The determination of projection neuron identity in the developing cerebral cortex
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Here we review the mechanisms that determine projection neuron identity during cortical development. Pyramidal neurons in the mammalian cerebral cortex can be classified into two major classes: corticocortical projection neurons, which are concentrated in the upper layers of the cortex, and subcortical projection neurons, which are found in the deep layers. Early progenitor cells in the ventricular zone produce deep layer neurons that express transcription factors including Sox5, Fezf2, and Ctip2, which play important roles in the specification of subcortically projecting axons. Upper layer neurons are produced from progenitors in the subventricular zone, and the expression of Satb2 in these differentiating neurons is required for the formation of axonal projections that connect the two cerebral hemispheres. The Fezf2/Ctip2 and Satb2 pathways appear to be mutually repressive, thus ensuring that individual neurons adopt either a subcortical or callosal projection neuron identity at early times during development. The molecular mechanisms by which Satb2 regulates gene expression involves long-term epigenetic changes in chromatin configuration, which may enable cell fate decisions to be maintained during development.

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The cerebral cortex is organized into layers that are generated sequentially over developmental time
Ever since the time of Cajal, scientists have appreciated that the cerebral cortex is organized in layers that are defined by the densities and morphologies of their constituent neurons. The advent of retrograde tracing techniques and intracellular dye injections revealed that, as a general rule, neurons in the upper layers 2 and 3 tend to form corticocortical connections, including projections to the contralateral hemisphere across the corpus callosum, whereas neurons in layers 5, 6, and the subplate are the source of subcortical projections to targets that include the spinal cord, pons, midbrain, and thalamus. Neurons in layers 1 and 4 extend axons locally within the cortex. Although it was long assumed that the interneurons of the cortex arise from the same progenitor population like those that generate projection neurons, cell labeling and genetic studies revealed that the bulk of these neurons derive from the ganglionic eminence, which serves as the progenitor pool for the striatum and basal ganglia as well. The regulation of interneuron fates has been reviewed recently and will not be discussed here [1,2].

Cortical projection neurons are derived from progenitor cells that line the dorsal aspect of the lateral ventricles in the forebrain. Mitotically active cells are found in the ventricular zone (VZ), immediately adjacent to the ventricles, and, at later stages, in the subventricular zone (SVZ), which forms between the VZ and the overlying intermediate zone (IZ). Classic 3H-thymidine ‘birthdating’ studies have revealed that neurons of different layers

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are generated in a stereotypic temporal sequence during development [3]. The first neurons to exit the cell cycle and migrate out of the VZ occupy the preplate, which is subsequently split into two zones by the arrival of neurons that form the cortical plate. The upper preplate, which is known during development as the marginal zone, is populated by Cajal–Retzius neurons, of which many or most are derived from a region known as the cortical hem (located near the hippocampal anlage) and then migrate tangentially to the populated neocortex [4,5]. The deeper domain of the preplate becomes the subplate, a largely transient zone of neurons that plays important roles in axon targeting during development [6]. Within the cortical plate, neurons of the deepest layers (6 and 5) are generated at the earliest stages, followed by neurons of layers 4, 3, and 2.

**Cellular studies of cell fate determination suggest a progressive restriction in developmental potential**

Transplantation experiments have probed the process by which neurons become committed to the laminar fate that is typical of their time of origin. These studies have demonstrated that by the time a young neuron has progressed through its final mitotic division and is ready to initiate migration, the cell has acquired the information needed to migrate to the layer typical of its birthday, even in an environment in which host neurons are destined for other layers [7–9]. However, at earlier stages of differentiation, cells can show a broader developmental potential and adopt alternative fates. Transplantation experiments revealed that early progenitors, which normally produce deep layer neurons, are multipotent: these cells can directly produce upper layer neurons when transplanted into an older brain environment [7]. Interestingly, the competence of progenitors to respond to fate-inducing cues changes over developmental time. The progenitors of layer 4 neurons retain the ability to differentiate into later-generated types when transplanted into older hosts, but have lost the ability to form layer 6 neurons if transplanted into younger brains [9]. The progenitors of layer 2/3 neurons are even more restricted; when transplanted into younger hosts, these cells generate only upper layer neurons, even if they divide again in the new environment [8]. These transplantation experiments addressed the laminar positions and connections of cortical neurons, but did not track the expression of layer-specific molecular markers. However, clonal analyses of cortical progenitor cells in culture have relied on such markers, and suggest that both the sequential production of distinct laminar phenotypes and the progressive loss of competence to produce early-generated deep layer neurons can occur in isolation [10]. This suggests that cortical progenitor cells may employ a cell-intrinsic clock as part of the mechanism by which to time the production of distinct laminar phenotypes, or that feedback is required only within an individual lineage in order to produce an appropriate sequence of cell types over time.

