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Division modes and physical asymmetry in cerebral cortex progenitors

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Neural stem cells go through a sequence of timely regulated gene expression and pattern of division mode to generate diverse neurons during brain development. During vertebrate cerebral cortex development, neural stem cells begin with proliferative symmetric divisions, subsequently undergo neurogenic asymmetric divisions, and finally gliogenic divisions. In this review, we explore the relationship between stem cell *versus* neural fate specification and the division mode. Specifically, we discuss recent findings on the mechanisms of asymmetric divisions, division mode, and developmental progression of neural progenitor identity.

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Transitions in division mode and temporal characteristics of precursor cells

During brain development, neural progenitor cells, called apical progenitors (AP) or radial glia (RG), undergo timely regulated changes in two fundamental aspects: proliferation-neurogenic nature and progeny fate potential. In the mammalian cortex, the temporally regulated change in division mode of APs involves both extrinsic factors such as Fgf10 [1] and retinoic acid [2], and intrinsic factors such as *trnp1* [3]. Interestingly, a recent study revealed that the shift of division mode occurs irreversibly in each AP lineage *in vivo* [4••], suggesting an internal program for the division mode transition in APs.

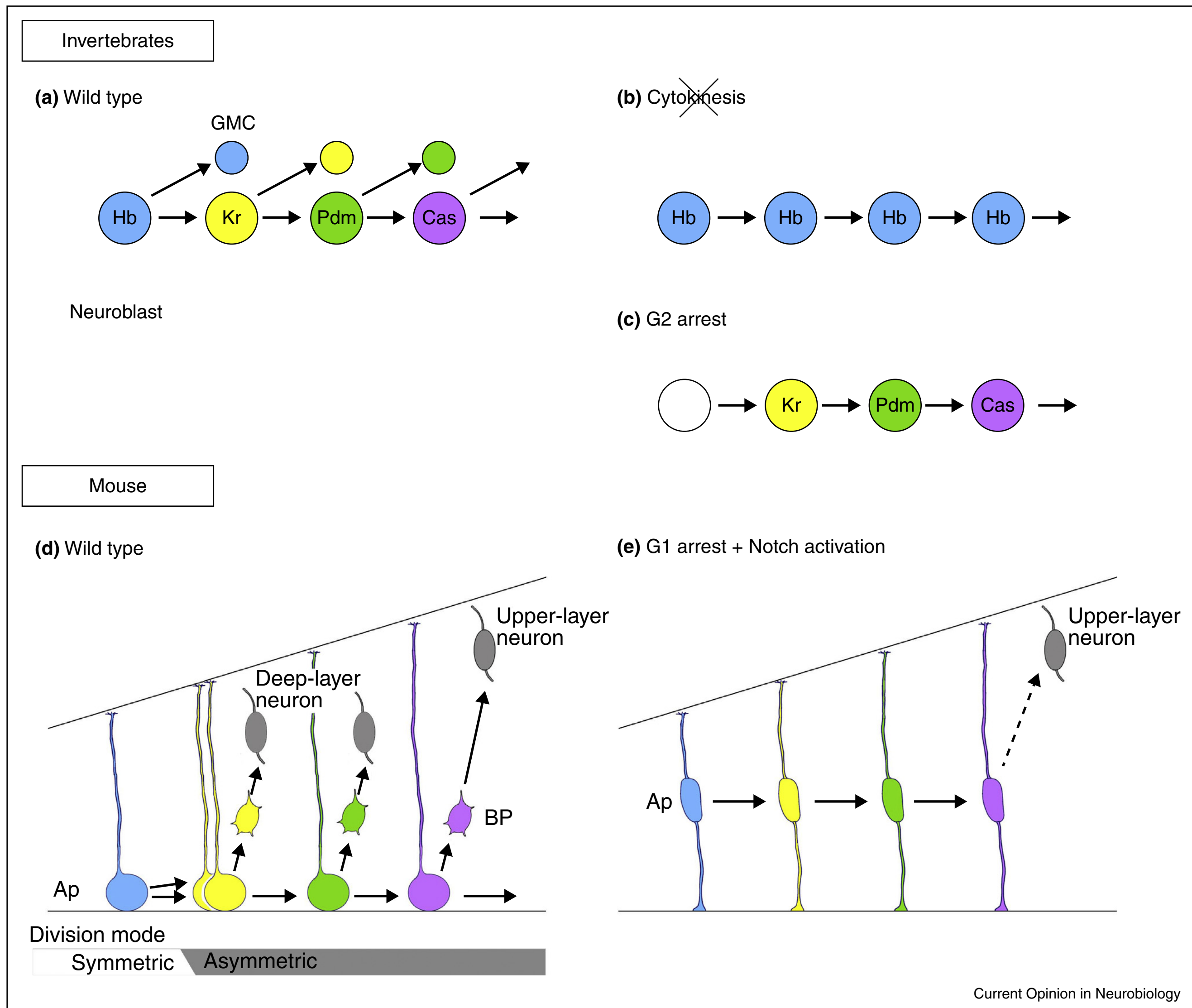
Drosophila neuroblasts have provided an excellent model for the temporal transition of the fate potentials, in which a sequential expression of the transcription factors is tightly coupled with generation of a particular progeny type [5]. In mammalian corticogenesis, APs also sequentially generate heterogeneous progenies: deep-layer neurons, upper-layer neurons, and finally glia. Such AP's potentials are progressively restricted [6]. Hanashima and colleagues recently unveiled that the transcriptional factor *foxg1* represses the initial temporal state of APs to initiate transitions [7], and proposed that the extrinsic cues from the early-type progeny switch APs to generate the late-type neurons [8•].

