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REVIEW ARTICLE

Cerebral cortex development: an outside-in perspective

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The cerebral cortex is a complex structure that contains different classes of neurons distributed within six layers and regionally organized into highly specialized areas. Cortical layering arises during embryonic development in an inside-out manner as forebrain progenitors proliferate and generate distinct waves of interneurons and projection neurons. Radial glial cells (RGCs) derive from neuroepithelial cells and are the founding cortical progenitors. At the onset of corticogenesis, RGCs expand their pool by proliferative divisions. As corticogenesis proceeds, they gradually undergo differentiative divisions to either generate neurons directly (direct neurogenesis) or indirectly via production of intermediate progenitors that further divide to generate pairs of neurons (indirect neurogenesis). The fate of RGCs is finely regulated during all the corticogenesis process and depends on time-scaled perception of external signals and expression of intrinsic factors. The present Review focuses on the role of physiological extracellular cues arising from the vicinity of neural progenitors on the regulation of dorsal neurogenesis and cerebral cortex patterning. It further discusses how pathogenic viral factors influence RGC behaviour and disrupt cerebral cortex development.

Keywords: cerebral cortex; environmental cues; neural progenitors; neurogenesis

Diversity of the progenitors during cerebral cortex development

Shortly after its closure, the neural tube forms rostrally three primary vesicles, namely the forebrain, the midbrain and the hindbrain. The forebrain and hindbrain subdivide into secondary vesicles, respectively, telencephalon/diencephalon and myelencephalon/metencephalon, which further generate specific brain structures. The cerebral cortex mainly derives from the dorsal part of the telencephalon. The ventral telencephalon includes the ganglionic eminences (GE) from where GABAergic interneurons originate and migrate tangentially to invade the developing cortical wall [1] (Fig. 1A,B).

Neuroepithelial cells (NECs) are the earliest progenitors of the cortex. They are organized in a pseudostratified neuroepithelium that result from the apico-basal movement of their nuclei during cell-cycle progression. These cells initially expand their pool by successive symmetric proliferative divisions and later divide asymmetrically to generate radial glial cells (RGCs) that sit in the ventricular zone (VZ) of the

Abbreviations
APs, apical progenitors; bHLH, basic-helix-loop-helix; BMPs, bone morphogenetic proteins; CMV, cytomegalovirus; CP, cortical plate; CSF, cerebrospinal fluid; DLL, delta-like; ECM, extracellular matrix; FGFs, fibroblast growth factors; GE, ganglionic eminences; hNSCs, human neural stem cells; IE, immediate early; IPs, intermediate progenitors; IZ, intermediate zone; LRP, lipoprotein receptor-related protein; MCMV, mouse CMV; MIB1, mind bomb 1; NECs, neuroepithelial cells; NICD, Notch intracellular domain; NS, nonstructural; oRGCs, outer radial glial cells; Ptch1, Patched1; RGCs, radial glial cells; Shh, Sonic hedgehog; Smo, Smoothened; SNPs, short neural precursor cells; SVZ, subventricular zone; VZ, ventricular zone; ZIKV, Zika virus.

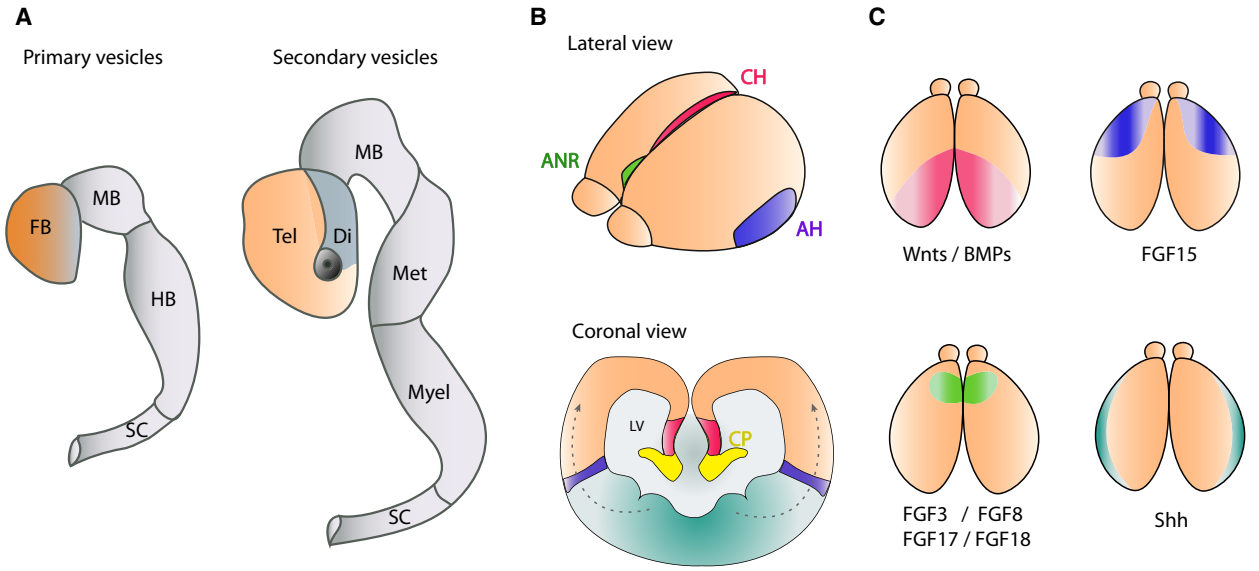

Fig. 1. Cerebral cortex development and morphogens expression. (A) The rostral part of the neural tube evolves rostrally into the primary forebrain (FB), midbrain (MB) and hindbrain (HB) vesicles while the caudal part gives the spinal cord (SC). The secondary vesicles telencephalon (Tel), diencephalon (Di), metencephalon (Met) and myelencephalon (Myel) develop from the primary vesicles. (B) The anterior neural ridge (ANR), cortical hem (CH) and anti-hem (AH) are organizing centres secreting, respectively, FGFs, Wnts/BMPs and FGF15 morphogens in the telencephalon. Shh is mainly present in the ventral part of the telencephalon, where ganglionic eminences are specified and generate interneurons that follow dorsal tangential path to invade the developing cortex. All morphogens are found in the CSF secreted by choroid plexus (CP) and filling the lateral ventricles (LV). (C) Morphogens gradients in the dorsal telencephalon.

cortex [2,3]. Similarly to NECs, RGCs maintain a bipolar morphology with apical and basal processes [4]. The neurogenesis time window of the developing cerebral cortex extends from E10.5 to E18.5 in rodents and precedes the gliogenesis period which terminates after birth [4].

At the onset of corticogenesis, direct neurogenesis is predominant as RGCs divide asymmetrically to self-renew and generate a projecting neuron. As corticogenesis proceeds, RGCs give rise to intermediate progenitors (IPs) that delaminate from the apical surface to invade the subventricular zone (SVZ) (Fig. 2). In contrast to RGCs and sometimes following one amplification step, IPs divide symmetrically to give birth to two identical neurons [5–7]. The process of indirect neurogenesis is more important in gyrencephalic species and is critical to generate the bulk of cortical neurons [8]. Projection neurons produced directly or indirectly from RGCs undergo a complex and temporally regulated migration process to reach the cortical plate (CP). Early born neurons rely on somal translocation to move basally and integrate the deep layers of the cortex. In contrast, later born neurons initially transit into multipolar morphology, further adopt a bipolar shape and finally attach the RGCs basal process to undergo locomotion towards the upper layers [9–12]. During the establishment of the cerebral cortex, the projection neurons are produced in successive waves and generate six layers organizing one above the other, resulting in an inside-out patterning [13,14].

Two additional minor populations of neuronal progenitors have been described in the developing cerebral cortex of the mouse: the short neural precursor cells (SNPs) and the outer RGCs (oRGCs). Similarly to RGCs, SNPs reside in the VZ but are transcriptionally distinct from RGCs. Moreover, they lack basal attachment and they are only programmed to generate neurons via symmetric differentiative divisions [15,16]. The oRGCs lack apical attachment and reside in the outer part of the SVZ. They share common molecular features with RGCs and are proportionally more important in the developing cortex of gyrencephalic mammals where they may contribute to the folding of the cortex [17–19].

