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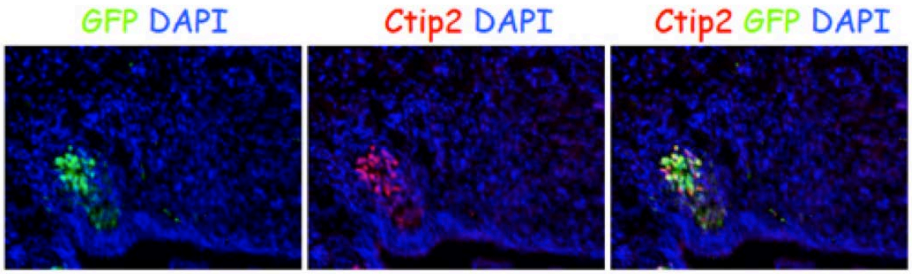
**Transcriptional switch controls neuronal fate in neocortex**

*Apr 5, 2013* – There is something to the notion that it is our neocortex that makes us human. This sheet of neurons covering the brain is the seat of the senses, cognition, language and other cerebral faculties. Its development is thus a matter of intrinsic interest, but of elegant complexity as well. Cortical neurons of various types form in sequential order, with the older neurons inhabiting deeper layers and younger neurons forming the upper strata. In total, there are six such layers in the neocortex, but the genetic controls that direct the transitions from one neuronal subtype to another have remained elusive.

New work by Takuma Kumamoto and others in the Laboratory for Neocortical Development (Carina Hanashima, Team Leader) provides insight into how a transcription factor known as *Foxg1* functions as the earliest switch in regulating neuronal cell fate in the mouse neocortex. Published in *Cell Reports*, this study opens new inroads into our understanding of the formation of neocortical neuronal diversity.




Cajal–Retzius (CR) cells, the earliest glutamatergic neurons to emerge, play a central role in neocortical development. These cells secrete factors that direct the cortical stratification and the radial projection of later generations of neurons, but are gradually lost after birth, disappearing altogether by adulthood. CR cells are rare in birds and reptiles, leading to speculation that they are important to the formation of the comparatively massive mammalian cortex. It had earlier been thought that these cells arose from a different progenitor domain than the neocortex, but a previous study by Hanashima found that *Foxg1*, which is expressed in neocortical progenitors, suppresses CR cell differentiation, revealing that CR cells share a common progenitor with projecting neurons.

Kumamoto set out to build on that work, seeking the mechanism by which *Foxg1* regulates neural stem cell differentiation. The first step was to create a knockout mouse lacking *Foxg1*, and analyze its phenotype. In these mutants, he found that projection neurons of all layers failed to form, while CR cells developed in greater than usual numbers. Migration patterns of neurons that appear in a distinctive radial fashion in wildtype were also aberrant in the knockout embryos. The loss of *Foxg1* function thus appeared to cause a failure in the transition to generation of projection neurons, resulting in overproduction of CR cells.

The team next made a conditional knockout (cK0) in which *Foxg1* expression could be switched off mid-development, to test whether upper-layer progenitor cells retain the ability to differentiate into CR cells following inactivation of the gene (something the lab had previously shown deep-layer progenitors capable of doing). Interestingly, upper-layer progenitor cells did not give rise to CR cells when Foxg1 was inactivated at embryonic day (E) 15, suggesting that competence is progressively restricted during the transition from deep- to upper-layer neurons, implying that cortical progenitors use an intrinsic program to steer transitions between cortical subtypes.

To test that possibility, the team generated a conditional mutant in which *Foxg1* was induced at a later stage than normal, the time of the transition from deep to upper-layer progenitors in wildtype. When *Foxg1* was induced at E14.5, Kumamoto observed a nearly immediate generation of deep-layer projection neurons after the excess CR cell production, indicating that *Foxg1* works to direct cell identity decisions. Intriguingly, upper-layer projection neurons also subsequently appeared in these late Foxg1-induced embryos, which ultimately developed a cortex with cells of the various types in numbers similar to those seen in wildtype. *Foxg1*, it seems, works as a transcriptional switch ensuring that the right types of cells emerge at the right timing during neocortical development.

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In an effort to hunt for genes downstream of *Foxg1*, the team conducted microarray analyses of progenitor cells taken at different timepoints from cK0 embryos in which its expression was switched on at E14.5. Their examination of gene expression patterns showed that Foxg1 strongly inhibited genes associated with CR cells; chromatin immunoprecipitation suggested this was the result of direct binding between the factors. Interestingly, the majority of these binding domain sequences appears to have emerged after mammalian evolution.

"The robust and elegant spatiotemporal cell fate switching system mediated by Foxg1 maintains the right balance between projection neurons and CR cells in mouse and human alike," says Hanashima. "We are excited to continue in our efforts to understand just what goes on in the building of the neocortex that underlies many of humanity's most fundamental traits."

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