PARSING THE PROSENCEPHALON

Murielle Rallu, Joshua G. Corbin and Gord Fishell

The forebrain, or prosencephalon, consists of the diencephalon and the telencephalon. The diencephalon is the conduit for ascending sensory information, whereas the telencephalon is the highest-order processor of neural function, and is consequently the most complex region of the nervous system. In this review, we discuss how fate restrictions, starting from the induction of neural character, result in the sequential specification of anterior neural tissue, forebrain and telencephalon, and finally dorsoventral patterning. Rather than relying on novel signalling pathways, the complexity of the mature brain seems to result from the unique ordering of signals used widely during development.

HOMEODOMAIN
A 60-amino-acid DNA-binding domain that comprises three α-helices and is found in many transcription factors.

BASIC HELIX–LOOP–HELIX
(bHLH). A structural motif present in many transcription factors that is characterized by two α-helices separated by a loop. The helices mediate dimerization, and the adjacent basic region is required for DNA binding.

NODE
A major organizing centre in primitive-streak-stage embryos that regulates pattern formation. It is known as Hensen's node in chick and the Spemann organizer in frog.

Developmental Genetics Program and the Department of Cell Biology, The Skirball Institute of Biomolecular Medicine, New York University Medical Center, 540 First Avenue, New York, New York 10016, USA.
Correspondence to G.F.
e-mail: fishell@saturn.med.nyu.edu
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Over the past decade, our understanding of regional patterning in the vertebrate telencephalon, and of the mechanisms that mediate its assembly, has moved forward significantly. This progress can be attributed largely to insights gained from studies in *Drosophila*[1,2], and to extrapolation from mechanisms that are known to pattern other levels of the neuraxis[3]. In general, the lesson has been that transient signalling centres produce diffusible cues that create positional information. Recipient cells translate these signals through the induction of combinatorial codes of transcription factors, and as a result, they acquire specific cellular identities[4].

The clearest example of a factor that provides positional information within the telencephalon is sonic hedgehog (Shh)[5]. Specifically, gain- and loss-of-function analyses of Shh signalling in the telencephalon have indicated that, as at other levels of the neuraxis, this diffusible signalling molecule is essential for the expression of characteristic ventral identities, as well as the repression of complementary dorsal fates[6–9]. A cadre of specific genes that bestow cellular identity in the telencephalon in response to Shh signalling has been found[10]. For the most part, these genes have been identified as the vertebrate homologues of those that establish neuronal populations in *Drosophila*[2]. So far, the proteins encoded by these genes have fallen primarily into two broad classes of transcription factors — those containing a characteristic DNA-binding HOMEODOMAIN sequence and those that contain a BASIC HELIX–LOOP–HELIX (bHLH) motif. Despite the similarities in the underlying logic of the mechanisms that establish different neural regions in vertebrates, or the brain in invertebrates, it is becoming clear that the telencephalon cannot simply be considered as an anterior-localized spinal cord or an elaborate fly head. In this review, we summarize what has been discovered so far about the extrinsic and intrinsic programmes that participate in the patterning of the telencephalon, and how these programmes interact. We argue that progress in our understanding of the telencephalon has entered a new phase, in which the key insights will come from direct examination of the vertebrate telencephalon, rather than from indirect inferences based on findings in other systems.

Induction of anterior neural character

The early patterning of both anterior and posterior neural tissues is mediated through signals that emanate from the primitive NODE or organizer. Studies in mammals indicate that, in addition to the organizer, the anterior visceral endoderm (AVE) is required for head induction and maintenance[11–15] (FIG. 1). The AVE is the extra-embryonic tissue that underlies the future neural plate or EPIBLAST[15] (FIG. 1). Removal of the AVE from mouse embryos at early stages of gastrulation leads to a loss or reduction of forebrain marker expression[15]. Also, several mutants that lack genes that are normally expressed in the AVE (for example, *Hesx1*, *Lim1* and *Otx2*) fail to develop anterior structures, including the forebrain[16]. Finally, transplantation of the mouse AVE into chick embryos results in the expression of forebrain markers in the epiblast. However, it is unclear whether the AVE has an active or a passive role in establishing

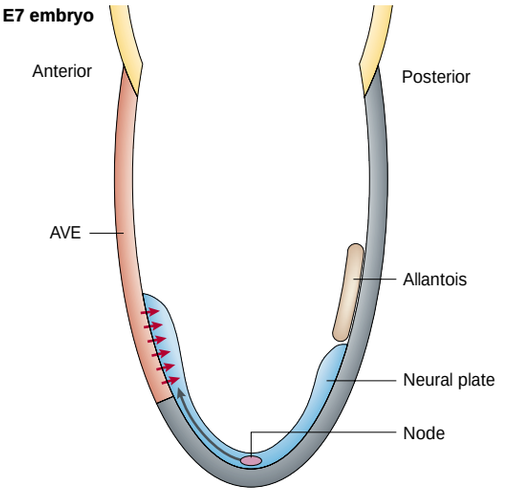

Figure 1 | **Signals and tissues involved in inducing anterior neural character.** Schematic of a mouse embryo at the early headfold stage. Signals that come from the node establish gross anterior pattern (black arrow). The anterior visceral endoderm (AVE), together with the node, acts to induce and/or maintain anterior neural character. The AVE is located beneath the future neural plate and expresses molecules, such as cerberus and dickkopf (red arrows), that inhibit factors that would otherwise act to posteriorize the anterior neural plate. This figure represents the end stage at which these signals are acting. E7, embryonic day 7.

anterior neural structures[12]. Transplantation of the chick hypoblast beneath the lateral epiblast/ectoderm (the equivalent of the AVE) can transiently induce anterior markers, but cannot sustain them. Furthermore, its removal does not prevent the expression of forebrain markers[17], indicating that the signals for head induction or maintenance might be present in different structures in mammals and birds.

