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TISSUE-SPECIFIC STEM CELLS

## The anti-tumorigenic response of neural precursors depends on subventricular proliferation and age

Joo Hee Walzlein <sup>1</sup>, Michael Synowitz <sup>2</sup>, Boris Engels <sup>3</sup>, Darko S. Markovic <sup>4</sup>, Konrad Gabrusiewicz <sup>5</sup>, Evgeni Nikolaev <sup>6</sup>, Kazuaki Yoshikawa <sup>7</sup>, Bozena Kaminska <sup>5</sup>, Gerd Kempermann <sup>8</sup>, Wolfgang Uckert <sup>3</sup>, Leszek Kaczmarek <sup>6</sup>, Helmut Kettenmann <sup>1\*</sup>, Rainer Glass <sup>1</sup>

<sup>1</sup> Cellular Neuroscience, Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany.

<sup>2</sup> Department for Neurosurgery, Charité University Hospital Berlin, 13353 Berlin, Germany.

<sup>3</sup> Molecular Cell Biology and Gene Therapy, Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany.

<sup>4</sup> Cellular Neuroscience, Max Delbrück Center for Molecular Medicine, 13125 Berlin, Germany. Department for Neurosurgery, Helios Klinikum, Schwanebecker Chaussee 50, 13125 Berlin

<sup>5</sup> Laboratory of Transcription Regulation, Dept. Cell Biology, Nencki Institute of Experimental Biology, 02-093 Warsaw, Poland.

<sup>6</sup> Department of Molecular and Cellular Neurobiology. Nencki Institute, 02-093 Warsaw, Poland.

<sup>7</sup> Laboratory of Regulation of Neuronal Development, Institute for Protein Research, Osaka University, Suita, Osaka 565-0871, Japan.

<sup>8</sup> DFG-Center for Regenerative Therapies Dresden, Cluster of Excellence/ TU Dresden, Tatzberg 47/49, 01307 Dresden, Germany.

\* To whom correspondence should be addressed. E-mail: [kettenmann@mdc-berlin.de](mailto:kettenmann@mdc-berlin.de).

### Abstract

**Glioblastomas, the most aggressive primary brain tumors, occur almost exclusively in adult patients. Neural precursor cells (NPCs) are anti-tumorigenic in mice, as they can migrate to glioblastomas and induce tumor cell death. Here, we show that the anti-tumor effect of NPCs is age-dependently controlled by cell proliferation in the subventricular zone (SVZ) and that NPCs accumulating at a glioblastoma are diverted from their normal migratory path to the olfactory bulb. Experimentally induced cortical glioblastomas resulted in decreased subventricular proliferation in adult (postnatal day 90), but not in young (postnatal day 30) mice. Adult mice supplied less NPCs to glioblastomas and had larger tumors than young mice. Apart from the difference in proliferation, there was neither a change in cell number and death-rate in the SVZ nor in angiogenesis and immune cell-density in the tumors. The ability to kill glioblastomas was similar in NPCs isolated from young and adult mice. The proliferative response of NPCs to glioblastomas depended on the expression of D-type cyclins. In young mice, NPCs express the cyclins D1 and D2, but the expression of cyclin D1 is lost during aging and in adult NPCs only cyclin D2 remains. In young and adult cyclin D2-deficient mice we observed a reduced supply of NPCs to glioblastomas and the generation of larger tumors, as compared to wild-type mice. We conclude that cyclin D1 and D2 are non-redundant for the antitumor response of subventricular NPCs. Loss of a single D-type cyclin results in a smaller pool of proliferating NPCs, lower number of NPCs migrating to the tumor and reduced anti-tumor activity.**

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Joo-Hee Walzlein, Michael Synowitz, and Rainer Glass contributed equally to this work.

**Key Words.** CNS neoplasms, tissue maintenance, stem and precursor cells of the CNS, tumor microenvironment

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