Chapter 6

Responses of the SVZ to Radiation and Chemotherapy

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Introduction

The largest germinal zone in the adult mammalian brain, the subventricular zone (SVZ), has been meticulously described with respect to its component cells and their morphologic orientations to one another (Doetsch et al., 1997). The SVZ is mitotically active throughout the life span of a living being and the products of this extensive proliferation include neurons (Lois and Alvarez-Buylla, 1993; Luskin, 1993; Doetsch and Alvarez-Buylla, 1996; Lois et al., 1996; Luskin, 1998) as well as glia (Levison and Goldman, 1993; Lois and Alvarez-Buylla, 1993; Luskin et al., 1993; Luskin and McDermott, 1994). In vitro analyses show that multipotent stem cells reside within the SVZ (reviewed in Alvarez-Buylla and Lois, 1995; Weiss et al., 1996; Temple and Alvarez-Buylla, 1999; Gage, 2000), a finding recently verified in vivo (Doetsch et al., 1999b; Johansson et al., 1999).

Cells produced in the SVZ are mobile, migrating long distances before differentiating into mature phenotypes. In adult rodents (Lois et al., 1996) and primates (Kornack and Rakic, 2001), the primary route of cell migration is to the olfactory bulb where migrating neuroblasts differentiate into granule neurons. This tangential migration presumably occurs along the entire rostrocaudal extent of the lateral ventricular walls (Lois and Alvarez-Buylla, 1994; Doetsch and Alvarez-Buylla, 1996), ultimately coalescing into the rostral migratory stream, which terminates in the olfactory bulb. While this pattern of cell movement is the most prevalent, radial cell movement away from the SVZ is also seen, particularly in the young brain (Suzuki and Goldman, 2003). Furthermore, in conditions of injury, disease,
or infusions of growth factors, SVZ precursor cells are mobilized and move into nearby areas where they can differentiate into astrocytes and oligodendrocytes (Craig et al., 1996; Kuhn et al., 1997; Nait-Oumesmar et al., 1999; Wagner et al., 1999; Fallon et al., 2000; Zhang et al., 2001; Decker et al., 2002a, 2002b; Picard-Riera et al., 2002). Given the migratory activity of cells produced in the SVZ and their ability to differentiate into divergent cells types, it is possible that the SVZ may play a role in response to brain injury. In fact, it has been suggested that the SVZ may act as a reserve population of undifferentiated cells that could be recruited after tissue damage (Morshead and van der Kooy, 1992; Luskin and McDermott, 1994; Doetsch et al., 1997; Alvarez-Buylla and Garcia-Verdugo, 2002). Furthermore, recently it has been suggested that it might be possible, using specific growth factors, to reprogram specific transit amplifying cells to allow them to function as multipotent precursor cells, perhaps expanding their potential to act in repair or recovery (Doetsch et al., 2002).

Brain cells can be injured or lost under a wide variety of circumstances including disease, injury, toxic substances or normal aging, and replacement of those cells, perhaps by stimulating normal neurogenic processes, could potentially ameliorate or change the evolution of damage within the brain. While such capabilities have not yet been realized, the idea of manipulating new cell production to affect recovery or repair seems possible given the proliferative, migratory and differentiation potential of cells in or from the SVZ. Understanding the regulation of cell proliferation, migration and differentiation under normal and pathologic conditions will not only enhance our overall understanding of neurogenesis, but also may provide keys to overcoming or ameliorating the adverse effects of injury or disease on the SVZ. This chapter will focus on how the SVZ responds to two insults associated with the treatment of certain types of cancer: ionizing irradiation and chemotherapeutic drugs.

Ionizing Irradiation

The brain is exposed to ionizing irradiation during the management of specific disease states, particularly cancer. In the case of brain tumors, the amount or dose of irradiation that can be given is dictated to a large extent by the tolerance of normal tissues surrounding the tumor (Sheline et al., 1980). Radiation injury is manifold in character, involving multiple regions and cell/tissue types and involves a variety of structural and functional consequences. A large number of physical and biologic factors influence the expression and extent of radiation injury (Hopewell, 1998; Tofilon and Fike, 2000). Generally, radiation injury is localized to the white matter and sophisticated imaging studies have shown that in many cases, imaging abnormalities can be seen in the periventricular area (Tsuruda et al., 1987; Stylopoulos et al., 1988; Valk and Dillon, 1991). In fact, the presence of neurological complications associated with irradiation were reported to be