Although the source of forebrain inducers might vary between different species, numerous lines of evidence indicate that the signalling mechanisms that specify the anterior neural tissue are widely conserved. Considerable molecular and genetic data support a model proposed by Nieuwkoop[18], who suggested that nascent neural tissue adopts an anterior identity by default (a process that he referred to as activation), and that the posterior nervous system is subsequently generated through a process that he called 'transformation'. Recently, this model has been revisited in the light of a wealth of new evidence[12]. Studies in fish and frogs have implicated Wnt, retinoids, and fibroblast growth factor (FGF) as 'posteriorizing' factors[19–22], indicating that inhibitors of these diffusible signals are responsible for maintaining anterior neural identity. With respect to the antagonism of Wnt signalling, two proteins with this activity, cerberus and dickkopf, are expressed in the anterior endoderm of frogs (the equivalent of the AVE) (FIG. 2), and can induce the formation of a head (but not a trunk) when misexpressed in frog embryos[23,24] (see note added in proof). The transforming growth factor-β (TGF-β)-related family of proteins, such as bone morphogenetic proteins (BMPs), activins and Nodal, also seem to play a part in this process. For example, mutants in which Nodal signalling is compromised have an enlarged telencephalon, indicating that the blockade of Nodal signalling is involved in forebrain development[25]. Interestingly, cerberus and dickkopf, which, in addition to their ability to block Wnt signalling, also function as Nodal or BMP antagonists[23,24], are only two of the many proteins that block these signalling pathways. These include chordin, noggin, follistatin and the Frizzled-related protein Frzb[26–28], all of which seem to act in the specification of the forebrain. Indeed, in mice that lack both chordin and noggin gene activities, the expression of AVE markers is induced correctly but is not maintained, and anterior neural fates are ultimately lost.

To complicate matters, it is clear that each of these proteins has many functions in addition to their roles in anteroposterior (AP) patterning of the nervous system; FGF is a potent mesoderm inducer, BMPs have a role in dorsoventral (DV) patterning of the early embryo, and both Wnt and Nodal signalling act in the establishment of the AP axis before neurulation[12,14,16,19,21,25,26,28]. Whether or not the role of these proteins in establishing anterior versus posterior neural structures can be neatly divided from their other functions is unclear at present.

Specification of telencephalic character

Subsequent to anterior neural induction, the cells at the junction between the anterior neural and non-neural ectoderm — the anterior neural ridge (ANR) or anterior neural boundary (ANB) — have an important role in promoting telencephalic development within the forebrain territory. Both in mice[29] and in fish[30], ablation of these cells prevents the expression of telencephalic markers such as Bf1 and Emx1. In zebrafish, transplantation of these cells into the midbrain can induce telencephalic and suppress midbrain marker expression in a cell-non-autonomous fashion. Other studies in zebrafish have indicated that the inhibition of Wnt signalling is a crucial step in the specification of the telencephalon and in the subdivision of the forebrain into telencephalic, optic and diencephalic territories. The *masterblind* mutation, which inactivates the Axin gene (a negative regulator of Wnt signalling)[31], transforms the telencephalon into diencephalic tissue[32]. Furthermore, Houart *et al.*[33] have shown that the telencephalon-inducing activity of the ANB cells is mediated by Tlc, a novel secreted Frizzled-related protein that acts as an extracellular antagonist of Wnt signalling (FIG. 2). Tlc not only mimics the activity of ANB cells, but *tlc* gene function is also required for telencephalic development in zebrafish[33]. Therefore, similar to the induction of the anterior neural tissues, the specification of telencephalic identity might require the inhibition of posteriorizing (diencephalic) signals, including, but probably not limited to, Wnt signalling.

Dorsoventral regionalization of the telencephalon

At the headfold stage (E8.0, four to eight somites), the mouse telencephalic anlage lies within the anterior third of the paired, downward-folded leaves of the neural plate, and the two sides of the anlage meet at the anterior

EPIBLAST
The outer layer of a blastula, which gives rise to the ectoderm after gastrulation.