Despite their variety, cortical progenitors possess common features. For instance, NECs, SNPs and RGCs, globally termed apical progenitors (APs), harbour a nonmotile and small microtubule-based primary cilium protruding in the lateral ventricle from their apical surface [20]. The primary cilium is immersed in the cerebrospinal fluid (CSF) and works as an antenna to probe extracellular signals and initiate intracellular transduction of specific molecular pathways [21,22]. The primary cilium is also required

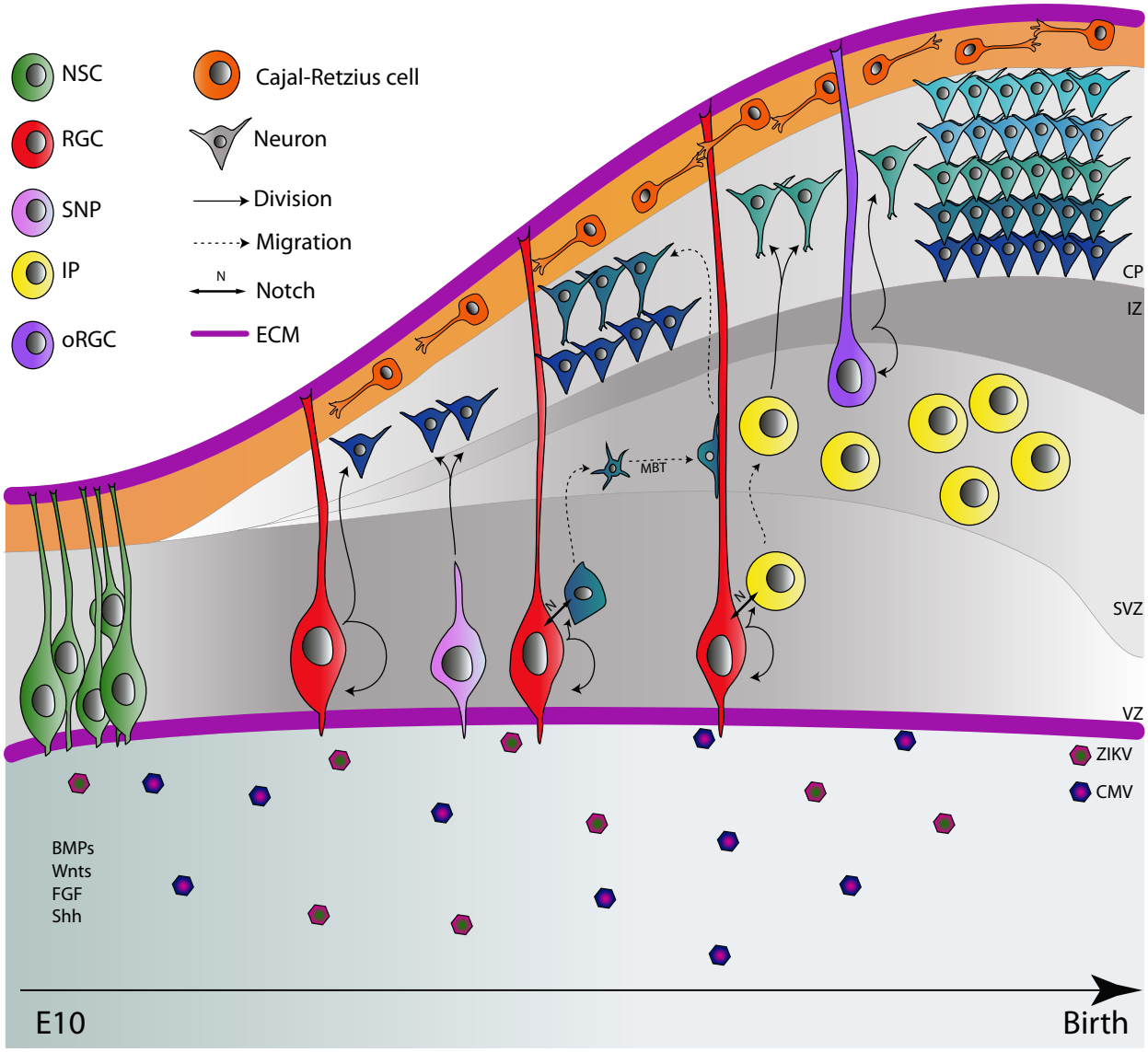

Fig. 2. Environmental influences on cortical neurogenesis. Morphogens and pathogens in the CSF can directly influence cortical development by interacting with the apical progenitors (NECs, RGCs and SNPs) lining the ventricular surface. Notch signalling is activated in the RGCs following cell-to-cell contact with neurons or IPs. Other abbreviations: ventricular zone (VZ), subventricular zone (SVZ), intermediate zone (IZ), cortical plate (CP), marginal zone (MZ), multipolar-bipolar transition (MBT).

for the maintenance of the apico-basal polarity of RGCs [23]. Interestingly, several studies have reported the presence of a primary cilium on IPs, immature neurons and interneurons arising from the GE [24–26].

The proliferative behaviour of cortical progenitors and the specification of their daughter cell fate result from the integration of genetic programmes with the decoding of extrinsic signals arising from their vicinity. In the developing brain, morphogen signallings not only impact on intrinsic features of APs, but also have a global influence on the organization and development of the cerebral cortex. The present Review focuses on the role played by key environmental cues in neurogenesis and patterning of the cortex and discusses the deleterious impact of viruses that infect RGCs and that are associated with human cortical malformations.

Regulation of the biology of cortical progenitors by CSF-derived cues

The APs contact the lateral ventricles that are filled with the CSF secreted by the choroid plexus. The CSF composition changes during the corticogenesis period

and contains diffusible morphogens that act as key drivers of cortical development [27] (Fig. 1B,C).

Sonic hedgehog

Sonic hedgehog (Shh) is a diffusible protein that belongs to the hedgehog family members. In the developing forebrain, Shh is mostly secreted from the ventral telencephalon into the CSF. However, it is also produced by the choroid plexus, the Cajal-Retzius cells in the marginal zone of the cerebral cortex and the interneurons that migrated to the CP [28,29]. The primary cilium is the core transduction platform for Shh signalling in the APs. The Shh receptor Patched1 (Ptch1) and its related signalling components accumulate into this structure [30–32]. Following Shh binding, Ptch1 delocalizes from the primary cilium, which relieves its inhibitory activity on Smoothened (Smo). Smo is a G-coupled protein that activates the downstream Gli2 and Gli3 transcription factors, otherwise processed into truncated isoforms that act as transcriptional repressors [30,32–35]. The targets of Gli2 and Gli3 include Gli1 that enhances the signalling, Ptch1 that negatively regulates the signalling, Nkx2.1 that control some aspect of the ventral telencephalon specification, FGF15, and cell-cycle regulators, such as cyclin D1, D2 and E.

In the ventral telencephalon, Shh contributes to the generation of oligodendrocytes and GABAergic interneurons, which later invade the CP by tangential migration [26,36–38]. The cortical interneurons display a short primary cilium probing Shh signalling that controls their intracortical dispersion from the tangential migratory streams, a process important for their colonization into the CP [26].

In contrast to the ventral telencephalon, the developing cortex undergoes limited Shh signalling whose physiological role remained poorly understood. Interestingly, an increase of Shh signalling in RGCs prolongs their self-renewal at the expense of the generation of IPs or neurons [39,40]. Despite their reduced generation from APs, IPs undergo multiple round of divisions and, together with supernumerary RGCs transiting into oRGC, contribute to the folding of the mouse neocortex. Similarly to gyrencephalic brains, the uppermost layers arising from IPs and oRGCs are the most expanded [40]. The reduction of Shh signalling in RGCs impairs their proliferation, their survival and their ability to generate IPs, oRGCs and thus projection neurons [28,40,41]. This impairment of Shh signalling results in a reduced neuronal output responsible for size reduction of the dorsal telencephalon, a phenotype termed microcephaly. Thus, this molecular signalling has key physiological roles in rodent brains to control the generation of IPs and to a lower magnitude oRGCs. Accordingly, Shh signalling is stronger in the developing cortex of gyrencephalic mammals as compared with the one of lissencephalic mammals [40,42].

