Building Bridges to the Cortex

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Innervation of the neocortex by the thalamus is dependent on the precise coordination of spatial and temporal guidance cues. In this issue of *Cell*, work by López-Bendito et al. (2006) reveals that tangentially migrating cells within the ventral telencephalon are essential for axonal navigation between the thalamus and the neocortex, a process apparently mediated by Neuregulin-1/ErbB4 short- and long-range signaling.

Establishing neuronal pathways to deliver topographic sensory information to the cortex is a daunting task that requires the precise guidance of thalamic axons through a series of convoluted bends and turns within the diencephalon and telencephalon. This has generated considerable debate as to the mechanisms underlying these phenomena and has made this topic one of the most exciting areas in developmental neuroscience. Historically, the navigation of thalamocortical axons was thought to depend on area-specific attracting signals from different cortical regions. Because such area-specific signals had not been found in organotypic cocultures, it was suggested that some of the guidance cues must lie outside the cortex (Molnár and Blakemore, 1995). The early-born cortical preplate axons descend from the cortex and extend into the internal capsule (striatocortical junction and ventral telencephalon) before thalamocortical projections reach this region. These observations led to the "handshake hypothesis," in which thalamocortical and corticothalamic fibers guide each others' reciprocal navigation. In this model, thalamocortical axons intermingle with corticothalamic fibers and use this scaffold as they grow past one another en route to their respective targets within the cortex and the dorsal thalamus (Molnár and Blakemore, 1995; Molnár et al., 1998).

Consistent with this model, the deletion of genes whose expression is restricted to either the cortex (*Tbr1*, *Emx1*/*Emx2*) or dorsal thalamus (*Gbx2*) perturbs the guidance of thalamocortical and corticothalamic axons within the internal capsule, in a region where these genes are not expressed (Hevner et al., 2002; reviewed in López-Bendito and Molnár, 2003). Tracing thalamocortical projections in various null mutants revealed characteristic default pathways associated with forebrain patterning abnormalities. One of the particularly sensitive regions was the pallial/subpallial boundary (PSPB), a region where, according to the handshake model, the early corticofugal projections are believed to play a role in axon guidance. The second vulnerable region for thalamocortical axon guidance was at the diencephalon/telencephalon boundary (DTB). Taken together, the stereotypic failures of TCA guidance at the pallial/subpallial and the diencephalic/telencephalic junctions in different null mutants (including *Mash1* nulls) suggested that positional information may reside in specialized "guideposts" in addition to that provided by the reciprocal projections. Consistent with these observations, intermediate target cells within the ventral pallium were identified (Mitrofanis and Guillery, 1993; Métin and Godement, 1996). These "guidepost cells" (within the perireticular nucleus/internal capsule) develop early projections to the dorsal thalamus (Tuttle et al., 1999; Molnár et al., 1998) and are thought to be required for the thalamocortical axon tracts to transit between the diencephalon and the telencephalon. In mice lacking *Mash1*, *Pax6*, or *Emx2* gene function, either a portion of the thalamocortical axons fail to enter the telencephalon or the axon tract is displaced, presumably due to the misspecification of guidepost cells. However, the widespread expression of these genes within the ventral telencephalon or the thalamocortical axon pathway has left the identity of the guidepost cells and the molecular basis of their contribution to these axonal interactions unclear.

In this issue of *Cell*, López-Bendito and colleagues propose a new mechanism of navigation for thalamocortical axons in which tangentially migrating cells within the ventral telencephalon guide thalamic axons toward their final destination in the neocortex. These migrating cells, referred to as "corridor cells," appear to create a permissive bridge between the diencephalic/telencephalic boundary and the pallial/subpallial boundary, completing the relay between the intermediate targets of the thalamocortical pathway (Figure 1).

As noted above, the idea that specific populations of cells in the

ventral telencephalon guide thalamocortical axons is not all that unexpected (Mitrofanis and Guillery, 1993; Métin and Godement, 1996; Molnár et al., 1998; Tuttle et al., 1999). What is surprising is the suggestion that these cells accomplish this task not by simply passively providing positional cues but by actively bridging a zone that is nonpermissive to the growth of thalamocortical axons within the ventral telencephalon. Moreover, unlike the well-characterized tangential migration of ventral telencephalic cells to the dorsal telencephalon (reviewed in Corbin et al., 2001), corridor cells migrate in the opposite direction. Although corridor cells originate within the lateral ganglionic eminence (LGE), they migrate downward to provide a bridge through the more ventrally positioned medial ganglionic eminence (MGE) prior to the arrival of the afferents of thalamocortical axons (see dark blue cells in Figure 1). Consistent with their origin in the LGE, they express a number of LGE-specific markers, including Islet1, *Ebf1*, and *Meis2*. Through transplantation experiments and the restriction of the migration of LGE cells using a semipermeable membrane, López-Bendito et al. (2006) directly demonstrate the ventral migration of this population. Furthermore, the authors show that this countermigration of LGE-derived corridor cells to the MGE is crucial for creating a permissive bridge in the ventral telencephalic territory. In this regard, they observe that dorsal thalamic explants, when cultured on telencephalic slices alone or in the presence of either the MGE or globus pallidus, preferentially invaded into the striatum through the Islet1-positive LGE corridor cells, thereby avoiding the MGE-derived structures. Even more dramatically, corridor cells transplanted into the caudal ganglionic eminence, an otherwise nonpermissive region, were sufficient to recruit thalamocortical axonal growth into this territory.