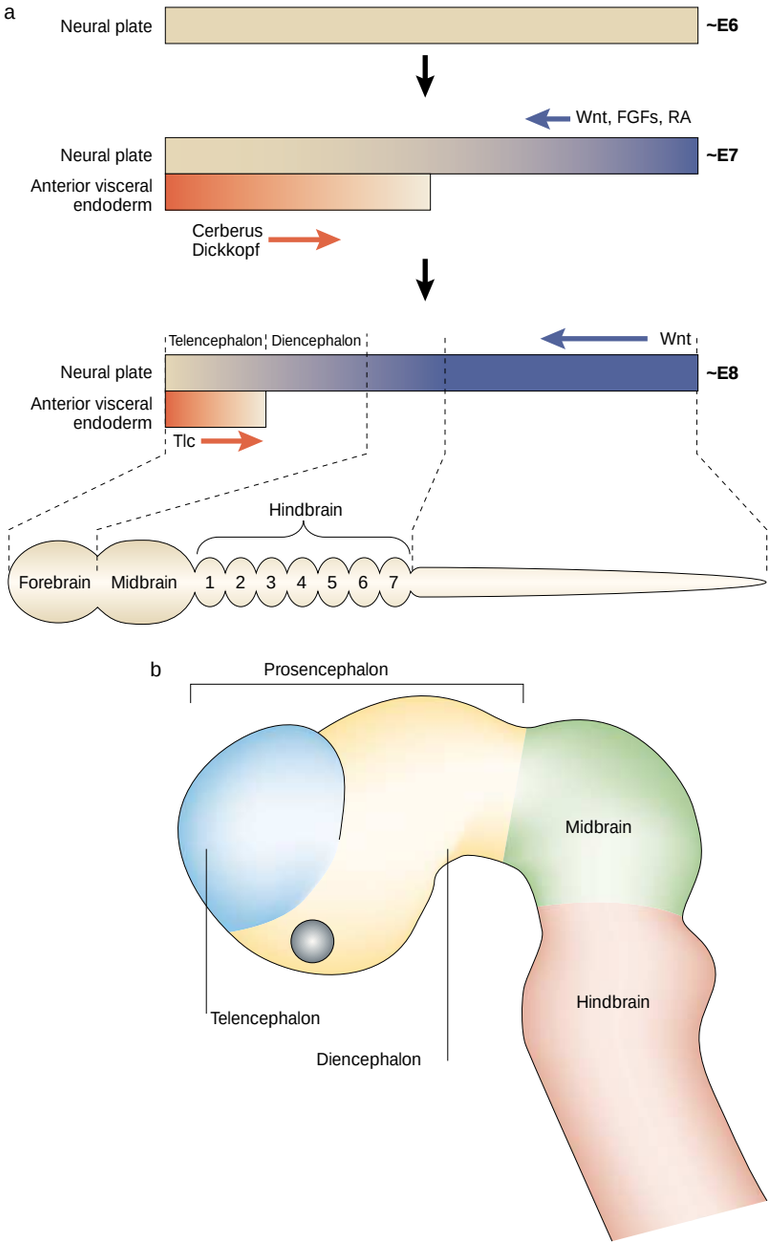

Figure 2 | **Progressive specification of the telencephalon. a** | Neural induction results in the formation of the neural plate. Markers expressed throughout the early neural plate will ultimately become restricted to anterior domains of the central nervous system. A number of molecules, including the Wnts, fibroblast growth factors (FGFs) and retinoids (RA), can function at this stage of development to induce posterior character in the neural plate. Conversely, antagonists of these factors, including cerberus and dickkopf, are expressed in the anterior visceral endoderm and act to maintain and stabilize the anterior neural plate character. Subsequently, the anterior neural domain is subdivided as a result of graded Wnt signalling. A key aspect of this process appears to be the expression of the Wnt antagonist Tlc, a Frizzled-related protein. E, embryonic day. **b** | Side view of the brain of a mouse embryo at around embryonic day 10 (E10), showing the main subdivisions.

midline. By coupling a dramatic set of morphogenetic movements with extensive proliferation, the telencephalon is transformed, by around E9 (the 20-somite stage), into a set of paired vesicles, complete with regionally restricted DV markers. These regional markers presage the morphological appearance of discrete dorsal (cortex), lateral (lateral ganglionic eminence or LGE) and ventral (medial ganglionic eminence or MGE) proliferative zones, which appear two days later, around embryonic day 11 (E11). When, and how, these telencephalic subdivisions are specified remain open questions. By contrast, DV patterning within the more posterior regions of the neural tube has been explained in considerable detail.

Shh signalling. Until recently, ideas about how the DV pattern is established in the forebrain have been largely borrowed from insights gained in the spinal cord. In both regions, a central player in this process is Shh. However, recent data have indicated that, despite some obvious similarities, the mechanisms that are used to establish DV patterning in the telencephalon differ from those used at more posterior regions of the neuraxis.

Shh signalling is crucial for ventral patterning at all levels of the nervous system[34,35]. Loss- and gain-of-function analyses in several species have shown that the Shh protein is necessary and sufficient for the development of ventral neural structures and the expression of associated neural markers. Embryos that lack Shh fail to form normal ventral telencephalic structures, and they show markedly reduced expression of ventral markers[6,9,36]. Furthermore, ectopic expression of *Shh* is sufficient to induce ventral telencephalic marker expression, both *in vitro* and *in vivo*[7–9]. However, precisely when Shh is required for ventral telencephalic patterning, and whether it acts to differentially specify distinct ventral telencephalic cell fates, is poorly understood. Furthermore, although *Shh* is expressed by a variety of anterior tissues throughout development, the precise source of Shh activity for telencephalic patterning has not been clearly identified.