The Wnt/β-catenin signalling pathway

The canonical Wnt signalling pathway plays major roles during brain development [43]. Wnt ligands are secreted glycoproteins binding to a complex made of Frizzled and the lipoprotein receptor-related protein (LRP) 5/6 localized at the plasma membrane of APs. Ligand binding induces stabilization of the cytoplasmic β-catenin, otherwise degraded following its phosphorylation by GSK3β. Once stabilized, β-catenin translocates into the nucleus and associates to TCF/LEF transcription factors family, which become activators and promote the transcription of downstream targets [44].

The cortical hem is a transient structure of the dorsomedial telencephalon that secretes both BMP and Wnt (2b, 3a, 5a, 7b, 8b) and acts as a signalling centre that orchestrates the patterning of the dorsoventral cerebral cortex [45–47]. Wnt activity is initially sparse in the developing cerebral cortex at E8.5, but from E10.5, it distributes along a dorsally restricted medial-to-lateral gradient [48]. This gradient is concomitant with the establishment of an opposing anteroposterior and lateromedial neurogenesis gradient [49]. Thus, Wnt signalling plays a pivotal role in the specification of the dorsoventral and mediolateral telencephalon [48,50].

Complementary studies uncovered the roles of Wnt signalling in the regulation of RGCs and IPs during cortical development by experimentally modulating the expression of Wnt ligands, receptor or downstream effectors. Increasing β-catenin from early corticogenesis strikingly expands the NEC population by decreasing their cell cycle exit and by delaying the neurogenic period [48,51–53]. In contrast, the forced activation of Wnt signalling in APs from early or mid-neurogenesis leads to the expansion of the SVZ, the IPs pool and the neuronal output [52,54,55]. The increased IPs and neuronal population following Wnt signalling gain of function results from its positive regulation on *N-myc* and *Ngn1* transcription, respectively.

Repressing this molecular pathway at mid-neurogenesis impairs the expression of *Pax6* and ultimately leads to the depletion of APs, IPs and projection neurons while increasing astrogliogenesis [54,56]. Indeed, it has been reported that Wnt signalling promotes the generation of oligodendroglial progenitors by RGCs during late embryogenesis, while a similar role is

attributed to Shh for the specification of ventrally derived oligodendrocyte progenitors [57].

Taken together, these observations suggest that the cellular and molecular outcomes of the canonical Wnt pathway are stage dependent. At the early corticogenesis, the pathway promotes self-renewal of NECs and RGCs, and then it favours IPs and neuronal differentiation as development proceeds and finally induces oligodendrocyte differentiation from RGCs at the end of corticogenesis.

In addition to its involvement in Wnt signalling, β-catenin has also an independent function in the regulation of adherens junction complex and thus participates to the establishment of the APs apico-basal polarity [58]. In order to segregate the dual function of β-catenin and delineate the consequences of Wnt/β-catenin signalling knockdown during cortical neurogenesis, a mouse model deficient for Wnt signalling but preserving the function of β-catenin towards the adherens junction was generated. Analyses of these transgenic mice showed a precocious loss of the APs pool following differentiation in IPs and an overall decrease in cortical wall thickness [59]. This suggests the existence of a β-catenin independent function of Wnt in the regulation of the AP biology.

Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are members of the TGF-β superfamily that bind to heterotetrameric complexes composed of pair type I/II receptors and co-receptors. Activation of these complexes results in the phosphorylation of cytoplasmic R-Smads 1, 5 or 8 which in turn bind to co-Smad4 and translocate to the nucleus to initiate transcriptional activity [60]. BMPs (2, 4, 5, 6, 7) are secreted by the cortical hem and cooperate with Wnts to promote the dorsomedial patterning of the telencephalon [45]. In addition, BMP signalling controls the specification of the dorsal midline and the development of the choroid plexus [61]. The impact of BMPs on corticogenesis has been investigated by depleting their receptors in the telencephalon. Interestingly, beside the midline defects and absence of choroid plexus, the cortical progenitor specification is preserved and the pattern of neurogenesis is maintained [62]. Moreover, continuous activation of BMP signalling in cortical progenitors induces plexus choroid cell formation, confirming the importance of BMP signalling in midline development [63].

In the developing cortex, BMP-2 and BMP-4 ligands are the main effectors of the BMP signalling. Previous studies reported that BMP signalling favours the neuronal differentiation of RGCs [64,65]. In accordance with these studies, it was also shown that lack of the histone deacetylase HDAC6, a negative regulator of BMP2/4 signalling during cortical development, leads to premature differentiation of RGCs into neurons [66]. Besides its role in neurogenesis, BMP signalling also controls postmitotic processes such as the transition of multipolar to bipolar morphology of projection neurons migrating in the SVZ and lower intermediate zone (IZ) through regulation of the expression of the microtubule-associated protein CRMP2 (collapsing response mediator protein 2) [67]. At later stage, during the period of gliogenesis, overexpressing BMP4 impedes the production of oligodendrocytes by RGCs at the expense of astrocytes [68].

Fibroblast growth factors

The fibroblast growth factors (FGFs) includes 22 secreted ligands subdivided into seven families [69]. The signalling is mediated by four different tyrosine kinase receptors: FGFR1 to FGFR4. The FGF signalling promotes downstream activation of distinct pathways such as the PI3-kinase, the Akt and the PKC pathways. However, the Ras/Erk1/2 Map kinase pathway is the predominant one and can be activated by all FGF receptors [69].

In the telencephalon, FGF 3, 8, 15, 17 and 18 are secreted from E9.5 by the anterior neural ridge located in the rostral edge of the telencephalon [70]. FGF7 and 15 are secreted by the anti-hem, another signalling centre located in the lateral part of the pallial/subpallial boundary [71]. The patterns of expression of the different FGFs are tightly regulated and contribute to the patterning of the cerebral cortex. For example, FGF8 and FGF17 are distributed along an anterior high/caudal low-expression pattern. The concomitant reduction of FGF8 and FGF17 expands the caudal part of the cortex at the expense of its rostral part, while reducing FGF15 has the opposite effect [72,73]. The experimental addition of a second source of FGF8 secretion in the caudal part of the telencephalon rostralizes it and duplicates part of the somatosensory cortex in the mutant adult mouse [74,75].

At the cellular level, FGFs promote the formation and self-renewal of RGCs [76]. Three of the four FGF receptors are expressed with specific spatial patterns along the progenitor region. FGFR1 shows a high rostrocaudal expression pattern while FGFR2 and FGFR3 have mirrored distribution [77]. Knocking down FGFR1 leads to loss of rostral identity together with a failure of the development of the olfactory bulbs [77]. Depleting all FGFRs in the dorsal telencephalon by E10 leads to precocious neurogenesis, resulting in a

reduced cortical surface area in both rostral and caudal parts [78,79]. Intriguingly, the phenotype is associated with reduced Notch signalling and downexpression of its associated genes [78]. Moreover, the loss of FGFR expression can be partially compensated by a simultaneous gain of function of Notch signalling, suggesting a cross-talk between these two pathways [78].

Fibroblast growth factor ligands can act synergistically to complete their function. For instance, the depletion of FGF8 leads to a severe rostral hypoplasia resulting from the reduction of progenitor proliferation and survival [72]. This phenotype is worsen by the inactivation of FGF3 in the FGF8 KO mouse line [80]. Other ligands such has FGF2, FGF8 and FGF15 show opposite functions, with FGF15 promoting progenitor differentiation while FGF8 and FGF2 favouring their self-renewal [73,81].