Specific patterns of gene expression and cell behavior correlate with the changes in cortical progenitor cells, and in their progeny, over time (Figure 1). For example, progenitors in the VZ at early stages of corticogenesis express a number of transcription factors (such as Fezf2, Otx1, Sox2, and Emx2) that are maintained by their progeny as young neurons populate the deep layers.
[11,12**,13,14]. However, at middle stages of neurogenesis, as progenitors begin to produce the neurons of layers 4 through 2, the cells undergo a series of interesting cellular and molecular alterations. The traditional view of cortical neurogenesis held that all neurons are derived from the VZ, and that the SVZ was the source of glial cells [15]. However, this view has been challenged first based on histological studies [16], and subsequently by the observation that SVZ cells show patterns of gene expression that are echoed by those in upper layer neurons. For example, the noncoding RNA Scet1 and several homodomain genes, including Cux1 and Cux2 are expressed both in the SVZ and in layers 2–4 [17,18*]. These corresponding patterns of gene expression suggested that upper layer neurons might be derived from the SVZ. Indeed, in the Pax6;small eye mutant, Scet1 expression is lost in both the SVZ and the upper layers, providing indirect evidence that the SVZ is necessary for the generation of upper layer neurons [18*].

Direct evidence that the SVZ is a neurogenic zone has been derived from a recent series of elegant imaging experiments [19,20] in conjunction with related work from other labs [21–23]. Noctor and colleagues used time-lapse confocal microscopy to track the behavior of individual GFP-labeled mitotic progenitors in the VZ and SVZ, and then to follow the behavior and fates of their daughter cells [19,24*,25**]. These studies revealed that cell divisions within the VZ are primarily symmetric during early development before the onset of neurogenesis, when the progenitor pool is expanding. At the onset of neurogenesis, most cell divisions in the VZ are asymmetric, with one daughter cell remaining in the VZ and the other cell exiting this zone to differentiate. Several imaging studies suggest that daughter cell fates may be regulated by the asymmetric inheritance of determinants associated with the apical membrane of the progenitor cell, such that the daughter cell that inherits this domain retains a progenitor cell fate [24*,25**,26,27]. At mid-to-late stages of neurogenesis, the outcomes of VZ cell divisions undergo a fundamental alteration. Although the cell divisions remain asymmetric, the daughter cell that exits the VZ does not differentiate directly into a neuron, but rather moves into the SVZ and undergoes one or more symmetric neurogenic divisions, thus serving as a transit amplifying cell [23,24*,25**,28]. It is these divisions that appear to be primarily responsible for generating the neurons that migrate into the upper layers.

Collectively, these studies suggest that the early-generated neurons of the deep layers are derived from progenitors in the VZ, whereas late-generated upper layer neurons are produced primarily from SVZ cells, which serve as intermediate progenitors. The corresponding patterns of gene expression between early VZ cells and the deep layers, and SVZ cells and upper layer neurons, suggest that the fates of young neurons are determined at the time of their generation. Below we review the roles of specific genes in the progressive establishment of laminar identity and patterns of connectivity among subtypes of cortical projection neurons.