The earliest site of *Shh* expression appears at around E7.5 in the midline mesoderm of the head process[37]. Shortly afterwards, both *Shh* and Indian hedgehog (*Ihh*) messenger RNA appear in the primitive node. As neurulation progresses, both the PRECHORDAL PLATE and the anterior MESENDODERM come to express *Shh*. Finally, just before the onset of neurogenesis, the expression of *Shh* occurs in the hypothalamus, and then in the ventral telencephalon itself[38]. Extirpation and genetic mutations that affect specific subdomains of *Shh* expression have been shown to perturb ventral telencephalic organization, but they have not yet allowed a clear determination of which sources of Shh are required for which aspects of ventral telencephalic patterning. By contrast, *in vitro* antibody perturbation experiments have given hints as to the temporal requirements for Shh during telencephalic development. These experiments indicate that the ventralmost telencephalic character (MGE-like fate) is acquired in response to Shh signals during gastrula stages[39], whereas later exposure of telencephalic tissue seems to be involved in the acquisition of ventrolateral telencephalic fate[7]. Gain-of-function studies have produced similar results[7,39].

PRECHORDAL PLATE
A tissue derived from the node, which lies at the rostral tip of the notochord.

MESENDODERM
Embryonic tissue that gives rise both to mesoderm and endoderm.

An important difference between the spinal cord and the telencephalon was revealed by *in vitro* experiments in which explants were exposed to various concentrations of Shh. Whereas spinal cord explants show concentration-dependent changes in the ventral genes that are induced by Shh, the fates induced by Shh in the telencephalon depend on the timing, rather than on the concentration, of Shh exposure[7,39]. The observation that the competence of the telencephalon to respond to Shh changes during development indicates that further mechanisms are involved in the establishment of DV patterning in this area. In accordance with this idea, careful analysis of ventral telencephalic markers in *Shh*-null mutants has raised the possibility that another pathway acts in parallel with Shh to specify DV pattern within the telencephalon. Specifically, the lateral telencephalic fates (LGE) seem to be correctly specified, although they are shifted ventrally at the expense of the most ventral (MGE) fates.

Function of Gli genes. To understand how Shh affects telencephalic patterning, the role of the three mammalian Gli genes, *Gli1*, *Gli2* and *Gli3*, must be considered. Gli genes are homologous to the *Drosophila* gene *cubitus interruptus* (*ci*), and genetic analysis has shown that all Hedgehog signalling is mediated through *ci* in flies, and similarly by the Gli genes in vertebrates[40,41]. Gli1 and Gli2 act principally as activators, whereas Gli3 acts mainly as a repressor[41]. With respect to the telencephalon, compound-mutant mice that lack *Gli1* and *Gli2* gene function develop relatively normally[42]. By contrast, in *Gli3* mutants, ventral telencephalic markers expand dorsally into the cortex[9,43,44]. The fact that opposite telencephalic phenotypes are observed in *Shh* and *Gli3* mutants indicates that the balance between *Shh* and *Gli3* gene function is crucial in the establishment of DV patterning within the telencephalon (FIG. 3).

To explore this hypothesis, we have recently analysed telencephalic patterning in *Shh*/*Gli3* compound mutants[9] (FIG. 3). Consistent with work in the spinal cord[45] and limb[46,47], we found that Shh is likely to act through the inhibition of Gli3 repressor activity. Indeed, the removal of one or both alleles of *Gli3* is sufficient to restore the ventral telencephalic gene expression that is lost in *Shh* mutants. Notably, in the absence of both *Shh* and *Gli3* gene function, not only are the lateral fates specified correctly (as in the spinal cord), but so is both the level and localization of *Nkx2.1* gene expression, consistent with the restoration of the MGE, the most ventral part of the telencephalon.

The hedgehog pathway in vertebrates is mediated through multiple ligands and Gli proteins, but all hedgehog signalling requires the function of the transmembrane protein Smo, a homologue of *Drosophila* Smoothened. Mice that lack both *Gli3* and *Smo* gene functions produce a similar phenotype to that observed in *Shh*/*Gli3* compound mutants. Together, these results indicate that Shh is the only hedgehog ligand that functions in the DV patterning of the telencephalon.

One caveat to these findings is that relatively few markers of DV pattern have been identified in the telencephalon, compared with the spinal cord. It remains possible that further analysis with more specific telencephalic markers will reveal that the rescue of DV pattern in these compound mutants is incomplete. For example, the possibility that a subdomain of *Nkx2.1* expression (equivalent to the floorplate in the spinal cord) remains absent in the double mutants cannot be ruled out. This cautionary note aside, these results indicate that the role of *Shh* in DV patterning varies at different levels of the neuraxis. Specifically, *Gli2* is required in the spinal cord for the specification of V3 interneurons and floorplate. By contrast, the loss of *Gli2* has no effect on patterning in the telencephalon. Given that

