic niches sparing resulted in a lower risk of developing neurological impairments, compared to more aggressive therapies (Blomstrand et al., 2012). Similarly, a phase II prospective study of patients with brain metastases demonstrated that conformal avoidance of the hippocampus during

whole-brain cranial radiation associates with preservation of memory and quality of life (Gondi et al., 2014). By contrast, published studies suggest that tumor outcomes in patients with high-grade gliomas may be improved with higher radiation doses to the SVZ (Chen et al., 2013; Gupta et al., 2012; Kast et al., 2013; Evers et al., 2010; Lee et al., 2013a; Lee et al., 2013b). For example, a retrospective review of patients with glioblastoma treated with radiation and temozolomide chemotherapy demonstrated improved progression-free survival (from 10.3 months to 15.1 months) in those patients that underwent gross total resection and received >40 Gy to the ipsilateral SVZ, compared with patients who received lower radiation doses to this area (Chen et al., 2013). Likewise, a prospective study of hypofractionated radiation therapy for newly diagnosed glioblastoma demonstrated improved outcomes in patients that developed necrosis within the SVZ after radiation (Iuchi et al., 2014). These studies base on the hypothesis that the SVZ plays a role in tumorigenesis, contributing to tumor progression (Chen et al., 2015; Galli et al., 2004; Yan et al., 2013; Quinones-Hinojosa et al., 2007; Jackson et al., 2006). In this context, tumor microenvironment radiation could be affecting the migration of SVZ cells into the tumor, improving patients' outcomes. Tumor cells need to modify the ECM to invade the normal brain parenchyma. These modifications affect ECM components, such as tenascin, fibronectin, laminin, vitronectin, and different types of collagen, which influence SVZ cells by attracting them into the tumor (Capilla-Gonzalez et al., 2015a; Ziu et al., 2006). However, after irradiating the tumor microenvironment, the incorporation of SVZ-derived cells into the tumor area could be modified, decreasing the SVZ cells-mediated tumorigenic effect. Prospective studies will be critical in further understanding the seemingly contradictory data regarding radiation dose to the SVZ,

Table 1
Positive and negative effects of radiation in brain tumor

Positive effects	References
Radiotherapy depletes cancer cells, decreasing tumor size and halting the progression and recurrence of tumors, which has been associated with prolonged patient survival.	Roth and Elvidge, *Journal of Neurosurgery* 1960 (Roth et al., 1960) Walker et al., *Journal of Neurosurgery* 1978 (Walker et al., 1978) Gaspar et al., *Int J Radiat Oncol Biol Phys.* 1997 (Gaspar et al., 1997) Stupp et al. *The New England Journal of Medicine* 2005 (Stupp et al., 2005) Jackson and Bartek, *Nature* 2009 Stupp et al., *The Lancet Oncology* 2009 (Stupp et al., 2009)
Tumor outcomes may be improved with higher radiation doses to the SVZ. These studies support the hypothesis that NSCs have tumorigenic properties.	Evers et al., *BMC Cancer* 2010 (Evers et al., 2010) Gupta et al., *Journal of Neuro-oncology* 2012 (Gupta et al., 2012) Chen et al., *Int J Radiat Oncol Biol Phys.* 2013 (Chen et al., 2013) Kast et al., *J Neurooncol* 2013 (Kast et al., 2013) Lee et al., *Int J Radiat Oncol Biol Phys.* 2013 (Lee et al., 2013b) Galli et al., *Cancer Research* 2004 (Galli et al., 2004) Jackson et al., *Neuron* 2006 (Jackson et al., 2006) Quinones-Hinojosa and Chaichana, *Experimental Neurology* 2007 (Quinones-Hinojosa et al., 2007) Yan et al., *Curr Opin Neurol* 2013 (Yan et al., 2013)
Radiation induces modification in the tumor microenvironment that could affect the migration of SVZ cells into the tumor, decreasing the SVZ cells-mediated tumorigenic effect and improving patients´ outcomes.	Ziu et al., *J Neurooncol* 2006 (Ziu et al., 2006)