**Fezf2 and Ctip2 define the fates of subcortical projection neurons**

VZ cells at early stages of cortical neurogenesis express a number of transcription factor genes that have the potential to determine or influence the fates of their daughter cells. Some of these (e.g. Otx1) show a clear correlation in expression between early progenitors and deep layer neurons, but have no obvious functional role in the establishment of neuronal fates or identities [13,29]. However, others do appear to play important roles in fate determination. For example, the zinc-finger transcription factor Fezf2 is expressed in telencephalic progenitor cells starting at E8.5, and its expression is retained by deep layer neurons during corticogenesis [12**,30,31,33**,34**]. Layer 5 and 6 neurons subsequently acquire the expression of a second zinc-finger transcription factor, Ctip2, during postmitotic differentiation [12**,33**,35**]. The expression domain of Fezf2 (which is most prominent in cortex and hippocampus, but is also found in a subset of hypothalamic cells) is much more limited than that of Ctip2, which is broadly expressed in the striatum, olfactory bulb, and other regions. However, within the cortex, both Fezf2 and Ctip2 are expressed by subcortically projecting neurons in layer 5 and in the corticothalamic projection neurons of layer 6 [12**,33**,35**]. Importantly, Ctip2 expression is lost in the cortices of Fezf2 mutant mice (but not in other brain regions) [12**,33**], whereas the converse is not the case: Ctip2 mutants continue to express Fezf2 (JD Macklis, unpublished data). Thus, the timing of Fezf2 and Ctip2 expression is consistent with the suggestion that Fezf2 acts upstream of Ctip2 during cortical development.

Genetic knockouts targeting either the Fezf2 or Ctip2 locus in mice have revealed striking similarities in the phenotypes of layer 5 neurons. In both cases, the development of subcortically projecting axons was highly abnormal, with the axons of corticospinal motor neurons (CSMNs) failing to extend into the corticospinal tract (CST) [12**,33**,34**]. In Fezf2 mutant mice, defects have also been noted in projections to other subcortical targets, including the midbrain and pons [12**]. Because mutation of Ctip2 causes lethality at about the time of birth [33**], it has been difficult to conduct extensive studies of the fates of CSMNs in these mutants. Such experiments have been feasible in Fezf2 mutant mice, which survive into adulthood, and particularly in a mouse line in which the Fezf2 coding sequence was replaced with placental alkaline phosphatase (PLAP), which marks the axonal projections of neurons that normally express Fezf2 [12**]. Unpublished evidence suggests that Fezf2 regulates a fate switch: in its absence, many layer 5 and 6
neurons acquire the phenotypes of callosal projection neurons [32**]. Conversely, the ectopic expression of Fezf2 in neurons that normally form corticocortical and callosal projections is sufficient to redirect their axons to subcortical targets [33**,34**].

Fezf2 encodes a zinc-finger protein that contains a putative repressor domain similar to that found in the Engrailed protein [36,37], and Ctip2 is known to repress transcription of the p57KIP2 locus [38]. Thus, it seems plausible that Fezf2 and Ctip2 function as transcriptional repressors in the regulation of deep layer neuron fates. However, some zinc-finger transcription factors can confer both activator and repressor activities [37], and in addition, Ctip2 has been implicated in chromatin remodeling at the HIV1 locus, where it recruits histone deacetylases and methylases to repress transcription [39]. The latter result suggests that the Fezf2–Ctip2 pathway has the potential to modify chromatin configuration; however, the detailed biochemical mechanisms by which these two proteins function in cortical neurons remain to be explored.

A role for Sox5 in the specification of distinct subtypes of deep layer neurons

Although substantial progress has been made in unraveling the genetic and molecular pathways that control deep layer neuronal identity, little is yet known about the pathways that act upstream of Fezf2 and Ctip2. Recently, however, the SRY-box gene Sox5 has been implicated in regulating the timing of deep layer differentiation [40**]. Sox5 is normally expressed by subcortically projecting neurons in layers 5, 6, and the subplate, and its expression is largely excluded from callosal projection neurons [40**]. In Sox5−/− mutants, neurons of layers 5 and 6 show aberrant migration patterns and fail to segregate into distinct layers, with cells expressing high levels of Fezf2 or Ctip2 occupying the deepest region of the cortical plate rather than their normal positions in layer 5. Cells expressing Ctip2 were also scattered throughout the upper layers, and many of these extended axons subcortically because they could be labeled retrogradely from the cerebral peduncle. Some of these neurons were likely to be mispositioned subplate cells; although mutant brains showed reduced expression of subplate-specific markers, BrdU labeling studies demonstrated that the earliest-generated neurons failed to form a subplate layer and instead were distributed throughout the cortical plate. Lai et al. [40**] argued that these subplate neurons acquired a novel fate, because many earliest generated neurons acquired Ctip2 expression, which is normally absent from the subplate. Interestingly, double mutant mice lacking both Sox5 and Ctip2 function showed a partial rescue of the migration defects seen in Sox5 mutants. These data suggest that Ctip2 expression by subplate neurons may prevent normal preplate splitting as the neurons of the cortical plate migrate into position, and thus lead to defects in lamination similar to those seen in reeler mice. Finally, Sox5 mutants displayed striking defects in the formation of subcortical projections, with axons extending along novel trajectories and apparently failing to form a coherent CST in caudal regions [40**].