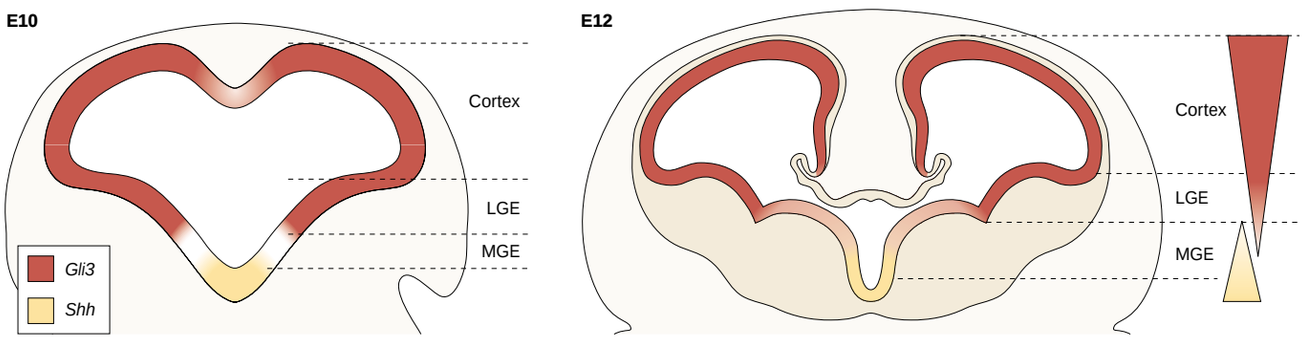

Figure 3 | **Model of genetic interactions between Shh and Gli3 in patterning the mouse telencephalon.** Schematic representation of a coronal section through an embryonic day 10 (E10; on the left) and E12 (on the right) mouse telencephalon, highlighting different domains along the dorsoventral (DV) axis. The expression domains of *Gli3* (in red) and sonic hedgehog (*Shh*; in yellow) are shown at early and late stages of telencephalic development. These genes maintain a complementary pattern of expression throughout development, and genetic analysis shows that their activities strongly antagonize one another. Specifically, in the absence of *Shh* gene function, the telencephalon is strongly ventralized, whereas in the absence of *Gli3* gene function, the telencephalon is strongly dorsalized. In the absence of both *Gli3* and *Shh*, the general aspects of DV patterning are rescued. The notable exceptions are the dorsal midline structures, which are lost in all three mutant genotypes: $Shh^{-/-}$, $Gli3^{-/-}$ and $Shh^{-/-}/Gli3^{-/-}$. These data indicate the existence of an unknown hedgehog-independent pathway that acts in parallel with *Shh* in the establishment of telencephalic DV pattern. MGE, medial ganglionic eminence; LGE, lateral ganglionic eminence.

several studies argue that Gli3 functions primarily as a repressor[45–47], whereas Gli1 and Gli2 act either primarily or wholly as activators[48], this indicates that only the repressive functions of Shh signalling are required for telencephalic patterning.

These results show that *Shh* is dispensable for the general DV patterning of the telencephalon, provided that *Gli3* function is also abolished. This strongly implies that other signalling pathways act in parallel with *Shh* to regionalize the telencephalon. Although the identities of the Shh-independent signals are unknown, there are several obvious candidates on the basis of patterning mechanisms detected in other studies, primarily in the spinal cord.

Other signalling pathways. BMP signalling, in addition to its role in the specification of dorsal neural tube cell types[49–51], also seems to influence the patterning of ventral cell types. Application of BMP proteins to spinal cord explants alters the response of neural progenitors to the Shh protein and results in a dorsal shift in their cellular identity. Moreover, the addition of BMP inhibitors in the same assay seems to potentiate the response to Shh signalling. Therefore, it seems that, in the spinal cord, Shh and BMP signalling pathways converge and potentially limit the actions of each other along the DV axis. Similarly, BMPs are expressed in and around the dorsal telencephalon, and they seem to have a role in the dorsal patterning of this tissue[43,52–56]. Furthermore, Shh and BMP signalling have been shown to cooperate to induce ventral diencephalic identity[57]. So, early BMP7 expression in the prechordal plate, or BMP4 in the PRESOMITIC MESODERM, might also be responsible for Shh-independent patterning. Perhaps the best evidence for a requirement for BMPs in telencephalic patterning comes from an analysis of the zebrafish *swirl* mutant, which is a *Bmp2b* null. The dorsal telencephalic gene *Emx1* is lost in *swirl* mutants, although it is unclear whether this indicates a loss of dorsal structures or loss of the telencephalon as a whole[58].

In addition to BMPs, Wnts are also involved in dorsal telencephalic development; in particular, in the specification of the hippocampus[55,59,60]. Recent work also indicates that inhibition of the Wnt pathway is an important feature in the formation of the telencephalon (see above). So, in addition to specifying the telencephalon as a whole, graded inhibition of Wnt signalling might also act to establish DV identity within the telencephalon.

In the spinal cord, a retinoid-activated pathway has been implicated in the generation of the ventrolateral V0 and V1 interneurons, independently of the Shh pathway[61]. In the telencephalon, markers of retinoid synthesis and signalling are expressed in the LGE and the developing striatum[62,63]. Furthermore, retinoid signalling has been shown to regulate striatal neuronal differentiation. However, earlier expression of the retinoids (in the lateral cranial mesoderm[64]) is more likely to have a role in the initial patterning of the telencephalon.

Other candidates that have been implicated in telencephalic patterning are the FGFs. Studies of zebrafish and mice have implicated FGF3 and FGF8 signalling in establishing regional patterning in the SUBPALLIAL region of the telencephalon[29,58,65]. Finally, experiments in zebrafish indicate that Shh and Nodal signalling might interact[66]. Indeed, *Shh* overexpression is able to restore ventral gene expression in the telencephalon of several zebrafish mutants with deficiencies in Nodal signalling. So, it seems that Nodal can mediate forebrain patterning through the regulation of the hedgehog signalling pathway. It is therefore likely that many or all of these signalling pathways act in some capacity in the DV patterning of the telencephalon, but their precise roles, and whether these pathways are acting in concert with or in parallel to Shh signalling, will require further examination.

