

# Distinct Behaviors of Neural Stem and Progenitor Cells Underlie Cortical Neurogenesis

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## ABSTRACT

Neocortical precursor cells undergo symmetric and asymmetric divisions while producing large numbers of diverse cortical cell types. In *Drosophila*, cleavage plane orientation dictates the inheritance of fate-determinants and the symmetry of newborn daughter cells during neuroblast cell divisions. One model for predicting daughter cell fate in the mammalian neocortex is also based on cleavage plane orientation. Precursor cell divisions with a cleavage plane orientation that is perpendicular with respect to the ventricular surface (vertical) are predicted to be symmetric, while divisions with a cleavage plane orientation that is parallel to the surface (horizontal) are predicted to be asymmetric neurogenic divisions. However, analysis of cleavage plane orientation at the ventricle suggests that the number of predicted neurogenic divisions might be insufficient to produce large amounts of cortical neurons. To understand factors that correlate with the symmetry of cell divisions, we examined rat neocortical precursor cells in situ through real-time imaging, marker analysis, and electrophysiological recordings. We find that cleavage plane orientation is more closely associated with precursor cell type than with daughter cell fate, as commonly thought. Radial glia cells in the VZ primarily divide with a vertical orientation throughout cortical development and undergo symmetric or asymmetric self-renewing divisions depending on the stage of development. In contrast, most intermediate progenitor cells divide in the subventricular zone with a horizontal orientation and produce symmetric daughter cells. We propose a model for predicting daughter cell fate that considers precursor cell type, stage of development, and the planar segregation of fate determinants. *J. Comp. Neurol.* 508:28–44, 2008. © 2008 Wiley-Liss, Inc.

**Indexing terms:** cortical development; ventricular zone; subventricular zone; radial glial cells; intermediate progenitor cells; precursor cells; neurogenesis; mitosis; cleavage plane; asymmetric division; symmetric division; neural stem cells; self-renewal; self-renewing divisions; mode of division

The human cerebral cortex consists of  $\approx 50$ –60 billion neurons and glia (Pelvig et al., 2007), with each classified into numerous subtypes (Peters and Jones, 1984). Regulation of the mode of cell division is required to properly amplify cell numbers through symmetric divisions and diversify cell types through asymmetric cell divisions. In *Drosophila*, cleavage plane orientation plays a crucial role in determining mode of division for some, but not all, precursor cell divisions. For example, in neuroblast cells a vertically oriented cleavage within the plane of the epithelium produces symmetric daughter cells, while a horizontal cleavage orientation produces asymmetric daughter cells based on an apico-basal segregation of fate determinants (Doe, 1996). However, *Drosophila* sensory

organ precursor cells also divide vertically within an epithelium, but these divisions produce asymmetric daughter

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