In summary, the general function of the FGF signalling seems to be the maintenance of RGCs stemness and consequently the control of the normal growth of the brain [78,79]. It is also worth noting that, as it was described for the Shh pathway, the FGF signalling contribute to the expansion of the SVZ during cortical development but the targeted population is controversial [40,82,83]. Rash *et al*. [82] reported that increased FGF signalling enhances the production of IPs without affecting oRGCs and leads to gyri formation in the rostrolateral developing forebrain. In contrast, Heng and colleagues reported that Erk-FGF signalling was more important in human compared to mouse RGCs and that increasing the signalling in mice leads to the generation of oRGCs population without inducing folding in the neocortex [83].

Fibroblast growth factor signalling has also been reported to play fundamental role in the specification of GE-derived interneurons and this, in a Shh-independent manner [84]. Indeed, the depletion of FGFR1 together with FGFR2 or FGFR3 prevents, respectively, the development or the differentiation of ventral progenitors. Unlike Shh knockout, the phenotype cannot be rescued following *Gli3* overexpression, suggesting a Shh-independent function for FGF signalling in the ventral telencephalon.

Local cues influencing the biology of cortical progenitors

Besides morphogens, other external factors arising from the cellular environment influence cortical neurogenesis. In the following section, we will highlight the role of direct cellular contacts in the control of neurogenesis by focussing on the Notch signalling pathway. We will next discuss the importance of integrins in the response of RGCs to the extracellular matrix (ECM).

Notch signalling: a neighbouring cell-derived signal

Notch receptors are transmembrane receptors composed of an extracellular EGF-like domain that bind ligands and an intracellular domain that upon ligand binding and enzymatic cleavage transduces an intracellular signal [85]. In the developing cortex, Notch1 and Notch3 receptors are expressed by RGCs and the ligands, belonging to the Jagged or Delta-like (DLL) families, are expressed by neighbouring neurons or IPs. The signalling pathway is activated in RGCs following cell-to-cell contact with neighbouring cells and can be reinforced by the expression of *lunatic fringe* in RGCs, which induce glycosylation of the EGF-like domain of the receptor. Once the ligand binds Notch receptor, Notch undergoes two successive cleavages. The first one is driven by ADAM10 and the second one by γ-secretase, releasing, respectively, the extracellular domain and the Notch intracellular domain (NICD). NICD translocates to the nucleus and binds to CBF1 or Rbpj co-factor to initiate the transcription of several genes, including the *Hairy enhancer of split* (*Hes*) genes. *Hes* are basic-helix-loop-helix (bHLH) transcription factors that repress the expression of proneural genes, further ensuring RGCs stemness maintenance [86].

Hes exert a negative feedback loop on their own promoter, leading to an oscillatory pattern of their expression [87,88]. This characteristic pattern is fundamental for RGCs cell-cycle progression and a sustained *Hes* expression impedes neuronal generation [89]. Hes1, the key effector of the Notch signalling, is expressed in RGCs in a cell-cycle-dependent fashion and absent from cells undergoing mitosis [90]. Its genetic loss leads to brain hypoplasia resulting from a failure of RGCs maintenance and premature neurogenesis [91,92].

Following asymmetric division of RGCs, *Hes1* gene is epigenetically silenced allowing some proneural genes, such as *Ngn2* or *Ascl1,* to become dominants and to promote the differentiation of the daughter cells into neuron or IPs [93,94]. The proneural transcription factors induce the expression of DLL that can activate Notch signalling on the RGCs remaining sister cell [95]. This process of lateral inhibition is necessary to avoid the simultaneous differentiation of all progenitors.

Furthermore, additional evidences demonstrating the importance of Notch signalling in the control of neurogenesis originate from loss of function studies

upstream of Notch receptor activation. The RING finger E3 ubiquitin ligase mind bomb 1 (MIB1) regulate DLL endocytosis in an ubiquitination-dependent manner in the signal sending cells and trans-endocytosis of the Notch extracellular domain by the signal receiving cells, promoting NICD cleavage and signal transduction [96,97]. The conditional deletion of MIB1 during neocortical development results in RGCs depletion and precocious neurogenesis [98]. Interestingly, this study reports that MIB1 is expressed in neurons and particularly in IPs, indicating that different progenitor populations can interact and mutually regulate each other to control the balance between self-renewal and neuronal differentiation in the mouse cortex. A recent work provided evidence that during neurogenic divisions, MIB1 is asymmetrically localized at the daughter centriole and then inherited by the future neuron, identifying the Notch regulator MIB1 as an intrinsic fate determinant [99].

Integrin signalling and the extracellular matrix

Integrins belongs to a large family of heterodimeric transmembrane receptors composed by the association of an α and a β subunit. Depending on the α subunit subtype involved in the complex, the receptor binds to specific components of the ECM such as collagens, laminins or fibronectins [100]. Upon ECM binding, integrins interact at the intracellular level with cytoskeletal proteins to mediate cell-adhesion and trigger signalling pathways such as Erk-MAPK signalling to promote proliferation and survival. In this context, integrins are key cellular receptors for sensing of the environment.

Conditional inactivation of β1-integrin in RGCs leads to defects in the organization of the laminar cytoarchitecture [101]. It is worth noting that these abnormalities are not associated with neither neuron-glia interactions nor neuronal migration defects. These defects are rather secondary to disruption of the pial basement membrane assembly and detachment of RGCs basal processes from the basement membrane, followed by enhanced apoptosis of RGCs [101,102]. In accordance, specific inactivation of β1-integrin in migrating neurons results in a normal cortical layers patterning, strengthening the idea that β1-integrin are primarily needed for RGCs attachment to the basement membrane [103].

Beside their role in the maintenance of position and morphology of RGCs through physical adhesions, integrins are necessary to convey signals originating from the ECM at the basal lamina, regulating the proliferation of neural progenitors. In particular, disruption of integrins in human and ferret, a gyrencephalic nonprimate, leads to a reduced number of proliferating oRGCs but not IPs that lack a basal process, suggesting that neocortical expansion is, at least in part, controlled by integrin signalling in the basal process [104]. This notion is in line with previous studies uncovering the role of the basal process for the self-renewing potential of RGCs [105–107]. More recently, it was shown that activation of integrin αvβ3 in IPs lacking a basal process results in their expansion via an increase of symmetric proliferative divisions at the expense of symmetric neurogenic divisions [108]. Interestingly, comparative transcriptomic analyses of the human and mouse VZ/SVZ suggested an implication of cell-ECM interactions in the expansion of the SVZ [109].

In addition to their role at the basal side of RGCs, integrins and their ligands, such as laminins, are also expressed within the VZ microenvironment, suggesting a role for laminin/integrin adhesive signalling in the regulation of RGCs proliferation [110]. At the apical domain of RGCs, β1-integrin localization was shown to be regulated by Ephrin B1 signalling [111]. Transient disruption of β1-integrin/laminin binding specifically in the VZ by antibody injections into the ventricles of the embryonic mouse brain induces the detachment of RGCs apical processes and proliferation defects due to abventricular mitosis, resulting in cortical layering abnormalities [112]. Interestingly, these defects were also observed in laminin α2-deficient brains [112].

Crosstalks between signalling pathways

Several external factors work in concert during embryogenesis to ensure proper cortical development. Such crosstalks are exemplified by the interplay between Notch and Shh signalling during neurogenesis. Indeed, activation of the Shh signalling pathway in RGCs leads to upregulation of Hes1 and Blbp transcription factors, two downstream targets of the Notch signalling pathway [113]. The subsequent consequence is an increase of RGCs symmetric proliferative divisions at the expense of neurogenic divisions. The concomitant attenuation of Notch signalling in Shh-activated RGCs rescues the balance between self-renewing/neurogenic divisions [113]. A new feedback signalling originating from immature neurons for the regulation of RGCs proliferation has recently been uncovered. Activation of Fzd3 and Celsr3, expressed at the surface of immature neurons, by Wnt7a, promotes Notch ligand Jag1 expression. Jag1 binds and stimulates Notch activation in RGCs, thus regulating their fate [114].

