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Cortical neurogenesis and morphogens: diversity of cues, sources and functions

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The cerebral cortex is composed of hundreds of different types of neurons, which underlie its ability to perform highly complex neural processes. How cortical neurons are generated during development constitutes a major challenge in developmental neurosciences with important implications for brain repair and diseases. Cortical neurogenesis is dependent on intrinsic and extrinsic cues, which interplay to generate cortical neurons at the right number, time and place. While the role of intrinsic factors such as proneural and Notch genes has been well established, recent evidence indicate that most classical morphogens, produced by various neural and non-neural sources throughout embryonic development, contribute to the master control and fine tuning of cortical neurogenesis. Here we review some recent advances in the dissection of the molecular logic underlying neurogenesis in the cortex, with special emphasis on the roles of morphogenic cues in this process.

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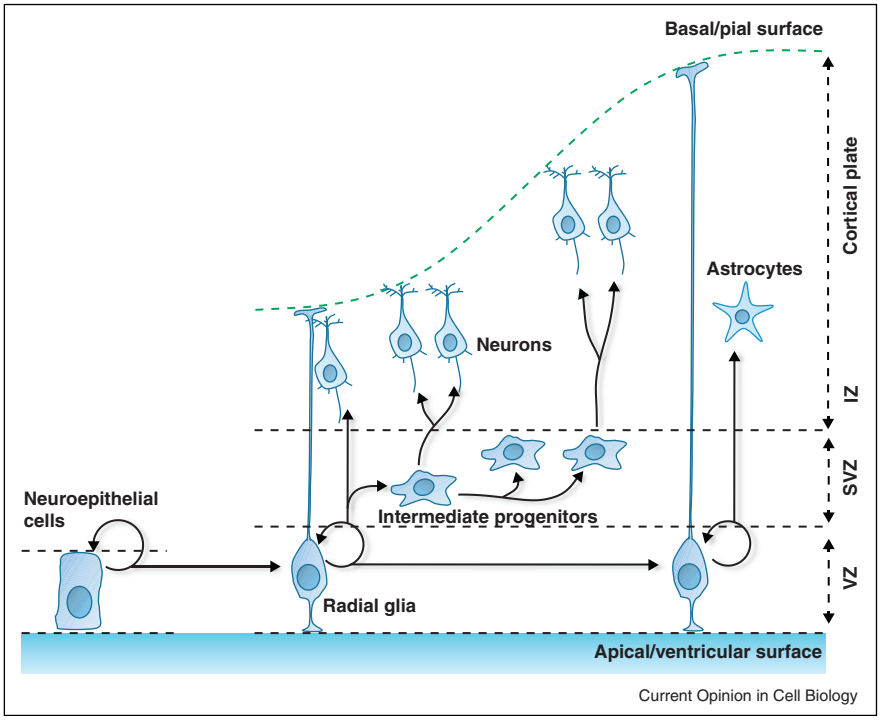
Introduction

The cerebral cortex is the most complex structure in the mammalian brain, consisting of hundreds of distinct neuronal subtypes. Neuronal diversity is at the core of cortical function and underlies its most sophisticated tasks. Neurons of the cerebral cortex belong to two broad classes: excitatory pyramidal neurons and inhibitory interneurons. Pyramidal neurons constitute the bulk (85%) of them and can be categorized further into many subtypes, each of which is characterized by a specific morphology, electrophysiology and connectivity [1]. Cortical neurons are organized spatially into specific cortical areas and layers, which broadly predicts their hodological properties. As for areas, they divide the surface of the cortex and consist of groups of neurons that are specialized in particular functions, such as visual or motor areas for instance. Each area is divided radially into six different layers, which contain specific subtypes of neurons characterized by specific patterns of axonal output and input.

