

[Development](#). 2008 Feb;135(4):729-41. [Links](#)

Cux2 (Cutl2) integrates neural progenitor development with cell-cycle progression during spinal cord neurogenesis.

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Neurogenesis requires the coordination of neural progenitor proliferation and differentiation with cell-cycle regulation. However, the mechanisms coordinating these distinct cellular activities are poorly understood. Here we demonstrate for the first time that a Cut-like homeodomain transcription factor family member, Cux2 (Cutl2), regulates cell-cycle progression and development of neural progenitors. Cux2 loss-of-function mouse mutants exhibit smaller spinal cords with deficits in neural progenitor development as well as in neuroblast and interneuron differentiation. These defects correlate with reduced cell-cycle progression of neural progenitors coupled with diminished Neurod and p27(Kip1) activity. Conversely, in Cux2 gain-of-function transgenic mice, the spinal cord is enlarged in association with enhanced neuroblast formation and neuronal differentiation, particularly with respect to interneurons. Furthermore, Cux2 overexpression induces high levels of Neurod and p27(Kip1). Mechanistically, we discovered through chromatin immunoprecipitation assays that Cux2 binds both the Neurod and p27(Kip1) promoters in vivo, indicating that these interactions are direct. Our results therefore show that Cux2 functions at multiple levels during spinal cord neurogenesis. Cux2 initially influences cell-cycle progression in neural progenitors but subsequently makes additional inputs through Neurod and p27(Kip1) to regulate neuroblast formation, cell-cycle exit and cell-fate determination. Thus our work defines novel roles for Cux2 as a transcription factor that integrates cell-cycle progression with neural progenitor development during spinal cord neurogenesis.

PMID: 18223201 [PubMed - in process]

Cux-2 Controls the Proliferation of Neuronal Intermediate Precursors of the Cortical Subventricular Zone.

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Whereas neurons of the lower layers (VI-V) of the cerebral cortex are first born from dividing precursors at the ventricular zone, upper layer neurons (II-IV) subsequently arise from divisions of intermediate neuronal precursors at the subventricular zone (SVZ). Little is known about mechanisms that control the proliferation of SVZ neuronal precursors. We herein report that the restricted expression of the homeodomain transcription factor Cux-2 in the SVZ regulates the proliferation of intermediate neuronal precursors and the number of upper layer neurons. In Cux-2-deficient mice (Cux-2^{-/-}), there is excessive number of upper layer neurons and selective expansion of SVZ neuronal precursors. Double-labeling experiments demonstrate that Cux-2^{-/-} upper layer precursors reenter the cell cycle in a higher frequency than wild-type precursors. Overexpression studies indicate that Cux-2 controls cell cycle exit in a cell-autonomous manner. Analysis of Cux-1^{-/-}; Cux-2^{-/-} double mutant revealed that Cux-2 controls SVZ proliferation independently of Cux-1, demonstrating that this is a unique function of Cux-2, not redundant with Cux-1 activities. Our results point to Cux-2 as a key element in the control of the proliferation rates of the SVZ precursors and the number of upper cortical neurons, without altering the number of deep cortical layers.

1: [Cell](#). 2008 Feb 8;132(3):487-98. [Links](#)

Visualizing spatiotemporal dynamics of multicellular cell-cycle progression.

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The cell-cycle transition from G1 to S phase has been difficult to visualize. We have harnessed antiphase oscillating proteins that mark cell-cycle transitions in order to develop genetically encoded fluorescent probes for this purpose. These probes effectively label individual G1 phase nuclei red and those in S/G2/M phases green. We were able to generate cultured cells and transgenic mice constitutively expressing the cell-cycle probes, in which every cell nucleus exhibits either red or green fluorescence. We performed time-lapse imaging to explore the spatiotemporal patterns of cell-cycle dynamics during the epithelial-mesenchymal transition of cultured cells, the migration and differentiation of neural progenitors in brain slices, and the development of tumors across blood vessels in live mice. These mice and cell lines will serve as model systems permitting unprecedented spatial and temporal resolution to help us better understand how the cell cycle is coordinated with various biological events.

PMID: 18267078 [PubMed - in process]