Some morphogens work in concert to establish transcription factors gradients in the developing brain. Wnts and BMPs cooperate to establish Emx2 gradient

in the dorsal telencephalon and require Gli3, a Shh effector [115,116]. Beside the critical role of Gli3 in opposing Shh effect in the dorsal telencephalon, it is also known to repress the activity of FGF8, 15, 17 and 18 ligands. Notably, it has been reported that FGFs can increase Wnt8b and Gli3 activity in the cortex, supporting some level of interaction between distinct factors controlling brain patterning [117].

Pathophysiological mechanisms triggered by viruses in cortical progenitors

Environmental factors that disrupt the early steps of cortical development can have major impact on brain growth and establishment of the cerebral cortex histology and function. This is exemplified by congenital infections after vertical (mother to foetus) transmission of viruses that impairs cortical neurogenesis and neuron survival in patients.

Cytomegalovirus

The cytomegalovirus (CMV) belongs to the herpes virus family. In most cases, CMV infection is asymptomatic but leads to dramatic consequences in immunodepressed patients, including visual impairment and brain lesions [118]. The risk of vertical transmission of CMV during pregnancy depends on the gestational stage but globally around 1% of newborns are infected [119,120]. CMV has a strong brain tropism and targets mostly APs [121]. Thus, congenital infection by CMV is associated with neurogenesis and subsequent neurological defects such as sensory neural hearing loss, microcephaly and intellectual deficit [121–123].

CMV enters APs via proteins expressed at the cell surface, such as integrin and EGF receptors [124]. Mouse embryos infected with mouse CMV (MCMV) show impaired self-renewal of neural progenitor, abnormal neuronal differentiation and migration impairments that can ultimately lead to microcephaly [125–127]. The same cell characteristics were observed on cultured human neural stem cells (hNSCs) infected with human CMV (HCMV) [127,128]. Since Notch signalling controls maintenance of NSC, this molecular pathway was investigated in the context of CMV infections. The analysis revealed that infected hNSC undergo downregulation of Notch1 receptor with an increased degradation and an abnormal perinuclear aggregation of both Jag1 ligand and NICD [129]. Immediate early (IE) genes from the viral genome are the first to be transcribed after cellular infection [130]. The Hes1 transcription factor is downregulated following excessive proteosomal IE1-mediated degradation. This in turns affect neurogenesis by disrupting its oscillatory pattern of expression [129,131].

A link between HCMV and Wnt signalling has been established. HCMV-infected cells have reduced Wnt signalling as a result of the increased degradation of β-catenin and the subsequent downregulation of its downstream targets [132,133]. However, these studies were carried on human foreskin fibroblasts and need to be replicated in hNSCs.

ZIKA virus

ZIKA virus (ZIKV) is a mosquito-borne flavivirus isolated for the first time in 1947 in a rhesus macaque from the Ugandian Zika forest [134]. Since its discovery, ZIKV spreads on different continents, underwent many mutations and is currently characterized by different strains, mostly African- or Asian-related. The contemporaries American Asian-derived strains are more virulent than their ancestors [135,136]. Major attention has been focused on ZIKV by the end of 2015, when congenital infections were correlated with an increased rate of microcephaly in newborns [137,138]. Similarly to CMV, ZIKV crosses the placental barrier and target the brain with a high tropism for APs [139–141]. Using hNPC as an *in vitro* model, many studies reported that ZIKV infection impaired the survival and proliferation of progenitors [139,142,143]. Importantly, ZIKV genome encodes structural and nonstructural (NS) proteins. The NS4A and NS4B viral proteins impair hNPC growth and neurogenesis by interfering with Akt-mTOR pathway, involved in autophagy process [144]. In brain organoids, ZIKV infection leads to precocious differentiation of RGCs resulting in a depletion of the progenitor pool [145]. *In vivo* infection of mouse embryos with ZIKV showed that the virus targets cortical progenitors and impairs their proliferation [146,147]. Moreover, the differentiation of RGCs is impaired resulting in a reduced neuronal output in the CP [147]. The microcephaly induced during the embryonic stage is maintained in early postnatal days [146]. It was also reported that gain of function of NS2A of ZIKV reduced RGCs proliferation and fasten their differentiation likely by promoting apical delamination after disruption of adherent junctions complex, including β-catenin [148].

Concluding remarks

The apical progenitors are the founding progenitors in the cerebral cortex. Their biology is shaped by the interplay between intrinsic and extrinsic factors, which

is critical for proper development of the cerebral cortex. Many studies focused on the role of cell intrinsic regulators of APs to drive cell-cycle progression or the mode of cell division. However, cortical patterning and neurogenesis are highly influenced by physiological environmental cues enriched in the CSF or at the vicinity of the developing cortex (Fig. 2). Growing evidences suggest that some of these factors are enriched in the embryonic brain of gyrencephalic species as compared to the lissencephalic ones and contribute to the expansion of the SVZ progenitors [40,82,83]. It is, however, controversial whether increasing IPs or oRGCs population ultimately leads to the folding of the cortex. Furthermore, the origin of the enrichment of these factors and the implication of other morphogens on the gyrification process are actually poorly investigated. Recent advances obtained with human cerebral organoid models will likely help us to better understand the role of physiological external factors on human corticogenesis [149,150]. Such models are currently used to characterize the impact of viral infection on the initial steps of neurogenesis, but they will require further technical improvement to address late event such as neuronal differentiation and migration [143,151].

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References

1 Anderson SA, Marín O, Horn C, Jennings K and Rubenstein JLR (2001) Distinct cortical migrations from the medial and lateral ganglionic eminences. *Development* **128**, 353–363.
2 Noctor SC, Flint AC, Weissman TA, Wong WS, Clinton BK and Kriegstein AR (2002) Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of Radial Glia. *J Neurosci* **22**, 3161–3173.
3 Taverna E, Götz M and Huttner WB (2014) The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. *Annu Rev Cell Dev Biol* **30**, 465–502.
4 Götz M and Huttner WB (2005) The cell biology of neurogenesis. *Nat Rev Mol Cell Biol* **6**, 777–788.
5 Noctor SC, Martínez-Cerdeño V, Ivic L and Kriegstein AR (2004) Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat Neurosci* **7**, 136–144.
6 Haubensak W, Attardo A, Denk W and Huttner WB (2004) Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. *Proc Natl Acad Sci USA* **101**, 3196–3201.
7 Miyata T, Kawaguchi A, Saito K, Kawano M and Muto T (2004) Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. *Development* **131**, 3133–3145.
8 Martinez-Cerdeno V, Noctor SC and Kriegstein AR (2006) The role of intermediate progenitor cells in the evolutionary expansion of the cerebral cortex. *Cereb Cortex* **16**, i152–i161.
9 Nadarajah B, Brunstrom JE, Grutzendler J, Wong ROL and Pearlman AL (2001) Two modes of radial migration in early development of the cerebral cortex. *Nat Neurosci* **4**, 143–150.
10 Tabata H and Nakajima K (2003) Multipolar migration: the third mode of radial neuronal migration in the developing cerebral cortex. *J Neurosci* **23**, 9996–10001.
11 Tabata H, Kanatani S and Nakajima K (2009) Differences of migratory behavior between direct progeny of apical progenitors and basal progenitors in the developing cerebral cortex. *Cereb Cortex* **19**, 2092–20105.
12 Rakic P (1972) Mode of cell migration to the superficial layers of fetal monkey neocortex. *J Comp Neurol* **145**, 61–83.
13 Cooper JA (2008) A mechanism for inside-out lamination in the neocortex. *Trends Neurosci* **31**, 113–119.
14 Englund C, Fink A, Charmaine L, Pham D, Ray DAM, Bulfone A, Kowalczyk T and Hevner RF (2005) Pax6, Tbr2, and Tbr1 are expressed sequentially by Radial Glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J Neurosci* **25**, 247–251.
15 Tyler WA and Haydar TF (2013) Multiplex genetic fate mapping reveals a novel route of neocortical neurogenesis, which is altered in the Ts65Dn mouse model of down syndrome. *J Neurosci* **33**, 5106–5119.
16 Stancik EK, Navarro-Quiroga I, Sellke R and Haydar TF (2010) Heterogeneity in ventricular zone neural precursors contributes to neuronal fate diversity in the postnatal neocortex. *J Neurosci* **30**, 7028–7036.
17 Hansen DV, Lui JH, Parker PRL and Kriegstein AR (2010) Neurogenic radial glia in the outer subventricular zone of human neocortex. *Nature* **464**, 554–561.
18 Nonaka-Kinoshita M, Reillo I, Artegiani B, Ángeles Martínez-Martínez M, Nelson M, Borrell V and Calegari F (2013) Regulation of cerebral cortex size