The entire pyramidal neuronal population arises from the cortical primordium, which consists of a diverse set of cortical progenitors in the proliferative zones lining the lateral ventricles of the dorsal telencephalon, the ventricular (VZ) and subventricular zones (SVZ) (Figure 1). Neuroepithelial (NE) progenitors constitute the first type to emerge, which are characterized by symmetric proliferative divisions that enable to amplify the initial pool of cortical progenitors. NE progenitors later convert into radial glial (RG) progenitors, which constitute the major subtype of cortical progenitors (reviewed in [2–4]). RG cells are characterized by their unique morphology, with a contact with the ventricular, or apical surface, and a radial process stretching from the VZ to the outer, or basal surface of the cortex. RG cells undergo patterns of symmetric and asymmetric cell divisions, thereby enabling the generation of diverse types of neurons, while maintaining a pool of progenitors, thus following a stem cell-like behavior [5,6]. In addition to RG cells, several other types of progenitors have been identified that are likely to contribute to neuronal diversity [5,7–9]. Of special interest among these are intermediate progenitor (IP) cells [5,10]. Unlike RG cells, IP cells divide symmetrically only once or twice (at least in the mouse) before generating neurons and thus act as transit amplifying cells. Newly generated IP cells lack any apico-basal processes and migrate away from the VZ to create an additional proliferative zone above the VZ, called the SVZ.

The molecular control of cortical neurogenesis involves the interplay of intrinsic and extrinsic cues that coordinate the pattern of neural progenitor division and differentiation. Intrinsic factors include proneural factors such as Neurogenins, which together with the Notch pathway control the balance between self-renewal and neurogenic transition [11,12]; in addition, a wealth of transcription factors as well as controllers of cell polarity and mitosis have been identified in this process, acting at the level of at least one type of progenitor to control cortical neurogenesis [2–4,13]. Indeed many aspects of cortical neurogenesis are thought to be built-in within the lineage of cortical progenitors, including the temporal pattern by

Figure 1



Cortical neurogenesis during mouse embryonic development.
Several types of cortical progenitors and their modes of division towards neurons and glial cells: neuroepithelial cells, radial glial cells, intermediate progenitors, with their specific location in ventricular (VZ) and subventricular (SVZ) and intermediate (IZ) zones.

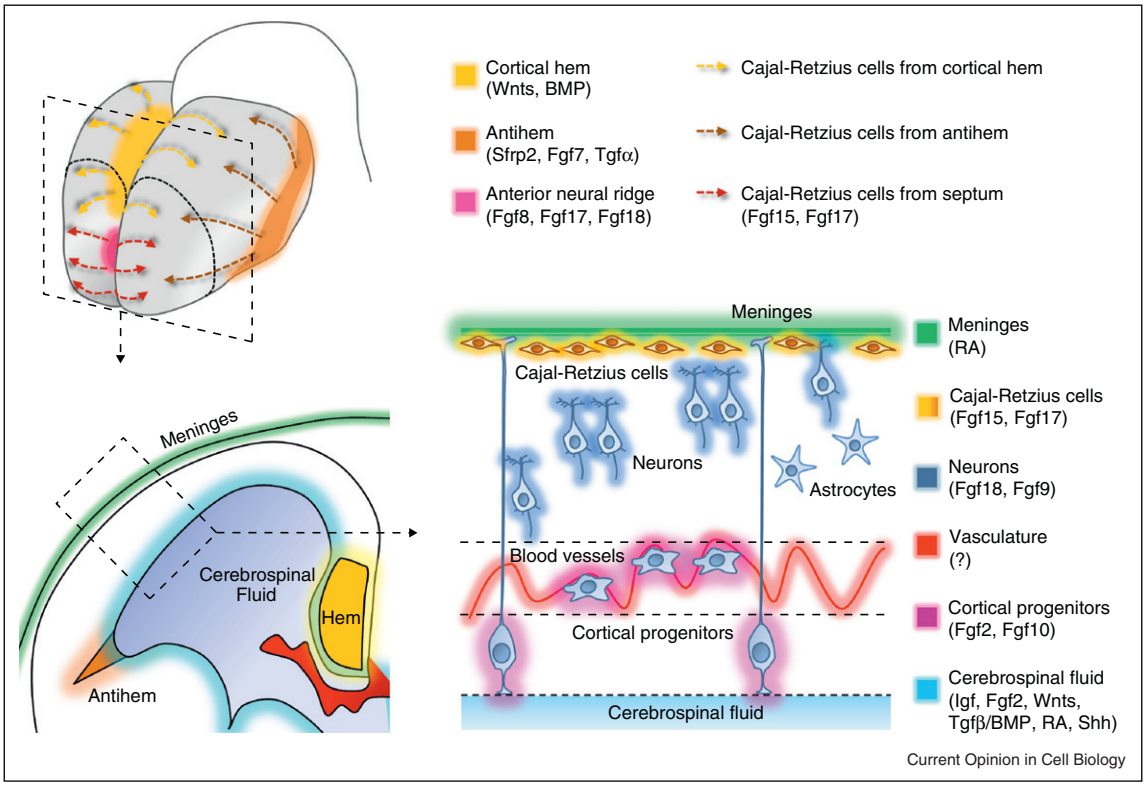
which single progenitors can generate sequentially different types of neurons [14,15]. But while these data suggest that a part of cortical neurogenesis is controlled cell-autonomously, a number of extracellular cues are also involved crucially, in particular members of the classical morphogen families, that is, retinoic acid (RA), Wnts, bone morphogenic proteins (BMP)/transforming growth factors (TGF), sonic hedgehog (Shh), and fibroblast growth factors (FGF). These morphogenic cues are expressed throughout cortical development, and while some of them are involved in setting up the regional patterning of the cortex, including early dorso-ventral and later cortical area patterning (reviewed in [16–18]), they also act on the control of neurogenesis itself. In addition, while many of these cues are thought to be produced by organizing centers, such as the anterior neural ridge (ANR) or the cortical hem (Figure 2), they are also produced by various other sources, including neural progenitors and neurons themselves, as well as by extra-neural components of the cortex, such as the surrounding meninges, the cerebrospinal fluid and the vasculature (Figure 2) (Table 1).