The authors next turn to mice deficient in *Mash1*, in which a defect in axonal pathfinding for thalamocortical neurons has been well documented (Tuttle et al., 1999). In mice lacking *Mash1*, thalamocortical axons fail to invade the telencephalic territory. Correspondingly, these mice have defects in multiple cellular domains along the thalamocortical pathway, including the LGE-derived corridor cells, which is missing in these mutants. With homotypic transplantation of wild-type LGE cells into the LGE, they demonstrate that, in half of their experiments, these wild-type cells can tangentially migrate to form the LGE corridor in mice lacking *Mash1*. Moreover, the restored corridor was sufficient to rescue dorsally oriented axonal growth of thalamic explants when in contact with these wild-type corridor cells in 70% of experimental cases. Through these elegant sets of experiments, López-Bendito et al. (2006) provide compelling evidence that the guidance of thalamocortical axons from the thalamus toward the cortex utilizes these bridging corridor cells.

So what is it about these corridor cells that thalamocortical axons find so appealing? Interestingly, López-Bendito et al. (2006) find that the navigation of thalamocortical axons utilizes the same mechanism previously identified as crucial for guiding interneuron migration from the MGE to the cortex (Flames et al., 2004). In their previous work, this group showed that isoforms of Neuregulin-1 (Nrg1), membrane bound Nrg1 (CRD-Nrg1) and secreted Nrg1 (Ig-Nrg1), act as short-range and long-range attractants for cortical interneurons, respectively. Now it appears that the same receptor/ligand combination is utilized in the guidance of thalamocortical axons. Through a series of in vitro explant studies complemented by genetic loss of function and a dominant-negative approach, the authors demonstrate

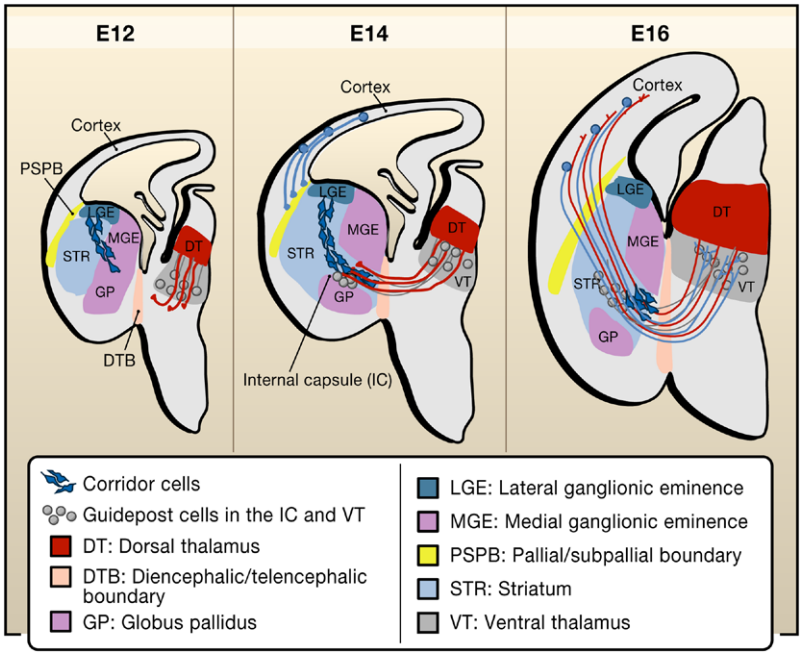

Figure 1. Corridor Cells Guide Thalamocortical Axons
A schematic diagram illustrates the migration of the corridor cells and their interactions with the thalamocortical projections. Corridor cells (dark blue) originate from the lateral ganglionic eminence (LGE) at embryonic day 12 (E12) and migrate tangentially toward the diencephalon, where they form a permissive "corridor" for the thalamic projections (red) to navigate them through the internal capsule. At E14, the ventral thalamus and internal capsule contain guidepost cells (gray) that have projections to the dorsal thalamus (DT).

that these isoforms of Nrg1 contribute to navigation of thalamocortical axons in the ventral telencephalon in distinct ways. Notably, the corridor cells themselves express CRD-Nrg1, and, in turn, thalamic neurons express the receptor for this ligand, ErbB4, from the onset of axon extension toward the telencephalon. In mutants that lack CRD-Nrg1, thalamic axon projections are perturbed and fewer axons are able to reach the cortex. Moreover, exogenous CRD-Nrg1-expressing COS cells are sufficient to attract thalamocortical axons in telencephalic slices. Together, these data suggest that the membrane bound Nrg1 expressed in the corridor cells can mediate short-range attraction of thalamocortical axons.