Negative effects	References
Experimental models with rodents showed that radiation depletes precursor cells within the SVZ and decreases neurogenesis in the OB, leading to olfactory deficits.	Balentova et al., *Acta Histochem* 2013 (Balentova et al., 2013) Lazarini et al., *PloS One* 2009 (Lazarini et al., 2009) Achanta et al., *Stem Cells* 2012 (Achanta et al., 2012)
Radiation impact on the SVZ reduces its ability to respond to brain damages, such as demyelinating injury.	Capilla-Gonzalez et al., *Stem Cells* 2014 (Capilla-Gonzalez et al., 2014)
Radiation impact on the neurogenic niches has been related to the developments of cognitive deficits, such as learning and memory impairments, in rodents and humans.	Tada et al., *Neuroscience* 2000 (Tada et al., 2000) Monje et al., *Nature medicine* 2002 (Monje et al., 2002) Raber et al., *Radiation Research* 2004 (Raber et al., 2004) Monje, *Developmental Disabilities Research Reviews* 2008 (Monje, 2008) Achanta et al., *Behavioral Neuroscience* 2009 (Achanta et al., 2009) Calabrese and Schlegel, *Recent Results Cancer Res* 2009 (Calabrese et al., 2009) Marazziti et al., *Current Medicinal Chemistry* 2012 (Marazziti et al., 2012) Padovani et al., *Nat Rev Neurol* 2012 (Padovani et al., 2012) Armstrong et al., *J Natl Cancer Inst* 2013 (Armstrong et al., 2013) Redmond et al., *Neuro Oncol* 2013 (Redmond et al., 2013) Sato et al., *Cell Death & Disease* 2013 (Sato et al., 2013)

toxicity, and tumor outcomes (Table 1). At present, two clinical trials are being conducted, in which the radiation treatment plan is modified to deliver higher radiation doses to the NSC compartments (ClinicalTrials.gov Identifiers: NCT02177578, NCT02039778). Another clinical trial, which has completed patient recruitment, aims to establish a relationship between stem cells sparing radiation and an improvement of neurocognitive outcomes in glioblastoma patients (ClinicalTrials.gov Identifiers: NCT01478854). These studies will help determine whether stem cell radiation therapy improves progression-free survival and other outcomes of patients with brain tumor or whether radiation definitively presents a toxic effect.

6. Preventing radiation-induced injury to the neurogenic niche

During the last decades, radiotherapy has significantly increased life expectancy in brain tumor patients. Unfortunately, radiation side effects are known to compromise health of long-term survivors, which raises the urgent need to develop effective strategies to prevent radiation-related effects and promote healthy cancer-free life. In this context, there is a constant effort to find innovative ways to prevent damage to the NSC compartments.

Among the many methods to limit injury to the neurogenic niches, fractionated radiotherapy is the first-line technique. Researchers have shown that dividing radiation into multiple smaller doses, results in a more effective depletion of cancer cells, while negative effects of radiation in neighboring normal healthy tissues are minimized (Marsh et al., 2010; Attia et al., 2014). A longitudinal study that assessed 65 patients with low-grade glioma, at a mean of 12 years after radiotherapy, found that the cognitive deficits among patients with fractioned doses were less severe than in patients who received conventional radiotherapy (Douw et al., 2009). Another radiotherapy technique that is in current use is conformal radiotherapy (Fike et al., 2007; Mizumatsu et al., 2003; Liu et al., 2010; Vallieres et al., 2002). This type of radiation limits the target area very precisely in 3 dimensions, delivering high doses of radiation to the tumor, while sparing the surrounding tissues.

Aside from radiotherapeutic methods, drug-based therapies have been used to ameliorate radiation-induced injury. In this context, the anti-inflammatory agents ramipril and pioglitazone are associated with mitigation of radiation effects on the neurogenic niches (Brown et al., 2005; Zhao et al., 2007; Jenrow et al., 2010; Kim et al., 2004). Continuous administration of ramipril, initiated 12-hours post-whole brain irradiation and maintained for 12 weeks, produced a reduction in the deleterious effects of radiation on neurogenesis in the rat dentate gyrus, recovering proliferation and neuronal differentiation capacities (Jenrow et al., 2010). Furthermore, combination of ramipril and atorvastatin enhanced these mitigating effects (Jenrow et al., 2011). A different study showed that dietary administration of pioglitazone before, during, and after completion of fractionated whole brain irradiation to young adult rats, significantly prevent the radiation-induced cognitive impairment (Zhao et al., 2007).

Stem cell therapies constitute a novel alternative to prevent radiation-induced brain injury. Animal studies have demonstrated promising results using a combination of NSCs transplant with radiation (Joo et al., 2012; Acharya et al., 2011; Acharya et al., 2015; Piao et al., 2015). Joo et al. described the benefits of supplementing whole-brain irradiated mice with fetal mouse NSCs, which were injected via tail vein 24 hours after radiation. The irradiated brain induced homing of the exogenous NSCs, which differentiated along glial and neuronal lineages. Two months after NSC administration, mice showed inhibited radiation-induced hippocampus atrophy and preserved short-term memory (Joo et al., 2012). Similarly, the use of human embryonic NSCs has shown to ameliorate radiation-induced cognitive dysfunction up to 4 months after irradiation, when they were transplanted into the rat hippocampus (Acharya et al., 2011), as well as to remyelinate the irradiated brain (Piao et al., 2015).