Downstream patterning mechanisms

In response to the reception of Shh and other extrinsic signals, cells express specific transcription factors. These, in turn, activate intrinsic cellular programmes, which cause progenitors to adopt specific cell fates. Our understanding of the downstream effectors of cell identity remains, at best, rudimentary, but it is known that many of the genes that act in response to extrinsic cues belong to a set of homeodomain-class transcription factors that are conserved across divergent species. For example, the homeodomain proteins that act to pattern the *Drosophila* nerve cord are homologous to those that act to delineate regional cell types in the vertebrate spinal cord and telencephalon[67,68]. In *Drosophila*, these genes include *vnd* (*ventral nervous system defective*), *ind* (*intermediate neuroblasts defective*) and *msh* (*muscle segment homeobox*), whereas patterning of the vertebrate spinal cord is dependent on the ventral expression of *Nkx2.2* and *Nkx6.1*, and on the intermediate expression of *Dbx1* and *Dbx2* (REF. 69), which are homologues of the *Drosophila H2.0* gene[70]. Similarly, future telencephalic territories can be defined early in the development of this region by the expression of a distinct set of homeodomain genes: *Nkx2.1*, *Gsh1*, *Gsh2* and *Pax6*, which are homologues of the *Drosophila* genes *vnd*, *ind* and *eyeless* (*ey*), respectively[71–74]. These mouse genes provide some of the earliest markers of dorsal (*Pax6*), intermediate (*Gsh2*) and ventral (*Nkx2.1*) domains of the telencephalon[10] (J.G.C. and G.F., unpublished observations; FIG. 4). Furthermore, these genes are essential for the normal development of the regions in which they are expressed. So, across divergent species, although the extrinsic signalling mechanisms that establish positional cues vary, the result of such signalling manifests itself in the expression of a conserved set of regionally expressed transcription factors.

Of the proteins that act to pattern the vertebrate and invertebrate nervous system, the Nkx/*vnd* family of genes is exceptionally well conserved, in terms of both expression and function[67]. In the absence of the *Nkx/vnd* genes, the fates of the ventral-most cells in the spinal cord[75] and the *Drosophila* nerve cord are transformed to that of their nearest dorsal neighbours[71,72].

PRESOMITIC MESODERM
Precursor unsegmented mesoderm, which generates somites on segmentation.

SUBPALLIAL
Belonging to the base of the telencephalon. The subpallium consists primarily of the basal ganglia, including the striatum, globus pallidus, and parts of the septum and amygdala.

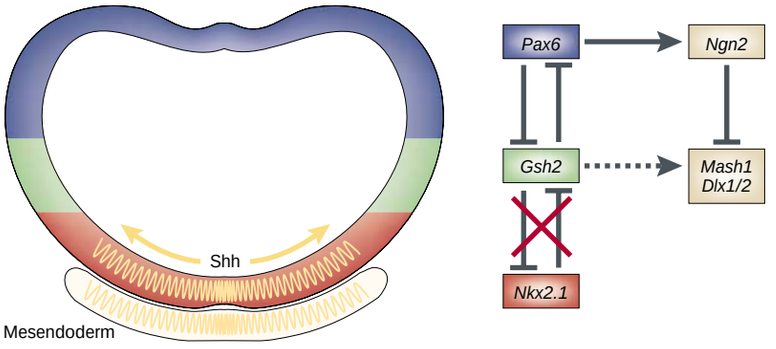

Figure 4 | **Homeodomain and bHLH genetic interactions in telencephalic development.** Schematic of a coronal section of the mouse telencephalon at 26 somites (about embryonic day 9.5), showing the expression pattern of the homeodomain transcription factors Nkx2.1, Gsh2 and Pax6. Sources of both ventral telencephalic and mesendodermal Shh are also shown in this schematic. At this age, shortly after Gsh2 is first detected in the lateral telencephalon, expression of these genes is mostly non-overlapping. Genetic analysis has revealed that while Pax6 and Gsh2 act in a cross-repressive manner, Nkx2.1 and Gsh2 do not. Furthermore, Pax6 may regulate the function of the basic helix–loop–helix (bHLH) transcription factor, Ngn2, which in turn regulates *Mash1* and *Dlx1*/*Dlx2* gene function.