Interestingly, CRD-Nrg1 appears not to be the only Nrg1 involved in early thalamocortical axon guidance. As with interneuron migration, the secreted form of Nrg1 (Ig-Nrg1) is required in this system to promote the extension of thalamocortical axon fibers. By ablating the angle region, where Ig-Nrg1 is highly expressed, the authors demonstrate that there is also a drastic reduction in the number of thalamocortical axons extending through the internal capsule toward the cortex, a defect that is restored by transplanting Ig-Nrg1-expressing COS cells. Interestingly, this restoration occurs even when Ig-Nrg1-expressing COS cells are placed ectopically, suggesting that the secreted form is chemotropic rather than chemotaxic. Furthermore, when both isoforms of Nrg1 were knocked out throughout the telencephalon, the majority of thalamocortical axons failed to progress through the ventral telencephalic region. To confirm that this defect is due to a lack of Nrg1 signaling, the authors examine mice lacking the receptor for Nrg1, *ErbB4*, and also determine the effect of focally expressing a dominant-negative form of ErbB4 in the thalamus. These results are extremely satisfying, as they nicely demonstrate that these manipulations can indeed phenocopy the phenotype of mice lacking *Nrg1*. Notably, Islet1-expressing corridor cells do not require Nrg1 signaling for their migration from the LGE to MGE, and the presence of the corridor cells in the *Nrg1* and *ErbB4* nulls implies that the specific axon navigation defect was due to the absence of Nrg1 signaling rather than a secondary effect of mislocalization of the corridor cells. Taken together, their data convincingly show that these distinct isoforms of Neuregulin-1 function respectively as short- and long-range guidance cues in mediating thalamic axon navigation toward the cortex.

Does Neuregulin-1 signaling entirely account for the corridor cells' ability to facilitate thalamocortical axon guidance? Probably not. In both *Nrg1* and *ErbB4* mutants (which possess their normal complement of corridor cells), some thalamocortical axons are at least able to enter the telencephalon territory, unlike those in mice lacking *Mash1*. In these mice, which lack corridor cells, the axons completely fail to pass this boundary. This implies that Nrg1-independent chemoattractants expressed in corridor cells are important for the navigation of thalamocortical axons.

These experiments raise a number of questions about the other axonal guidance and migratory events that are occurring concomitantly with thalamocortical axon pathfinding. For instance, these experiments suggest an interesting parallel between the dorsally directed thalamocortical axons and the MGE-derived tangentially migrating cortical interneurons. Interestingly, despite the fact that both utilize Nrg1 for their guidance, each follows a distinct pathway, suggesting that other aspects of the mechanisms that guide axons versus dorsally directed tangentially migrating cortical interneurons are distinct. Furthermore, given their reciprocal pathfinding, it will be interesting to see whether the loss of *Nrg1* has any effect on the guidance of corticothalamic axons. In this regard, it will also be intriguing to examine how the different sets of corticofugal projections (subplate, layer 6 or layer 5) interact with the corridor cells, as it is known that corticothalamic projections rearrange while en route to their targets (Mitrofanis and Guillery, 1993). Therefore, it is possible that corridor cells have a direct role in mediating this topographic reorganization.

More questions also exist with regards to the identity and fate of corridor cells. Specifically, what happens to them? Are they in the process of migration to their final destination, where they exhibit more mature functions, or do they purely serve a role as pioneer guiding neurons (like subplate neurons, Cajal-Retzius neurons, and guidepost neurons) and disappear during the early postnatal period? The distinction and relationship between the guidepost neurons in the internal capsule (perireticular nucleus) (Mitrofanis and Guillery, 1993) and the corridor cells (López-Bendito et al., 2006) also merit further investigation. Do these neurons represent two separate populations? This seems likely, as the guidepost neurons in the internal capsule share markers with cells of the thalamic reticular nucleus of the diencephalon (Métin and Godement, 1996) and develop projections to the dorsal thalamus around embryonic day 13 (Tuttle et al., 1999), which is later than the migration of corridor cells. Clearly, uncovering gene-expression patterns that are specific to each group of cells will enable us to follow these populations with greater precision. These limits aside, the discovery of bridging cells is a significant step toward understanding the early process of thalamocortical navigation to the cortex. Whatever their further roles might be, their bridging function in shepherding thalamocortical axons toward the cortex suggests that guideposts play a more dynamic function in pathfinding than simply providing cues for turning.

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