# CANCER RESEARCH

VOLUME

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Evaluating the role of a single transgene in breast cancer Evaluating novel therapeutics to target breast cancer

Evaluating the role of multiple transgenes in breast cancer

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Evaluating novel imaging approaches to detect breast cancer earlier

Evaluating the impact of factors influencing breast cancer

Evaluating the role of novel vaccines for breast cancer

Edited by
Kenneth D. Tew
Paul B. Fisher



#### **VOLUME ONE HUNDRED AND TWENTY ONE**

## ADVANCES IN CANCER RESEARCH

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## Glial Progenitors as Targets for Transformation in Glioma

Shirin Ilkanizadeh\*,†, Jasmine Lau\*,†,1, Miller Huang\*,†,1, Daniel J. Foster\*,‡,§,1, Robyn Wong\*,†,1, Aaron Frantz\*,‡,§, Susan Wang\*,‡,§, William A. Weiss\*,†,‡,¶, Anders I. Persson\*,‡,§,2

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#### Abstract

Glioma is the most common primary malignant brain tumor and arises throughout the central nervous system. Recent focus on stem-like glioma cells has implicated neural stem cells (NSCs), a minor precursor population restricted to germinal zones, as a potential source of gliomas. In this review, we focus on the relationship between oligodendrocyte progenitor cells (OPCs), the largest population of cycling glial progenitors in the postnatal brain, and gliomagenesis. OPCs can give rise to gliomas, with signaling pathways associated with NSCs also playing key roles during OPC lineage development. Gliomas can also undergo a switch from progenitor- to stem-like phenotype after therapy, consistent with an OPC-origin even for stem-like gliomas. Future in-depth studies of OPC biology may shed light on the etiology of OPC-derived gliomas and reveal new therapeutic avenues.

## 1. INTRODUCTION

Gliomas are the most common malignant primary brain tumor and associated with approximately 16,000 cancer-related deaths in United States per year (Louis et al., 2007). Recent advances in the molecular characterization of gliomas have defined subgroups of tumors that are genetically and epigenetically distinct (Noushmehr et al., 2010; Phillips et al., 2006; Sturm et al., 2012; Verhaak et al., 2010). The temporal and regional specificity of genetically distinct gliomas (Sturm et al., 2012), argue that either several discrete populations of precursor cells may be vulnerable to transformation, or that multiple glioma subgroups share a common cell of origin. Glial cells outnumber neurons by 10-fold in the human brain and are composed mainly of terminally differentiated cells and minor discrete precursor populations. Modeling of glioma in mice has demonstrated that cells at various differentiation stages throughout glial and neuronal lineages have the potential to generate gliomas. In this review, we present recent findings suggesting that the most wide-spread population of cycling cells in the pediatric and adult brain of mammalians, the oligodendrocyte progenitor cells (OPCs), represents a likely origin for large cohorts of gliomas. We propose that more in-depth studies of OPC biology will inform novel preventive measures and therapeutic interventions to reverse the fatal outcome of most glioma patients.

Gliomas can grossly be divided into astrocytic, oligodendrocytic, and ependymal phenotypes. Classification by the World Health Organization (WHO) distinguishes malignancy by grade (I–IV).

Based on histological appearance, gliomas of most grades and types are found in children and adults. Recent molecular profiling of grade IV glioblastoma (GBM) exemplifies that subsets of tumors in children, young adults, and adolescents, that are indistinguishable by histology, can be segregated based on genetic alterations, broad-scale gene expression, and methylation patterns. Here, we will present recent experimental advances on the understanding of why humans are diagnosed with a certain type of glioma and where it came from.

Gliomas show profound cellular heterogeneity and influences from the tumor microenvironment; with treatment-resistant tumor cells displaying a high degree of stemness. The failure to target glioma stem cells (GSCs) along with the inability to fully debulk tumors through surgical resection, radiation and chemotherapy, all contribute to poor survival of glioma patients (Huse & Holland, 2010). In this review, we will discuss ways to identify GSCs, their interactions with tumor microenvironment, and therapeutic advances to target GSCs. In 2012, Yanoko Nishiyama and John Gurdon were awarded the Novel Prize in Medicine for identifying factors that can reprogram somatic cells into pluripotent stem cells. Since these factors are also expressed in stem-like cancer cells, it is possible that they arose from more differentiated cells. In fact, viral transduction of oncogenes into mature neurons and astrocytes generate gliomas in mice (Friedmann-Morvinski et al., 2012). Similarly, it is plausible that OPCs also can give rise to more stem-like gliomas.

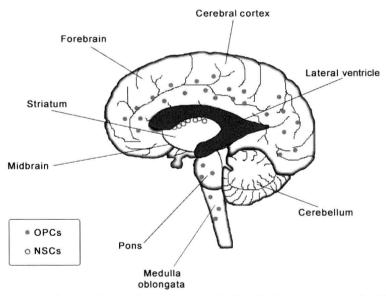
### 2. GLIAL CELL LINEAGES

The central nervous system (CNS) represents a mosaic organization of neural stem cells (NSCs) and astrocyte precursors, that generate neurons, astrocytes, and oligodendrocytes with a high degree of regional specificity (Merkle, Mirzadeh, & Alvarez-Buylla, 2007; Tsai et al., 2012). The positional identity is an organizing principle underlying cellular subtype diversification in the brain and is controlled by a homeodomain transcriptional code (Hochstim, Deneen, Lukaszewicz, Zhou, & Anderson, 2008). During embryonic development, expansion and cell fate determination of neural precursors is controlled by gradients of secreted molecules along rostrocaudal and dorsoventral axes. Radial glia and embryonic NSCs

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generate neurons, glial cells, and ependymal cells during neural development (Rakic, 1990). As a remnant from fetal development, postnatal neurogenesis in mammalians is mainly restricted to the dentate gyrus of the hippocampus and the subventricular zone (SVZ) lining the lateral ventricles (Doetsch, 2003; Eriksson et al., 1998; Sanai et al., 2011), with NSCs also lining the third and fourth ventricles (Weiss et al., 1996; Xu et al., 2005). In the postnatal rodent cerebellum, Bergmann glia express markers associated with NSCs (Koirala & Corfas, 2010; Sottile, Li, & Scotting, 2006). In contrast to rodents, functional SVZ neurogenesis in humans ceases after 18 months, indicating that few SVZ NSCs are present in the aging human brain (Sanai et al., 2011). Given the extensive self-renewal capacity of NSCs, these cells have been suggested as the cell of origin for gliomas (Fig. 1.1). Considering the low abundance of NSCs and the wide distribution of gliomas throughout the human postnatal brain, it is puzzling how such a rare and anatomically restricted cell type could represent the origin of the most common primary malignant brain tumor.

A first wave of oligodendrocyte progenitors arises from the embryonic ventral forebrain, followed by a second wave originating from the lateral and caudal ganglionic eminences, and finally a third wave arises within



**Figure 1.1** Distribution of neural precursor populations in the postnatal brain. OPCs are the most widely distributed population of cycling cells in forebrain and hindbrain regions. In contrast, a discrete population of NSCs is found in the SVZ lining the lateral ventricles. (See the color plate.)