Metabolic therapy has become trendy in attenuating the side effects of glioma treatment (Schwartz et al., 2015; Zuccoli et al., 2010; Seyfried et al., 2015). This type of therapy is designed to disrupt tumor microenvironment, while enhancing the health and vitality of normal cells. It has been demonstrated that high-dose radiation creates a microenvironment rich in glucose and glutamine, which may contribute to tumor recurrence as they are required for rapid tumor growth (Seyfried et al., 2015; Szerlip et al., 2011; Derr et al., 2009; Abbadi et al., 2014). In this context, a restricted diet will help lowering glucose availability in the tumor microenvironment. A case series report in patients receiving chemotherapy suggested that fasting has the potential to ameliorate side effects caused by this mode of cancer treatment (Safdie et al., 2009). Studies indicate that fasting has the potential to maximize the differential toxicity of chemotherapy to normal and cancer cells in vitro (Raffaghello et al., 2008), while slows progression of a variety of tumors in vivo, allowing long-term cancer-free survival (Lee et al., 2012). Furthermore, calorie restricted ketogenic diet presented anti-angiogenic, anti-inflammatory, and pro-apoptotic effects in experimental mouse and human brain tumors (Seyfried et al., 2015; Zhou et al., 2007). Studies in rodents demonstrated that survivors of acute ionizing radiation damage ameliorated life shortening if they were fed a diet based on non-essential antioxidant and chemoprevention mixture (Epperly et al., 2011). The use of inhibitors of nitric oxide synthase, such as T1023, has also been related to the prevention of radiotherapy complications. T1023 was found to selectively protect the non-malignant tissue during radiation therapy in a sarcoma rat model (Filimonova et al., 2015). Therefore, metabolic therapy could be used as a tool to avoid radiation effects not only in the NSCs, but in all normal cells.

Based on the SVZ microenvironment alterations that have been described after radiation, i.e., inflammation, revascularization, ECM modifications, and fibrosis among others, there are numerous potential targets in the tumor microenvironment that could be used to ameliorate the adverse effects associated with radiation (Barker et al., 2015). Many microenvironmental therapies are being developed to be given alone or in combination with radiotherapy, showing promising results preventing tumor progression and recurrence. For example, SD-208, an inhibitor of the transforming growth factor beta-receptor 1, reduces tumor growth and fibrosis (Medicherla et al., 2007; Uhl et al., 2004). Acriflavine is a drug used to inhibit the hypoxia-inducible factor 1-alpha (HIF1α), a factor that is upregulated during hypoxia, reducing tumor growth and vascularization (Lee et al., 2009). However, these microenvironmental therapies have so far not been tested for their ability to reduce radiotherapy-related adverse effects.

The multi-directional efforts that are being made in order to alleviate the disadvantages of radiotherapy give optimism to patients suffering from brain tumor. Furthermore, lately, nonradiation-based therapies have significantly improved, such as anti-tumor immunotherapy (Mitchell et al., 2015; Everson et al., 2015), providing new alternatives for fighting this devastating disease.

7. Concluding remarks and future directions

The detrimental effects of radiation on the NSC niche have been demonstrated over the last years. Animal studies have shown that both the proliferative and migratory capacities of neural precursor cells are deeply disrupted following radiation, leading to functional impairments. For instance, olfaction and memory are altered by radiation, as well as the endogenous capacity of the brain to respond to subsequent damages. Similarly, studies in patients with brain tumor have suggested a potential risk of develop neurocognitive sequelae when the NSC compartments are irradiated during radiotherapy. In contrast, studies focused on the SVZ of patients that received radiotherapy indicate that tumor outcomes may be improved with increased radiation doses to this neurogenic area.

The dichotomy of radiation effects could be due to the fact that tumors have a complex biology. Some of these tumors may transition from being localized to being invasive, but the time when this occurs remains unknown. Consequently, radiotherapy is given to the patients at different times, doses, and areas, which may result in a different tumor outcome. The heterogeneous pathological conditions in cancer, and particularly brain cancer, among patients call for the development of a personalized medicine to successfully treat brain tumors. Understanding the biology of brain tumors and determining the subcategory of each specific tumor will likely help us to decide which patients would benefit from including the SVZ in the radiation protocol and at which time. Future studies in this matter will be critical in gaining an improved understanding of the use of radiation to maximize not only patient survival but also their healthspan after treatment.

Conflict of interest

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Acknowledgments

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