and folding by expansion of basal progenitors. *EMBO J* **32**, 1817–1828.
19 Fernández V, Llinares-Benadero C and Borrell V (2016) Cerebral cortex expansion and folding: what have we learned? *EMBO J* **35**, 1021–1044.
20 Cohen E (1987) Ultrastructural analysis of primary cilium in the embryonic nervous tissue of mouse. *Int J Dev Neurosci* **5**, 43–51.
21 Lepanto P, Badano JL and Zolessi FR (2016) Neuron's little helper: the role of primary cilia in neurogenesis. *Neurogenesis* **3**, e1253363.
22 Willaredt MA, Tasouri E and Tucker KL (2013) Primary cilia and forebrain development. *Mech Dev* **130**, 373–380.
23 Higginbotham H, Guo J, Yokota Y, Umberger NL, Li J, Verma N, Hirt J, Caspary T and Anton ES (2013) Arl13b-regulated activities of primary cilia are essential for the formation of the polarized radial glial scaffold. *Nat Neurosci* **16**, 1000–1007.
24 Wilsch-Brauninger M, Peters J, Paridaen JTML and Huttner WB (2012) Basolateral rather than apical primary cilia on neuroepithelial cells committed to delamination. *Development* **139**, 95–105.
25 Arellano JI, Guadiana SM, Breunig JJ, Rakic P and Sarkisian MR (2012) Development and distribution of neuronal cilia in mouse neocortex. *J Comp Neurol* **873**, 848–873.
26 Baudoin J, Viou L, Launay P, Luccardini C, Gil SE, Alvarez C, Rio J, Boudier T, Lechaire J and Kiyasova V (2012) Tangentially migrating neurons assemble a primary cilium that promotes their reorientation to the cortical plate. *Neuron* **76**, 1108–1122.
27 Lehtinen MK, Zappaterra MW, Chen X, Yang YJ, Hill AD, Lun M, Maynard T, Gonzalez D, Kim S, Ye P *et al.* (2011) The cerebrospinal fluid provides a proliferative niche for neural progenitor cells. *Neuron* **69**, 893–905.
28 Komada M, Saitsu H, Kinboshi M, Miura T, Shiota K and Ishibashi M (2008) Hedgehog signaling is involved in development of the neocortex. *Development* **135**, 2717–2727.
29 Huang X, Liu J, Ketova T, Fleming JT, Grover VK, Cooper MK, Litingtung Y and Chiang C (2010) Transventricular delivery of Sonic hedgehog is essential to cerebellar ventricular zone development. *Proc Natl Acad Sci USA* **107**, 8422–8427.
30 Rohatgi R, Ljiljana M and Scott MP (2007) Patched1 regulates Hedgehog signaling at the primary cilium. *Science* **317**, 372–376.
31 Eggenschwiler JT and Anderson KV (2007) Cilia and developmental signaling. *Annu Rev Cell Dev Biol* **23**, 345–373.
32 Corbit KC, Aanstad P, Singla V, Norman AR, Stainier DYR and Reiter JF (2005) Vertebrate smoothened functions at the primary cilium. *Nature* **437**, 1018–1021.
33 Varjosalo M and Taipale J (2008) Hedgehog : functions and mechanisms. *Genes Dev* **22**, 2454–2472.
34 Pan Y, Bai CB, Joyner AL and Wang B (2006) Sonic hedgehog signaling regulates Gli2 transcriptional activity by suppressing its processing and degradation. *Mol Cell Neurosci* **26**, 3365–3377.
35 Wang B, Fallon JF, Beachy PA and Hughes H (2000) Hedgehog-regulated processing of Gli3 produces an anterior/posterior repressor gradient in the developing vertebrate limb. *Cell* **100**, 423–434.
36 Chiang C, Litingtung Y, Lee E, Young KE, Corden JL, Westphal H and Beachy PA (1996) Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function. *Nature* **383**, 407–413.
37 Fuccillo M, Rallu M, McMahon AP and Fishell G (2004) Temporal requirement for hedgehog signaling in ventral telencephalic patterning. *Development* **131**, 5031–5040.
38 Xu Q, Guo L, Moore H, Waclaw RR, Campbell K and Anderson SA (2010) Sonic hedgehog signaling confers ventral telencephalic progenitors with distinct cortical interneuron fates. *Neuron* **65**, 328–340.
39 Yabut OR, Fernandez G, Yoon K, Pleasure SJ, Yabut OR, Fernandez G, Huynh T, Yoon K and Pleasure SJ (2015) Suppressor of fused is critical for maintenance of neuronal progenitor identity during corticogenesis. *Cell Rep* **12**, 2021–2034.
40 Wang L, Hou S and Han Y (2016) Hedgehog signaling promotes basal progenitor expansion and the growth and folding of the neocortex. *Nat Neurosci* **19**, 888–896.
41 Komada M, Iguchi T, Takeda T, Ishibashi M and Sato M (2013) Smoothened controls cyclin D2 expression and regulates the generation of intermediate progenitors in the developing cortex. *Neurosci Lett* **547**, 87–91.
42 Romero CDJ, Bruder C, Tomasello U and Sanz-anquela JM (2015) Discrete domains of gene expression in germinal layers distinguish the development of gyrencephaly. *EMBO J* **34**, 1859–1874.
43 Harrison-Uy SJ and Pleasure SJ (2012) Wnt signaling and forebrain development. *Cold Spring Harb Perspect Biol* **4**, 1–11.
44 Cadigan KM (2012) TCFs and Wnt/β-catenin signaling: more than one way to throw the switch. *Curr Top Dev Biol* **98**, 1–34.
45 Furuta Y, Piston DW and Hogan BLM (1997) Bone morphogenetic proteins (BMPs) as regulators of dorsal forebrain development. *Development* **124**, 2203–2212.
46 Grove EA, Tole S, Limon J, Yip L and Ragsdale CW (1998) The hem of the embryonic cerebral cortex is defined by the expression of multiple Wnt genes and is compromised in Gli3-deficient mice. *Development* **125**, 2315–2325.
47 Caronia-brown G, Yoshida M, Gulden F, Assimacopoulos S and Grove EA (2014) The cortical