FGF signals: from regional patterning to control of cortical size and neural fate

Several FGF play key complementary roles in the regional patterning and neurogenesis of the cortex. Among these, FGF8 has emerged as a central regulator, from its earliest steps during telencephalon induction and dorso-ventral regionalization, to the later patterning of cortical areas [17,19]. Indeed, FGF8 is normally produced by the ANR, at the anterior-most aspect of the cortical primordium (Figure 2). Disruption of FGF8 leads to contraction of the anterior parts of the cortex [20], while its overexpression at the posterior pole of the cortex can result in anterior respecification, and even duplication of some cortical areas [21]. In this context FGF8 was recently shown to act at a distance and with graded functionality, thus providing the first suggestive evidence of a bona fide cortical morphogen [22•]. Other FGF cues secreted at the anterior pole of the cortex interact with FGF8, such as FGF17 that also promotes anterior cortical fates, while FGF15 opposes this action [23,24], thus constituting a complex FGF-triumvirate controlling areal patterning.

On the other hand, FGF8 was also shown to be required for normal patterns of proliferation and survival of cortical progenitors in the cortical primordium [26,27], as well as the production of specific populations of Cajal-Retzius cortical neurons [28], while FGF15 displays the converse effect by promoting the generation of cortical pyramidal neurons [24]. It will be interesting to determine whether these effects on neurogenesis correspond to distinct regulatory mechanisms, or are in fact related, to FGF8/15/17-dependent regional areal patterning. Interestingly,

Figure 2



Diversity of sources of morphogen signals in the developing cortex.The three classical signalling centers that pattern the developing cortex are the cortical hem (yellow), the antihem (brown) at the pallio-subpallial boundary, and the anterior neural ridge (pink) close to the septum. From these regions, at least three different types of migrating Cajal-Retzius cells (yellow, brown and red dashed arrows) originate, which can also produce patterning morphogens as they spread along the cortical surface. Other sources of morphogens that regulate neurogenesis are found at the basal and apical boundaries of the cortical neuroepithelium: the meninges (green) are situated at the basal surface, while the cerebrospinal fluid (light blue) borders the apical ventricular zone. Within the cortex itself, pioneer Cajal-Retzius cells (yellow), pyramidal neurons (dark blue), blood vessels (red), and cortical progenitors (purple) also secrete a variety of morphogens affecting neuronal differentiation and maturation.

