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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

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

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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,

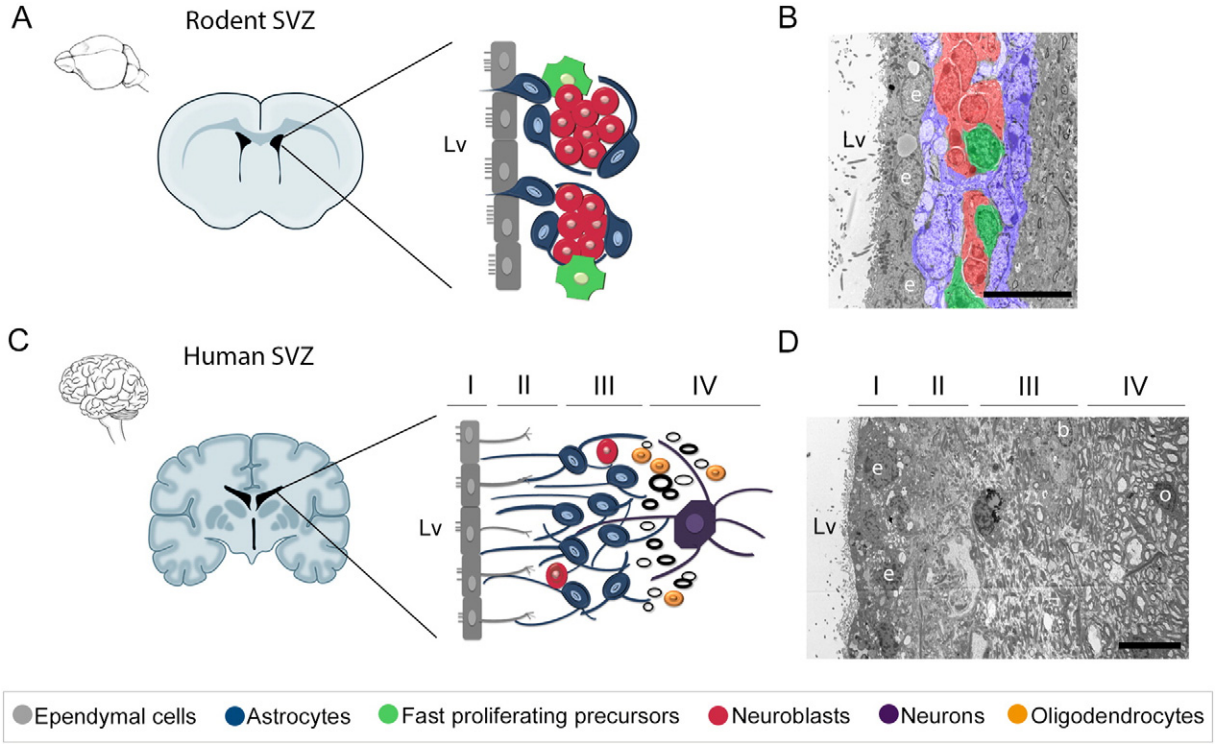

Fig. 1. Cell organization of the SVZ neurogenic niche. (A) Schematic representation of the SVZ in a coronal view of the mouse brain. The enlarged area depicts the cytoarchitecture of the neurogenic niche. (B) Electron microscopy image of the rodent SVZ. (C) Schematic representation of the SVZ in a coronal 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.