hem regulates the size and patterning of neocortex. *Development* **141**, 2855–2865.
48 Machon O, Backman M, Machonova O, Kozmik Z, Vacik T, Andersen L and Krauss S (2007) A dynamic gradient of Wnt signaling controls initiation of neurogenesis in the mammalian cortex and cellular specification in the hippocampus. *Dev Biol* **311**, 223–237.
49 Takahashi T, Goto T, Miyama S, Nowakowski RS and Caviness VS Jr (1999) Sequence of neuron origin and neocortical laminar fate : relation to cell cycle of origin in the developing Murine cerebral wall. *J Neurosci* **19**, 10357–10371.
50 Backman M, Machon O, Mygland L, Johannes C, Den Bout V, Zhong W, Taketo MM and Krauss S (2005) Effects of canonical Wnt signaling on dorso-ventral specification of the mouse telencephalon. *Dev Biol* **279**, 155–168.
51 Chenn A and Walsh CA (2002) Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* **297**, 365–369.
52 Hirabayashi Y, Itoh Y, Tabata H, Nakajima K and Akiyama T (2004) The Wnt/β-catenin pathway directs neuronal differentiation of cortical neural precursor cells. *Development* **131**, 2791–2801.
53 Wrobel CN, Mutch CA, Swaminathan S, Taketo MM and Chenn A (2007) Persistent expression of stabilized β -catenin delays maturation of radial glial cells into intermediate progenitors. *Dev Biol* **309**, 285–297.
54 Munji RN, Choe Y, Li G, Siegenthaler JA and Pleasure SJ (2011) Wnt signaling regulates neuronal differentiation of cortical intermediate progenitors. *J Neurosci* **31**, 1676–1687.
55 Kuwahara A, Hirabayashi Y, Knoepfler PS, Taketo MM and Sakai J (2010) Wnt signaling and its downstream target N-myc regulate basal progenitors in the developing neocortex. *Development* **137**, 1035–1044.
56 Gan Q, Lee A, Suzuki R, Yamagami T, Stokes A and Chau B (2013) Pax6 mediates β-catenin signaling for self-renewal and neurogenesis by neocortical radial glial stem cells. *Stem Cells* **32**, 45–58.
57 Langseth AJ, Munji RN, Choe Y, Huynh T, Pozniak D and Pleasure SJ (2010) Wnts regulate the timing and efficiency of OPC generation in the telencephalon. *J Neurosci* **30**, 13367–13372.
58 Chenn A, Zhang YA, Chang BT and Mcconnell SK (1998) Intrinsic polarity of mammalian neuroepithelial cells. *Mol Cell Neurosci* **11**, 183–193.
59 Draganova K, Zemke M, Zurkirchen L, Valenta T, Cantu C, Okoniewski M, Schmid M-T, Hoffmans R, Gotz M, Basler K *et al*. (2015) Wnt/b-catenin signaling regulates sequential fate decisions of murine cortical precursor cells. *Stem Cells* **33**, 170–182.
60 Bond AM, Bhalala OG and Kessler JA (2012) The dynamic role of bone morphogenetic proteins in neural stem cell fate and maturation. *Dev Neurobiol* **72**, 1068–1084.
61 Hébert JM, Mishina Y and McConnell SK (2002) BMP signaling is required locally to pattern the dorsal telencephalic midline. *Neuron* **35**, 1029–1041.
62 Fernandes M, Gutin G, Alcorn H, Mcconnell SK and Hébert JM (2007) Mutations in the BMP pathway in mice support the existence of two molecular classes of holoprosencephaly. *Development* **3794**, 3789–3794.
63 Panchision DM, Pickel JM, Studer L, Lee S, Turner PA, Hazel TG and Mckay RDG (2001) Sequential actions of BMP receptors control neural precursor cell production and fate *Genes Dev* **6**, 2094–2110.
64 Li W, Cogswell CA and Loturco JJ (1998) Neuronal differentiation of precursors in the neocortical ventricular zone is triggered by BMP. *J Neurosci* **18**, 8853–8862.
65 Martynoga B, Morrison H, Price DJ and Mason JO (2005) Foxg1 is required for specification of ventral telencephalon and region-specific regulation of dorsal telencephalic precursor proliferation and apoptosis. *Dev Biol* **283**, 113–127.
66 Shakèd M, Weissmüller K, Svoboda H, Hortschansky P, Nishino N, Wölfl S and Tucker KL (2008) Histone deacetylases control neurogenesis in embryonic brain by inhibition of BMP2/4 signaling. *PLoS ONE* **3**, e2668.
67 Sun Y, Fei T, Yang T, Zhang F, Chen YG, Li H and Xu Z (2010) The suppression of CRMP2 expression by Bone Morphogenetic Protein (BMP)-SMAD gradient signaling controls multiple stages of neuronal development. *J Biol Chem* **285**, 39039–39050.
68 Gomes WA, Mehler MF and Kessler JA (2003) Transgenic overexpression of BMP4 increases astroglial and decreases oligodendroglial lineage commitment. *Dev Biol* **255**, 164–177.
69 Mason I (2007) Initiation to end point: the multiple roles of fibroblast growth factors in neural development. *Nat Rev Neurosci* **8**, 583–596.
70 Bachler M and Neubuser A (2001) Expression of members of the Fgf family and their receptors during midfacial development. *Mech Dev* **100**, 313–316.
71 Iwata T and Hevner RF (2009) Fibroblast growth factor signaling in development of the cerebral cortex. *Dev Growth Differ* **51**, 299–323.
72 Storm EE, Garel S, Borello U, Hebert JM, Martinez S, Mcconnell SK, Martin GR and Rubenstein JLR (2006) Dose-dependent functions of Fgf8 in regulating telencephalic patterning centers. *Development* **133**, 1831–1844.
73 Borello U and Rubenstein JLR (2008) FGF15 promotes neurogenesis and opposes FGF8 function during neocortical development neocortical development. *Neural Dev* **3**, 17.

74 Fukuchi-shimogori T and Grove EA (2001) Neocortex patterning by the secreted signaling molecule FGF8. *Science* **294**, 1071–1075.
75 Toyoda R, Assimacopoulos S, Wilcoxon J, Taylor A, Feldman P, Suzuki-hirano A, Shimogori T and Grove EA (2010) FGF8 acts as a classic diffusible morphogen to pattern the neocortex. *Development* **137**, 3439–3448.
76 Sahara S and O'Leary DDM (2009) Fgf10 regulates transition period of cortical stem cell differentiation to radial glia controlling generation of neurons and basal progenitors. *Neuron* **63**, 48–62.
77 Hébert JM, Lin M, Partanen J, Rossant J and Mcconnell SK (2003) FGF signaling through FGFR1 is required for olfactory bulb morphogenesis. *Development* **130**, 1101–1111.
78 Rash BG, Lim HD, Breunig JJ and Vaccarino FM (2011) FGF signaling expands embryonic cortical surface area by regulating notch-dependent neurogenesis. *J Neurosci* **31**, 15604–15617.
79 Kang W, Wong LC, Shi S-H and Hebert JM (2009) The transition from radial glial to intermediate progenitor cell is inhibited by FGF signaling during corticogenesis. *J Neurosci* **29**, 14571–14580.
80 Theil T, Dominguez-frutos E and Schimmang T (2008) Differential requirements for Fgf3 and Fgf8 during mouse forebrain development. *Dev Dyn* **237**, 3417–3423.
81 Raballo R, Rhee J, Lyn-cook R, Leckman JF, Schwartz ML and Vaccarino FM (2000) Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J Neurosci* **20**, 5012–5023.
82 Rash BG, Tomasi S, Lim HD, Suh CY and Vaccarino FM (2013) Cortical gyrification induced by fibroblast growth factor 2 in the mouse brain. *J Neurosci* **33**, 10802–10814.
83 Heng X, Guo Q, Leung AW and Li JYH (2017) Analogous mechanism regulating formation of neocortical basal radial glia and cerebellar Bergmann glia. *Elife* **6**, e23253.
84 Gutin G, Fernandes M, Palazzolo L, Paek H, Yu K, Ornitz DM, Mcconnell SK and Hébert JM (2006) FGF signalling generates ventral telencephalic cells independently of SHH. *Development* **135**, 2937–2946.
85 Zhang R, Engler A and Taylor V (2017) Notch : an interactive player in neurogenesis and disease. *Cell Tissue Reasearch*, https://doi.org/10.1007/s00441-017-2641-9.
86 Kageyama R, Ohtsuka T and Kobayashi T (2008) Roles of Hes genes in neural development. *Dev Growth Differ* **50**, 97–103.
87 Imayoshi I, Isomura A, Harima Y, Kawaguchi K, Kori H, Miyachi H, Fujiwara T, Ishidate F and Kageyama R (2013) Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* **342**, 1203–1209.
88 Harima Y, Imayoshi I, Shimojo H and Kobayashi T (2014) The roles and mechanism of ultradian oscillatory expression of the mouse Hes genes. *Semin Cell Dev Biol* **34**, 85–90.
89 Baek JH, Hatakeyama J, Sakamoto S, Ohtsuka T and Kageyama R (2006) Persistent and high levels of Hes1 expression regulate boundary formation in the developing central nervous system. *Development* **133**, 2467–2476.
90 Lui JH, Hansen DV and Kriegstein AR (2011) Development and evolution of the human neocortex. *Cell* **146**, 18–36.
91 Ishibashi M, Ang S-L, Shiota K, Nakanishi S, Kageyama R and Guillemot F (1995) Targeted disruption of mammalian hairy and Enhancer of split homolog-1 (HES-1) leads to up-regulation of neural helix-loop-hellx factors, premature neurogenesls, and severe neural tube defects. *Genes Dev* **9**, 3136–3148.
92 Ohtsuka T, Sakamoto M, Guillemot F and Kageyama R (2001) Roles of the basic helix-loop-helix genes Hes1 and Hes5 in expansion of neural stem cells of the developing brain. *J Biol Chem* **276**, 30467–30474.
93 Ochiai W, Nakatani S, Takahara T, Kainuma M and Masaoka M (2009) Molecular and cellular neuroscience periventricular notch activation and asymmetric Ngn2 and Tbr2 expression in pair-generated neocortical daughter cells. *Mol Cell Neurosci* **40**, 225–233.
94 Lopez CI, Saud KE, Aguilar R and Andr F (2016) The chromatin modifying complex CoREST/LSD1 negatively regulates notch pathway during cerebral cortex development. *Dev Neurobiol* **76**, 1360–1373.
95 Castro DS, Skowronska-krawczyk D, Armant O, Donaldson IJ, Parras C, Hunt C, Critchley JA, Nguyen L and Hill M (2006) Proneural bHLH and Brn proteins coregulate a neurogenic program through cooperative binding to a conserved DNA motif. *Dev Cell* **11**, 831–844.
96 Itoh M, Kim CH, Palardy G, Oda T, Jiang YJ, Maust D, Yeo SY, Lorick K, Wright GJ, Ariza-McNaughton L *et al.* (2003) Mind bomb is a ubiquitin ligase that is essential for efficient activation of notch signaling by delta. *Dev Cell* **4**, 67–82.
97 Koo B-K, Lim H-S, Song R, Yoon M-J, Yoon K-J, Moon JS, Kim YW, Kwon MC, Yoo KW, Kong MP *et al.* (2005) Mind bomb 1 is essential for generating functional Notch ligands to activate Notch. *Development* **132**, 3459–3470.
98 Yoon KJ, Koo BK, Im SK, Jeong HW, Ghim J, Kwon MC, Moon JS, Miyata T and Kong YY (2008) Mind bomb 1-expressing intermediate progenitors generate notch signaling to maintain radial glial cells. *Neuron* **58**, 519–531.