Table 1

Morphogens, cortical patterning, and neurogenesis

Morphogen	Source	Functions	Ref.
FGF2	Cortical progenitors	Maintains proliferative divisions of early cortical progenitors, frontal cortex mostly affected	[30–33]
FGF8/FGF17	ANR	Promote the development of anterior cortical areas	[20–23]
		Increase proliferation and survival of cortical progenitors	[26,27]
FGF9	Cortical neurons	Promotes generation of astrocytes from RG cells	[38••]
FGF10	Cortical progenitors	Promotes conversion of NE cells into RG cells, mostly in frontal cortex	[29•]
FGF15	Rostral forebrain	Inhibits the development of frontal cortical areas Promotes differentiation of RG cells	[24]
BMP	Cortical Hem CSF	Patterning of dorso-medial cortex	[62,63]
FGF18	Cortical neurons	FGF18 signalling controls migratory behavior of cortical neurons	[39]
Tgfβ1/2/3	Meninges and CSF, cortical progenitors	Tgfβ ligands promote neurogenesis from cortical progenitors	[64,65]
RA	Meninges	RA promotes conversion of RG cells into neurons	[75••]
Wnts	Cortex	Patterning of dorso-medial cortex	[42]
		Promotes self-renewal of RG cells and conversion of IP cells into neurons	[43–51,53•]
Shh	Ventral telencephalon; cortex	Ventral patterning of the telencephalon, synergizes FGF signalling	[69,70]
		Promotes proliferation and survival of cortical progenitors	[71–73]

FGF15/17 are also produced by a specific population of Cajal-Retzius cells that originates from the septum (Figure 2) [25•]. These pioneer neurons migrate along the surface of the cortex at the early stages of its expansion and populate the marginal zone of the frontal cortex, from where they can affect not only the regional identity, but also the proliferation and differentiation of neural progenitors. This way, Cajal-Retzius cells provide further means to spread spatially the pattern of FGF signalling in the developing cortex, beyond the ANR organizing center [25•]. It is possible that other populations of Cajal-Retzius cells (from the cortical hem and antihem; Figure 2) exert similar functions in other cortical regions.

The link between areal patterning and regulation of neurogenesis is however most strikingly illustrated by the role of another FGF cue: FGF10 [29•]. FGF10 is expressed early on in the cortical anlage throughout the proliferative zone, at the crucial time of transition of proliferative NE to neurogenic RG cells, and is rapidly downregulated as this conversion is completed. Loss and gain of function analyses in mice then demonstrated that FGF10 acts as a tight controller of this phase, as its disruption results in a prolonged amplification phase of NE cells. As a consequence, the appearance of neurogenic (RG and IP) progenitors is delayed, resulting in an initial decrease of neuronal production, followed by an increased number of neurons at later stages, consistent with the hypothesis that FGF10-mediated control of the initial pool of progenitors has a direct influence on the number of neurons being generated. Interestingly, as FGF10 is mostly expressed in the most frontal areas of the developing cortex, this results in a selective enlargement of the frontal cortex at birth. The role of FGF10 thus exemplifies how a single cue integrates early patterning of neurogenesis, and later shaping of cortical areas.

FGF2 is another prominent ligand expressed by cortical progenitors that controls their balance of proliferation and neurogenesis. It is required for the expansion of NE cells [30], and negatively regulates cortical neurogenesis [31]. The effects of FGF2 on neurogenesis may also contribute to regional patterning, since neurons of the anterior parts of the cortex are more affected than other types of cortical neurons in FGF2 knockout mice [32]. The role of FGF signalling in neurogenesis in relation to areal patterning is further substantiated by analyses of mice deficient for the three FGF receptors expressed in the developing cortex: FGFR1/2/3 [33,34]. The disruption of FGFR1/2/3 at the stage of NE cell amplification results in a drastic reduction of the size of the posterior cortex, correlated with initial precocious neurogenesis, thus probably caused by early depletion of the progenitor pool [33]. Disruption of the same genes at later stages in RG cells results in their increased conversion into IP cells and neurons, while their proliferation and survival rates seem to be unaffected [34•]. Conversely, gain of function mutations in the FGFR3 gene in mice increases the conversion of cortical progenitors to neurons [35]. This effect is also most striking in the posterior cortex, which is reminiscent of a cortical malformation that mostly affects the posterior (occipital) cortex, and is caused by a similar FGFR3 mutation in humans [36]. These data are also consistent with analyses of mouse mutant for the Sprouty genes, negative regulators of FGF signalling, which display FGF gain of function-like phenotypes in neurogenesis and regional patterning [37].

