<Further Development 16.03>

Horizontal and Vertical Specification of the Cerebrum

I. Radial migration of the pyramidal neurons

As mentioned in the textbook, the cerebral neocortex becomes segregated, into six horizontal layers, and each of these strata contains molecularly and functionally distinct sets of glutamate-synthesizing excitatory pyramidal neurons and GABA-synthesizing inhibitory interneurons. The pyramidal neurons migrate radially to form the six layers, and their migration is controlled by specific transcription factors (Kwan et al. 2012). The failure to properly activate these transcription factors at the appropriate times and places has been linked to brain anomalies and psychiatric disorders.

The first cortical neurons to be generated migrate out of the germinal zone to form the transient preplate (Kawauchi and Hoshino 2008). Subsequently, generated neurons migrate into the preplate and separate it into two layers: the Cajal-Retzius layer and the subplate. The Cajal-Retzius layer becomes and remains the most superficial layer of the neocortex, and its cells express the cell surface glycoprotein Reelin. The subplate remains the deepest layer through which the successive waves of neuroblasts travel to form the cortical plate. The Reelin-producing cells of the Cajal-Retzius layer are critical in the separation of the preplate. In Reelin-deficient mice, the preplate fails to split, and the neurons produced by the germinal layers pile up behind the previously generated neurons (instead of migrating through them). By activating the Notch pathway, Reelin on the surface of the Cajal-Retzius cells allows the neuronal stem cell to produce a long fiber that extends through the cortical plate (Hashimoto-Torii et al. 2008; Nomura et al. 2008). This (and the fact that it produced some proteins thought to be glial-specific) caused the neural stem cell to be called the *radial glial cell*. The process from this cell becomes critical for the migration of the neural cells produced by the germinal zones.

We also know that there are mutations that specifically affect the microtubular cytoskeleton of the migrating neuroblasts. Mutations in the *DISC1* gene prevent neuronal migration in the cortex by interfering with microtubule assembly; humans with such mutations have been seen to suffer from mental dysfunctions, among them autism, bipolar disorder, and schizophrenia (Kamiya et al. 2005, 2008).

We still do not know the nature of the information given to the cell as it becomes committed. However, Hanashina and her colleagues (2004) have shown that there are several genetic switches that get “thrown” at these division times. One of these switches is the gene encoding the transcription factor *Foxg1*. When the mouse neuronal progenitor cells divide to form the first layer of cortical neurons, *Foxg1* is not expressed in the progenitor cells or in the first-formed neurons. However, later, when the progenitor cells generate those neurons destined for layers 4 and 5, they express this gene. If the *Foxg1* gene is conditionally knocked out of this lineage, the neural precursor cells continually give rise to layer 1 neurons. Therefore, it seems that the *Foxg1* transcription factor is required to suppress the “layer 1” neural fate.

Neither the vertical nor the horizontal organization of the cerebral cortex is clonally specified—that is, none of the functional units form from the progeny of a single cell. Rather, the developing cortex forms from the mixing of cells derived from numerous stem cells. The early regionalization of the neocortex is thought to be organized by paracrine factors secreted by the epidermis and neural crest cells at the margins of the developing brain (Rakic et al. 2009). The paracrine factors induce the expression of transcription factors in the specific brain regions, which then mediate the survival, differentiation, proliferation, and migration of the newly generated neurons.

For instance, Fgf8 protein is secreted by the anterior neural ridge and is important for specifying the telencephalon (textbook Figure 10.24). If Fgf8 is overexpressed in the ridge, specification of the telencephalon is extended caudally, whereas if Fgf8 is ectopically added to the caudal region of the cortex, part of that caudal region will become anterior (Fukuchi-Shimogori and Grove 2001, 2005). Sonic hedgehog is secreted by the medial ganglionic eminence and helps form the ventral neurons of the cortex, including those of the substantia nigra (whose absence causes Parkinson disease).

II. Tangential migration of cortical interneurons

The *interneurons* coordinate the activity of the cortex, generating the temporal synchrony of the excitatory neurons. Di Christo (2007) compares "interneuron function to the music director of a symphony orchestra, who structures and coordinates the overall musical performance. Without proper direction, the ensemble cannot produce the right melody."

Whereas the migration of the excitatory pryramidal neurons is primarily radial, to form layers, the migration of the inhibitory interneurons is primarily tangential and secondarily radial. Cortical interneurons originate in the ventral telencephalon, and they then migrate to the other ares of the brain. This long-distance tangential migration and short-range radial migration is regulated by internal and external signals, the most interesting being GABA, itself. GABA (*g*amma-*a*mino*b*utyric *a*cid) is the major neurotransmitter secreted by these mature interneurons. It is also the major chemotactic factor regulating the migration of the *immature* interneuron precursors (see Faux et al. 2012). Here, errors in GABA production early in development can lead to brain anomalies associated with a number of cognitive defects in children and adults.

The pyramidal neurons and the interneurons develop from different progenitors. The pryramidal neurons differentiate in place, while the interneurons migrate from the ventral telencephalon. Different regions of the ventral telencephalon produce interneurons that migrate to different areas of the cortex. Migration occurs through the marginal zone at early stages, then through the intermediate zone, and finally through the subventricular zone. This is done (as in the neural crest cell migrations) by combining repulsive cues (semaphorins, chondoitin sulfate proteoglycans, Slit, and ephrin) with chemoattractants such as CXCL12 and neuregulin.

What has become a fascinating area of study, though, is the notion one of the most important chemotactic factors regulating this migration is GABA, which is produced along the migratory pathays (Cuzon et al. 2006; Lopez-Bendito et al. 2003; Inada et al. 2011). Not only are gradients of GABA found along the migratory pathways; GABA receptors on the migrating neurons bind GABA more avidly than those on the mature neurons. Pharmacologically disrupting the GABA receptor interaction stops or severely impedes the migration of the interneuron precursors (Cuzon et al. 2006; Inada et al. 2011). The addition of extra GABA leads to enhanced migration. In other words, unlike the peripheral nervous system, the shaping of the developing brain may modulated by spontaneous neural activity. GABA appears to be functioning to open ion channels (especially calcium ion channels) that regulate cell morphology, neurite extension, and cell migration (Inada et al. 2011; Yamamoto and Lopez-Bendito 2012).

Once in the specific region of the brain, the intraneuron precursor cells stop migrating tangentially and being radial migration. The switch for this is not known. It may have to do with the GABA receptor density on the precursor or with the amount of dendritic branching that has occurred. The branching may be critical for the cessation of migration and the eploration of cues within the column to find its appropriate place (see Martini et al. 2009; Tanaka et al. 2006, 2009).

The control of migration and lamination in the cortex remains one of the most exciting (no pun intended) areas of developmental biology. It may lead to the discovery of the origins of schizophrenia, mental retardation, hyperactivity syndromes, autism, and bipolar phenotypes. It can also lead to knowledge about knowledge: how do we become able to think, imagine, plan, and assemble data into patterns. Think about it.

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