The ectopic expression of Sox5 in upper layer neurons prevented them from extending axons across the corpus callosum and stimulated the extension of corticofugal axons, suggesting that Sox5 actively promotes the differentiation of subcortical projection neurons. In light of the normal expression of this gene in three distinct types of deep layer neurons (layer 5 subcortical, layer 6 corticocallosal, and subplate neurons), Lai and colleagues hypothesized that varying levels of Sox5 act in combination with distinct levels of Tbr1 and Ctip2 to control the specific identities of subplate and deep layer neurons. For example, subplate neurons are characterized by high levels of Tbr1 expression, little or no Ctip2, and an intermediate level of Sox5, whereas layer 6 neurons normally express high levels of both Sox5 and Tbr1 and an intermediate level of Ctip2. As a known repressor of transcription, it is conceivable that Sox5 may directly repress Ctip2 expression in subplate neurons.

Finally, it is clear that Tbr1 plays an important role in cortical development, particularly in regulating the differentiation of subplate neurons. Tbr1 is expressed in the preplate and layer 6 during early corticogenesis [41], and Tbr1-deficient mice show defects in preplate splitting and in the positioning of early-born neurons (similar to the migration defects observed in reeler mice) [42]. Indeed, in the absence of Tbr1, the expression of reelin by Cajal–Retzius cells in the marginal zone is reduced [42]. Tbr1 knockouts also exhibit a variety of axon projection defects, with corticocallosal projections growing only as far as the internal capsule, callosal projections mostly terminating in Probst bundle without crossing the midline, and thalamocortical projections reaching the internal capsule, but then turning away from the cortex and extending into the external capsule and amygdala. These complex phenotypes highlight the difficulty in teasing apart nonautonomous gene functions in regulating processes such as migration, from possible cell-autonomous alterations in neuronal identity and connectivity. Clearly, much remains to be learned about the function of Tbr1 in cortical neurogenesis.

Mechanisms that direct upper layer neuronal identity

Although our understanding of the mechanisms that produce distinct subtypes of subcortical projection neurons in the deep layers is growing, much less is known about how the brain produces the classes of neurons that populate the upper layers. As with VZ cells and their deep layer progeny, gene expression patterns in the SVZ are
correlated with those of neurons in layers 2–4. However, the functional roles of these genes remain poorly understood. For example, the T-box gene *Tbr2* is expressed prominently in the SVZ [41,43], but *Tbr2* knockout mice die early at the blastocyst stage [44], precluding an analysis of *Tbr2* function in cortical development.

The homeodomain genes *Cux1* and *Cux2* are expressed in the developing brain [45], particularly in SVZ cells and their progeny in layers 2–4 [46]. The generation and analysis of *Cux2* knockout animals has revealed that *Cux2* promotes the exit of SVZ cells from the cell cycle, thereby limiting the numbers of upper layer neurons that are generated from this zone. *Cux2*−/− mice experience an increase in the proliferation of SVZ cells and a moderate increase in the densities of cells in layers 2–4 [47]. Birthdating experiments suggest that *Cux2*-deficient SVZ progenitors reenter the cell cycle at a higher frequency than in wild-type controls, leading to an increase in the size of the SVZ progenitor pool.