Finally, FGF9 constitutes a striking example of a feedback mechanism controlling the generation of neuronal cells during corticogenesis: it is released by cortical neurons as they differentiate, and once reaching a certain level it promotes gliogenesis, thus contributing to the shift from neurogenesis to gliogenesis that concludes corticogenesis [38••]. FGF18 is also expressed in postmitotic neurons and seems to be part of a similar feedback signal to differentiating neurons controlling their specification and migration [39].

Wnt and neurogenesis: cell context-dependent pleiotropy

Early studies on Wnt signals in the cortical primordium revealed their prominent expression in the cortical hem, an organizing center located at the dorsal midline of the cortical anlage [40] (Figure 2). Wnts coming from the hem, in particular Wnt3a, play a major role in the regulation of cortical structures located adjacent to the midline such as the hippocampal cortex, and also promote proper dorsalization of the telencephalon [41,42].

Wnt-dependent signalling pathways also exert complex effects on neurogenic transitions of cortical progenitors. The effects of Wnts on cortical neurogenesis are diverse and appear to be highly dependent on the stage and cell type considered. Overexpression of activated forms of β-catenin, a major component of the Wnt canonical pathway, results in drastic expansion of cortical surface, together with a thinner cortex and decreased cell cycle exit of cortical progenitors [43,44]. Conversely, inactivation of Wnt/β-catenin can lead to increased conversion of RG cells into IP cells and neurons [45,46]. Consistent with this hypothesis, many Wnts are expressed highest medially originating from the hem, while Wnt-antagonists like Sfrp2 are most strongly expressed in the antihem (Figure 2). The inverse correlation of this Wnt-gradient with the spatial/temporal gradients of cortical neurogenesis, proceeding from antero-lateral to postero-medial parts of the cortex, suggests that Wnts may delay the onset of neurogenesis [47]. On the contrary, Wnt ligands can exert potent proneurogenic effects in the cortex, and the proneural factor Neurogenin1 is directly under the transcriptional control of Wnt-dependent TCF/LEF factors [48–52]. Recent data using direct comparison

of activating or inhibitory Wnt ligands *in vivo* reveals a scenario that may reconcile partly those apparently conflicting results [53•]: Wnt signals promote RG cell renewal, but they also accelerate the conversion of IP cells into cortical neurons. It will be interesting to find out how Wnt signals seem to act as a break in RG stem cells and as an accelerator in its IP transit amplifying progeny. Important parameters that remain to be considered include the exact identity of the Wnt ligands and receptors that act physiologically on NE, RG or IP cells, the concentrations at which they act, and their dynamics. In view of recently described oscillations of the Notch pathway in cortical progenitors on the one hand [54,55], and the oscillating Notch-Wnt-FGF networks during somitogenesis on the other hand [56], it would be exciting to explore whether oscillatory actions of Wnt/β-catenin in cortical progenitors could explain some of the above described phenotypes as well. Also, the various downstream signalling pathways involved should be considered further. For instance, β-catenin is very likely to exert other effects than those purely linked to the Wnt pathway. Indeed, conditional mutation of GSK3, which lies directly upstream of β-catenin, revealed that it is a mediator of many morphogen pathways in the developing cortex, including Shh and FGF [57]. Furthermore, β-catenin is involved in N-cadherin-dependent signalling [58], and adhesion [59]. The importance and complexity of the Wnt/β-catenin pathway in cortical neurogenesis is further emphasized by its links with DISC1, a candidate gene for schizophrenia that regulates cortical neurogenesis and β-catenin phosphorylation [60••,61].