Similarly, in the absence of *Nkx2.1*, the ventral-most aspect of the telencephalon — the MGE — becomes trans-fated to that of the adjacent, more dorsal LGE[76]. However, despite the apparent conservation of the function of Nkx/*vnd* genes in the generation of the ventral-most aspect of the neuraxis, how these genes regulate, and in turn are regulated by, other genes differs between invertebrates and vertebrates. For example, in *Drosophila*, *vnd* and *ind* mutually repress the expression of each other[71,72]. However, *Gsh2* (the *ind* homologue) and *Nkx2.1* (the *vnd* homologue), which initially maintain complementary patterns of expression, seem to have no direct effect on each other's expression (FIG. 4). Specifically, the loss of *Gsh2* (or the combined loss of *Gsh1* and *Gsh2*) does not result in an expansion of *Nkx2.1* expression, nor does the loss of *Nkx2.1* result in the precocious expression of *Gsh2* in ventral regions (J.G.C. and G.F., unpublished observations). Interestingly, however, *Gsh2* and *Pax6* (a homologue of the *Drosophila ey* gene), the complementary expression of which forms a sharp border at the intermediate–dorsal boundary (LGE–cortex), do cross-repress one another (J.G.C. and G.F., unpublished observations; FIG. 4). Loss of *Gsh2* function leads to an expansion of *Pax6* expression (as well as other dorsally restricted genes, most notably *Ngn2*) into the intermediate, LGE domain[77–79]. Conversely, loss of *Pax6* function in small-eye (sey) mice leads to an expansion of *Gsh2* into the *Pax6* domain[78,79]. In the *Drosophila* nerve cord, the dorsal repression of *ind* is known to be mediated by *msh*. However, on the basis of findings in mammals, it would also be interesting to explore the interactions between *ind* and *ey* in the establishment of the intermediate–dorsal boundary in the fly nervous system. It is worth noting that, in the vertebrate nervous system, the cross-repression of *Pax6* and *Gsh2* is specific to the telencephalon; in the spinal cord, their expression domains overlap[73]. This, again, emphasizes that to understand the role of the various genes in the patterning of the telencephalon, this structure must be studied directly.

Normal patterning of the telencephalon also seems to require the function of conserved members of the bHLH transcription-factor gene family. These genes include *Mash1* (a homologue of the genes in the *Drosophila achaete-scute complex*), which is expressed at its highest levels in the ventral telencephalon (MGE and LGE), and *Ngn1*/*Ngn2* (homologues of the *Drosophila atonal* genes), the expression of which is restricted to the dorsal telencephalon[10]. The absence of either *Mash1* or *Ngn1*/*Ngn2* gene function in mice leads to defects in DV patterning, showing the indispensable role of these bHLH genes in the normal allocation of territories in the telencephalon.

The regulatory mechanisms of bHLH and homeodomain regional gene expression are interdependent (FIG. 4). For example, in the absence of *Gsh2*, the expression of *Mash1* is lost in the LGE, and the expression of *Ngn2*, along with that of *Pax6*, is expanded into the intermediate region. In *Pax6* mutant mice, on the other hand, *Ngn2* expression is lost in the lateral cortex and *Mash1* expression expands into this region[77–79]. Conversely, in *Mash1*-null mice, *Nkx2.1* expression is lost in the rostral MGE[80], whereas in *Ngn1*/*Ngn2* compound null mice, the normal ventral restriction in the expression of homeodomain genes, such as *Dlx2*, is compromised, resulting in their expansion into dorsal regions[81]. Collectively, these data indicate that correct DV patterning of the telencephalon is dependent not only on the interactions of conserved homeodomain genes, but also on their interactions with the bHLH genes. In addition to their role in patterning, Mash1 and Dlx1/Dlx2 regulate specific aspects of neurogenesis. Genetic loss-of-function studies have revealed that *Mash1* and *Dlx1*/*Dlx2* are required for the generation of early- and late-born subpallial progenitors, respectively[80,82–84]. It is notable that the bHLH genes are also regulated by components of the Notch/lateral signalling pathway[85,86]. Indeed, abnormalities in neural differentiation are hallmarks of mutants that lack either *Mash1* or *Ngn1*/*Ngn2* gene function. Given that an obligate part of the telencephalic patterning mechanism is the generation of regional differences in the regulation of proliferation and differentiation, it seems likely that the bHLH genes provide an important juncture by which these two processes are linked. An important area of future research will be to delineate more clearly the connection between the control of regional patterning and the means by which proliferation in dorsal versus ventral regions of the telencephalon is coordinately regulated.

One of the specific functions of *Shh* is to induce oligodendrocyte development in ventral regions of the central nervous system, including the telencephalon[87,88]. Two novel bHLH factors, *Olig1* and *Olig2*, have been identified that are essential for the specification of oligodendrocytes in response to Shh signalling[89,90]. Recently, single and compound null alleles of these genes have been generated[91,92]. These studies indicate that oligodendrocytes and motor neurons in the spinal

cord have an absolute requirement for these genes, and that they act in combination with *Nkx2.2* and *Ngn1*, respectively, to establish these populations[93–95]. *Olig2* is expressed widely in the ventral telencephalon, but the phenotype that results from the loss of this gene in this region has not yet been reported in detail. Given that both oligodendrocytes and interneurons originate from ventral telencephalic regions[87,96], and might share a common precursor[97], it will be of interest to see how the loss of *Olig1*/*Olig2* affects the generation of these cell types. More broadly, these genes no doubt provide a good example of the kind of combinatorial code that is required for the generation of specific cell types; for example, in spinal cord, progenitors that co-express *Olig1*/*Olig2* and *Nkx2.1* become oligodendrocytes, whereas progenitors that co-express *Olig1*/*Olig2* and *Ngn1* become motor neurons[93–95]. Indeed, an important aim, which further analysis of the telencephalon must address, is to uncover the logic of how combinatorial codes of homeodomain and bHLH genes act to establish specific neural populations within the telencephalon.