The POU domain transcription factors *Brn-1* and *Brn-2* also regulate the generation of upper layer neurons. Both genes are expressed in the VZ and SVZ starting at mid-neurogenesis [48]. Although single mutations in either *Brn-1* or *Brn-2* yield phenotypes in only limited areas of the brain, double mutants show severe proliferation defects in VZ and SVZ cells after E14.5, with no obvious changes in the proliferation of progenitors at earlier times [48]. Double mutant animals also show striking decreases in the numbers of layer 4 neurons, and the brains of surviving *Brn-1/2* double knockouts seem to lack the upper layers as the thickness of the cortex was significantly reduced. This suggests a cell-autonomous role for *Brn* genes in upper layer neurogenesis. Interestingly, although the numbers of deep layer neurons did not appear to be affected in mutants, their migration was perturbed. Analysis of lamination using layer-specific markers revealed that layer 5 neurons (which normally reside above layer 6) were positioned below layer 6 in the mutant cortex. The authors further provide evidence that the defects in migration could be because of a reduction in mDab1, a protein that acts downstream of reelin signaling. Although the two phenotypes (loss of upper layer cortical progenitors and defects in migration) might be independent of each other, further analysis is required to unravel the precise role of *Brn* genes in upper layer generation.

**Satb2 and the determination of callosal projection neuron identity**

Neurons that extend axons across the corpus callosum to the opposite cerebral hemisphere are a subtype of neurons that form corticocortical connections. Callosal projection neurons are particularly prominent in the upper layers, although they are present in the deep layers. Recent work has revealed that callosal projection neurons require the chromatin remodeling protein *Satb2* for the formation of their normal projections, and that in the absence of *Satb2*, these cells extend axons toward subcortical targets.

*Satb2* is expressed by a subset of neurons throughout the cortical layers, but its expression is most prominent in layers 2–4 [18,49,50,51]. Targeting of the *Satb2* locus with a *lacZ* gene revealed that *Satb2* expressing neurons normally extend axons across the corpus callosum [50]. Strikingly, these axons fail to cross the corpus callosum in *Satb2* mutant brains [50,51], although some β-galactosidase-labeled axons do cross the midline, suggesting that the corpus callosum itself is intact [50]. Instead, β-galactosidase-labeled axons assume an alternate trajectory and extend subcortically along the CST. In addition to adopting the axon trajectory of deep layer neurons, *Satb2* mutants display alterations in the expression of several axon guidance molecules and a dramatic expansion of *Ctip2* expression into the upper layers and within the deep layers, although the expression of *Fezf2* was not obviously affected [50,51]. These data suggest that *Satb2* functions to repress the expression of *Ctip2* in callosal projection neurons. Indeed, the ectopic expression of *Satb2* in neurons markedly reduces the fraction of cells that express *Ctip2* [50,51], and alters the projections of deep layer neurons, such that the axons of electroporated cells fail to extend past the cerebral peduncle [51]. This axonal phenotype is reminiscent of that observed in *Ctip2*−/− brains [35], suggesting that the ectopic expression of *Satb2* might alter the fate of deep layer neurons by regulating *Ctip2* expression.

Collectively, these data suggest that *Satb2* promotes a callosal projection neuron identity in the cortex by repressing *Ctip2* expression. Indeed, the repression of *Ctip2* by *Satb2* appears to be direct: *Satb2* binds directly to matrix attachment regions (MARs) in the *Ctip2* locus, where it recruits histone deacetylases [51,52] and modifies chromatin configuration to assume a less activated state [50,52]. It is not yet clear whether this repression is mutual, because *Satb2* expression in *Ctip2* mutant brains has not yet been reported. However, the expression of *Satb2* is significantly upregulated in the deep layers of *Fezf2* mutants [32], suggesting that *Fezf2* can repress *Satb2* expression in subcortical projection neurons. It remains to be determined whether this effect is direct or indirect, and whether *Fezf2* can also directly promote the expression of *Ctip2* in deep layer neurons.

**Conclusions**

Collectively, the studies of the roles of *Sox5*, *Fezf2*, *Ctip2*, and *Satb2* during cortical development suggest that an elegant genetic mechanism exists to control the identity of a subcortical versus callosal projection neuron.
A working model for the specification of callosal versus subcortical projection neuron identity during the development of the cerebral cortex. This model is based on genetic (rather than biochemical) studies, which suggest that Fezf2 acts upstream of Ctip2 and that both play essential roles in the specification of subcortical projection neuron fates. Satb2 is required for the development of callosal projection neurons and represses the expression of Ctip2 in these cells. In the absence of Satb2, callosal projection neurons extend axons subcortically. Conversely, in the absence of Fezf2, Satb2 expression is derepressed, enabling cells to take on a callosal projection neuron fate.