BMP/TGFβ and sonic hedgehog: beyond dorso-ventral patterning

Similarly to Wnts, BMPs are expressed in the dorsal midline and regulate the regional patterning of the dorsal-most parts of the forebrain primordium, but their impact on neurogenesis remains essentially unexplored *in vivo* [62,63]. On the contrary, TGFβ ligands are necessary and sufficient to trigger neurogenesis of hippocampal and cortical neurons [64,65], and are involved in the production of Cajal-Retzius neurons [66], but disruption of their main receptor TGFβR2 does not show obvious effects [67]. Although Activin seems to be involved in neuron–astrocyte transition in the olfactory bulb [68], the roles of Nodal-signalling during cortical development remain to our knowledge unexplored.

Shh is a key morphogen in the early patterning of the ventral telencephalon [69], but it also has indirect impact on cortical patterning, partly through modulation of FGF signalling [70]. In addition, Shh pathways may be involved in cortical neurogenesis itself. Indeed, several mutants displaying Shh gain of function show altered proliferation and survival of cortical progenitors [71,72], and cortex-specific deletion of Shh or its receptor Smo can result in decreased cortical size and neurogenesis [73].

Retinoic acid and other cues released by non-neural tissues

Apart from a role of RA in specification of a subtype of cortical progenitors at the pallio-subpallial boundary [74], recent studies have further investigated the role of RA in cortical neurogenesis, and revealed the key impact of the meninges in support and control of cortical development [75••]. This was first revealed by analysis of Foxc1 mutants, which display striking defects in the generation of meninges. Subsequent analysis of the RA pathway in these mutants revealed that the meninges constitute an important source of RA, which can rescue most of the defects observed. RA release from meninges illustrates the role of non-neural sources on the control of cortical neurogenesis (Figure 2).

While meninges are located at the basal side of the cortex, morphogens located in the cerebrospinal fluid (CSF), thus acting on the apical side of the cortical neuroepithelium, are also likely to play important roles. CSF has long been known to contribute to the adult brain homeostasis, but its role in development has only emerged recently [76,77••]. IGF ligands, playing a crucial role in the proliferative patterns of cortical progenitors, but also Wnts and BMPs have been recently found to be present in the CSF [76,77••]. It will be interesting to explore further the identity and function of morphogens produced from the meninges and the CSF, as they could generate complex apico-basal gradients that would differentially affect cortical progenitors, depending on their apico-basal polarity, asymmetry or position.

Finally, a last source of extrinsic cues or morphogens that will be exciting to explore further are developing blood vessels. Recent evidence suggests that, in analogy to adult neurogenesis, the vascular niche may impact cortical neurogenesis, given the striking spatial and temporal correlation between blood vessel development and neurogenesis, but the cues involved remain to be identified [78–81].

Conclusions and future directions

Classical morphogens are involved in most aspects of cortical neurogenesis, in addition to their better known role in regional patterning. Many of the studies reviewed here raise in fact many questions to address in the future. Perhaps the most interesting one conceptually will be to determine whether and how morphogens control regional patterning in direct relation with neuronal production and fate acquisition. For instance, different cortical areas are enriched in specific neuronal populations, such as layer V neurons in the motor cortex or layer IV neurons in the visual area: it is tempting to speculate that patterns of morphogens could control the production of specific neuronal fates in a region-specific manner, thereby providing a direct link between areal specificity and cytoarchitecture. Another issue will be to determine

how neurogenesis can be affected in a combinatorial way by morphogens of different classes, inasmuch that some of the downstream pathways seem to be shared, and to determine how they articulate with the intrinsic components of the neurogenic machinery, such as cell polarity and asymmetry, Notch and proneural pathways, and cell cycle dynamics. Resolving these issues may not only provide important insights on how the cortical complexity emerges during normal and pathological brain development, but may also be fruitful for the rational design of directed differentiation of cortical neurons from pluripotent stem cells, with potentially important implications for studies on cortical diseases [82].

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