Since the shifts of these temporal characters go along with sequential cell cycles, cell division has been a candidate 'timer' to govern the temporal pattern of precursor cell characters. *Drosophila* embryonic neuroblasts need cell division, however, only for their first transition in temporal identity genes, and the subsequent transitions require no cell division [5]. While the timing mechanism in mouse neural progenitors has been elusive, a recent study challenging the above classical idea showed that the cell cycle arrest does not affect the transition of temporal gene expression, nor laminar fate progression (Figure 1) [9••]. Thus, cell division is unlikely a 'timer' in APs. A cascade of transcriptional regulation [5], epigenetic modifications [10], and subnuclear genome re-organization [11] are potential candidates for the molecular clock in APs, while further studies are necessary to clarify it.

Identity from the cradle: early positioning and cell fate

Although transient cell cycle arrest *in vivo* does not interfere with the deep layer to upper layer laminar fate transition of APs during neurogenesis [9••], cell cycle progression is however essential for proper cortical neuron generation and neuronal heterogeneity during cortical development. During neurogenic division in the VZ (one AP gives rise to one AP and one neuron), the stem cell sibling was assumed to locate apically- in order to maintain contact with the apical membrane, a requirement to maintain stemness [12–14] – while the neuron sibling was positioned basally. Development of high resolution imaging techniques combined with live observations of progenitors behavior have challenged this view. In zebrafish and chick spinal cord, detailed live monitoring of daughter cells movements following neurogenic

Figure 1



Cell cycle progression and transition of temporal character of precursors. (a-c) In Drosophila neuroblast lineages, neuroblasts sequentially express four temporal identity genes, Hb (*hunchback*), Kr (*Kruppel*), Pdm (*pdm1*), and Cas (*caster*), in that order. The Hb-Kr transition requires neuroblast cytokinesis **(b)**, while the Kr-Pdm-Cas transitions can occur normally in G2-arrested neuroblasts in *hb* mutant **(c)**. **(d)** In the mouse, apical progenitors (APs) undergo a change from the symmetric to asymmetric division, and shift their laminar fate potential from lower-layer neurons to upper-layer neurons. Major changes in 'temporal-axis' genes from early to late neurogenic stages, are inherited by BPs from APs. **(e)** Cell cycle progression of APs is not necessary for their transitions of temporal character. The G1-arrested APs, which have been co-expressed Cdk inhibitor and NICD to maintain self-renewal potential, transit the expression of temporal-axis genes as normal APs do. Transient cell-cycle arrest also does not interfere with the laminar fate transition of APs from deep layers to upper layers.

division in the VZ demonstrated that in most instances, the apically born daughter cell gives rise to the neuron, indicating that the physical contact with the apical membrane is not mandatory for maintaining stemness. In the zebrafish spinal cord, Alexandre et al. [15], identified the lower apical cell inheriting PAR3 as the neuron (92%), and the upper cell (Par3 free) as the self-renewing AP, which re-grows an apical process and re-synthesizes Par3. In the chick neural tube, Storey and colleagues [16,17•] describe a similar phenomenon. In accordance with the chick and the zebrafish observations, live imaging of mouse APs direct neurogenic divisions at mid-corticogenesis revealed that, in most cases (80%) the lower (apically positioned) sibling gives rise to the neuron. Preliminary observations also suggest a similar positioning of the siblings during indirect neurogenesis — where an AP generates an AP and a basal progenitor (BP), which will in turn give rise to two neurons [18••].

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