(Figure 2). Early in development, when deep layer neurons are generated, Fezf2 expression in VZ cells may promote the expression of Ctip2 in young neurons, and together these genes confer a subcortical projection neuron fate during differentiation. Differences in the levels of expression of Sox5, Tbr1, and Ctip2 can further confound specific identities onto subtypes of deep layer and subplate neurons. At the same time, Fezf2 appears to confer specific identities onto subtypes of deep layer and subplate neurons. At the same time, Fezf2 appears to repress Satb2 (directly or indirectly) thereby repressing callosal identity. At later times during corticogenesis, when upper layer neurons are generated, Fezf2 expression is absent, which relieves the repression of Satb2. This, in turn, enables Satb2 to actively repress Ctip2 expression and promote the adoption of a callosal or corticocortical projection neuron identity. Interestingly, these two pathways also operate within a layer: for example, both subcortical and callosal projection neurons coexist within layer 5 [53], where Satb2 and Ctip2 are coexpressed by individual neurons during a brief window of time, just as layer 5 neurons are settling into their final positions within the cortical plate [50].

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest


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12. Chen B, Schaeavitz LR, McConnell SK: Fezf2 regulates the differentiation and axon targeting of layer 5 subcortical projection neurons in cerebral cortex. Proc Natl Acad Sci U S A 2005, 102:17184-17189. This paper describes the phenotype of Fezf2 mutant mice, with particular emphasis on the misrouting of corticospinal axons from deep layer neurons and changes in gene expression patterns (particularly that of Ctip2) in the mutants.


Development


In one of the first papers to track the lineage of upper layer neurons during cortical development, the authors use Svet1 as a marker to provide evidence that upper layer neurons are generated from the SVZ of the developing cortex.


This report demonstrates directly that neural progenitor cells divide in both the VZ and SVZ to give rise to neurons. A series of elegant time-lapse experiments establishes the SVZ as a region of active neurogenesis.


This paper describes real-time imaging of cell divisions in the VZ and SVZ and their correlation with precursor cell types.


This paper shows that in the absence of Fez2, subcortical projection neurons in layers 5 and 6 alter their normal fates and adopt the connections, physiological properties, and gene expression patterns typical of callosal projection neurons.


This paper shows that Fezl (Fezf2) is required for the specification of corticospinal motor neurons and, conversely, that overexpression of Fezl leads to overproduction of subcortical projection neurons.


This paper describes both the effects of knocking down Fezf2 (Zip312) using sRNAs in deep layer neurons and the misexpression of Fezf2 in upper layer neurons by in utero electroporation. The authors present evidence that Fezf2 regulates the formation of subcortical axonal projections in deep layer neurons.


This paper describes a screen to identify genes enriched in deep layer neurons and the functional characterization of Ctip2 (a gene identified in the screen) through the analysis of axonal connections in Ctip2 mutant mice.


This paper reports that Sox5 controls the timing of layer 5 neuron generation by suppressing Ctip2 expression in subplate and layer 6 neurons. Misexpression of Sox5 in upper layer neurons appears to convert theirs to resemble those of layer 6 neurons.


This paper shows that Cux-2 positively regulates cell cycle exit in SVZ progenitors, leading to an increased number of upper layer neurons in Cux-2 knockout animals.


This paper describes the phenotype of Satb2 mutant mice using a LacZ knockin construct to analyze the axonal projections of neurons that normally express Satb2. In the absence of Satb2, callosal projections extend axons toward subcortical targets. Satb2 binds to and modifies chromatin configuration at the Ctip2 locus.


This paper describes the phenotype of Satb2 mutant mice and the effect of ectopic expression of Satb2 in deep layer neurons by *in utero* electroporation. The authors provide evidence that Satb2 interacts with the Ctip2 locus, where it controls chromatin remodeling.


These authors demonstrate that SATB2 binds to histone deacetylase 1 and metastasis-associated protein 2, members of the nucleosome-remodeling complex and histone deacetylase complex.