Tangential migration broadens regional diversity

By E12.5 in mice, as a result of regional patterning, the telencephalon develops a series of characteristic proliferative zones. In the dorsal telencephalon, both cortical and hippocampal regions become evident, and three distinct eminences appear ventrally: the MGE, the LGE anteriorly, and the caudal ganglionic eminence (CGE) posteriorly[98–100]. Until recently, these different regions of the forebrain were thought to develop as independent compartments, with cortical cells originating entirely from the cortical ventricular zone, and the striatum, globus pallidus and amygdala arising from the ventral eminences[101–103]. A wealth of genetic, lineage-tracing and fate-mapping analyses has revealed the situation to be considerably more complicated[102,103]. Although many details remain to be worked out, it now seems clear that extensive mixing of progeny occurs through tangential migration, with cells from the MGE and CGE ultimately populating the cortex, and cortically derived neurons migrating ventrally to invade the amygdala. The logic of why such a baroque scheme of development has been selected for probably reflects the fact that different progenitor zones generate specific subsets of neural cell types. For example, the MGE and CGE make large populations of interneurons and oligodendrocytes, whereas the LGE, hippocampal and cortical proliferative zones generate primarily projection neurons. So, regional patterning not only generates specific telencephalic structures, but also acts as a means of producing large populations of particular neuronal subtypes.

Summary and future directions

Work over the past ten years has begun to give us a mechanistic understanding of telencephalic development. In summary, telencephalic development follows a discrete series of steps. First, around the time of gastrulation, an interplay between posteriorizing signals (such as FGFs, Wnts and retinoids) and anteriorizing factors (such as cerberus and dickkopf) results in the polarization of the nervous system[12,14]. Anterior neural tissue later becomes further subdivided into the diencephalon and telencephalon, at least partially by the graded modulation of Wnt signalling[31–33]. This is followed by the emergence of regional patterning in the telencephalon itself, which requires the action of Shh, as well as other extrinsic factors, possibly including FGF, BMPs, Wnts, retinoids and Nodal signalling. Although there might be some redundancy between the factors that establish positional information within the telencephalon (as shown by the persistence of DV patterning in the telencephalon of *Shh*/*Gli3* compound mutants[9]), such signalling seems to converge on the induction of a combinatorial code of homeodomain and bHLH transcription factors within progenitors at different DV positions[10]. Notably, this code results not only in the emergence of regional territories, but also in characteristic patterns of proliferation in dorsal versus ventral regions of the telencephalon. In addition, it seems that specific populations of cell types, including interneurons, oligodendrocytes and projection neurons, are each born in different telencephalic regions and become distributed appropriately only later in development, through characteristic patterns of tangential migration.

Obviously, there are many unanswered questions that relate to each of these steps. For example, we have not yet characterized the full range of extrinsic factors that act to establish the telencephalon and its subdivisions. Similarly, it seems certain that further transcription factors that contribute to the combinatorial code, as well as the logic by which this code results in the generation of specific subpopulations, remain to be discovered. Furthermore, recent fate-mapping efforts indicate that tangential migration within the telencephalon is widespread and includes dorsal-to-ventral migration of neurons, in addition to the well- characterized ventral-to-dorsal migration of interneurons. Nonetheless, it is clear that the signalling cascades for establishing telencephalic pattern are widely used in other regions of the embryo, as well as across species. Therefore, the molecular requirements for generating brain structures are variations of mechanisms used elsewhere. The specificity that allows the development of the telencephalon involves a unique combination and ordering of these common signals in time and space. Now that a broad outline of telencephalic development is crystallizing, it seems likely that further resolution of the underlying mechanisms will rely on a direct examination of this region, using the growing complement of cellular and genetic approaches that are available.

Note added in proof

A recent paper by Lupo *et al.*[104] has implicated the inhibition of Wnts and BMPs by cerberus as a crucial step towards the generation of dorsal telencephalic identity.

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Online links

DATABASES

The following terms in this article are linked online to:

Entrez: http://ncbi.nlm.nih.gov/Entrez/
cerberus | dickkopf | Tlc | Wnt

FlyBase: http://flybase.bio.indiana.edu/
achaete-scute complex | *atonal* | *cubitus interruptus* | *eyeless* | *H2.0* | Hedgehog | *ind* | *msh* | Smoothened | *vnd*

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/
Axin | Bf1 | *Bmp2b* | BMP4 | BMP7 | chordin | *Dbx1* | *Dbx2* | *Dlx1* | *Dlx2* | Emx1 | FGF3 | FGF8 | follistatin | Frzb | *Gli1* | *Gli2* | *Gli3* | *Gsh1* | *Gsh2* | *Hesx1* | Ihh | *Lim1* | *Mash1* | *Ngn1* | *Ngn2* | *Nkx2.1* | *Nkx2.2* | *Nkx6.1* | Nodal | noggin | Notch | *Olig1* | *Olig2* | *Otx2* | *Pax6* | Shh | Smo | TGF-β

FURTHER INFORMATION

Encyclopedia of Life Sciences: http://www.els.net/
bone morphogenetic proteins and their receptors | hedgehog signalling | mammalian embryo: Wnt signalling | neural development: bHLH genes | neural subtype identity regulation | signal transduction pathways in development: Wnts and their receptors | vertebrate central nervous system: pattern formation

The Fishell Lab: http://skirball.med.nyu.edu/groups/FishellLab/

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