99 Tozer S, Baek C, Fischer E, Goiame R and Morin X (2017) Differential routing of mindbomb1 via centriolar satellites regulates asymmetric divisions of neural progenitors. *Neuron* **93**, 542.e4–551.e4.
100 Harburger DS and Calderwood DA (2009) Integrin signalling at a glance. *J Cell Sci* **122**, 159–163.
101 Graus-Porta D, Blaess S, Senften M, Littlewood-Evans A, Damsky C, Huang Z, Orban P, Klein R, Schittny JC and Müller U (2001) β1-Class integrins regulate the development of laminae and folia in the cerebral and cerebellar cortex. *Neuron* **31**, 367–379.
102 Radakovits R, Barros CS, Belvindrah R, Patton B and Müller U (2009) Regulation of radial glial survival by signals from the meninges. *J Neurosci* **29**, 7694–7705.
103 Belvindrah R, Graus-Porta D, Goebbels S, Nave K-A and Muller U (2007) Beta1 integrins in Radial Glia but not in migrating neurons are essential for the formation of cell layers in the cerebral cortex. *J Neurosci* **27**, 13854–13865.
104 Fietz SA, Kelava I, Vogt J, Wilsch-Bräuninger M, Stenzel D, Fish JL, Corbeil D, Riehn A, Distler W, Nitsch R *et al*. (2010) OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. *Nat Neurosci* **13**, 690–699.
105 Konno D, Shioi G, Shitamukai A, Mori A, Kiyonari H, Miyata T and Matsuzaki F (2008) Neuroepithelial progenitors undergo LGN-dependent planar divisions to maintain self-renewability during mammalian neurogenesis. *Nat Cell Biol* **10**, 93–101.
106 Shitamukai A, Konno D and Matsuzaki F (2011) Oblique Radial Glial divisions in the developing mouse neocortex induce self-renewing progenitors outside the Germinal Zone that resemble primate outer subventricular zone progenitors. *J Neurosci* **31**, 3683–3695.
107 LaMonica BE, Lui JH, Hansen DV and Kriegstein AR (2013) Mitotic spindle orientation predicts outer radial glial cell generation in human neocortex. *Nat Commun* **4**, 1665.
108 Stenzel D, Wilsch-Brauninger M, Wong FK, Heuer H and Huttner WB (2014) Integrin v 3 and thyroid hormones promote expansion of progenitors in embryonic neocortex. *Development* **141**, 795–806.
109 Fietz SA, Lachmann R, Brandl H, Kircher M, Samusik N, Schröder R, Lakshmanaperumal N, Henry I, Vogt J, Riehn A *et al*. (2012) Transcriptomes of germinal zones of human and mouse fetal neocortex suggest a role of extracellular matrix in progenitor self-renewal. *Proc Natl Acad Sci USA* **109**, 11836–11841.
110 Lathia JD, Patton B, Eckley DM, Magnus T, Mughal MR, Sasaki T, Caldwell MA, Rao MS, Mattson MP and Ffrench-Constant C (2007) Patterns of laminins and integrins in the embryonic ventricular zone of the CNS. *J Comp Neurol* **505**, 630–643.
111 Arvanitis DN, Behar A, Tryoen-Toth P, Bush JO, Jungas T, Vitale N and Davy A (2013) Ephrin B1 maintains apical adhesion of neural progenitors. *Development* **140**, 2082–2092.
112 Loulier K, Lathia JD, Marthiens V, Relucio J, Mughal MR, Tang SC, Coksaygan T, Hall PE, Chigurupati S, Patton B *et al*. (2009) Beta1 integrin maintains integrity of the embryonic neocortical stem cell niche. *PLoS Biol* **7**, e1000176.
113 Dave RK, Ellis T, Toumpas MC, Robson JP, Julian E, Bartlett PF, Cooper HM, Reynolds BA and Wainwright BJ (2011) Sonic hedgehog and notch signaling can cooperate to regulate neurogenic divisions of neocortical progenitors. *PLoS ONE* **6**, e14680.
114 Wang W, Jossin Y, Chai G, Lien W-H, Tissir F and Goffinet AM (2016) Feedback regulation of apical progenitor fate by immature neurons through Wnt7–Celsr3–Fzd3 signalling. *Nat Commun* **7**, 10936.
115 Theil T, Aydin S, Koch S, Grotewold L and Rüther U (2002) Wnt and Bmp signalling cooperatively regulate graded Emx2 expression in the dorsal telencephalon. *Development* **129**, 3045–3054.
116 Theil T, Alvarez-bolado G, Walter A and Rüther U (1999) Gli3 is required for Emx gene expression during dorsal telencephalon development. *Development* **126**, 3561–3571.
117 Hasenpusch-theil K, Watson JA and Theil T (2017) Direct interactions between Gli3, Wnt8b, and Fgfs underlie patterning of the dorsal telencephalon. *Cereb Cortex* **27**, 1137–1148.
118 Griffiths P, Baraniak I and Reeves M (2015) The pathogenesis of human cytomegalovirus. *J Pathol* **235**, 288–297.
119 Slavuljica I, Kvestak D, Csaba Huszthy P, Kosmac K, Britt WJ and Jonjic S (2015) Immunobiology of congenital cytomegalovirus infection of the central nervous system — the murine cytomegalovirus model. *Cell Mol Immunol* **12**, 180–191.
120 Tardieu M, Tejiokem M and Nguefack S (2013) Virus-induced lesions and the fetal brain : examples of the transmission of HIV-1 and CMV from mother to offspring. *Handb Clin Neurol* **112**, 1103–1108.
121 Teissier N, Fallet-bianco C, Delezoide A, Marcorelles P, Khung-savatovsky S, Laquerrie A, Nardelli J, Cipriani S, Csaba Z, Picone O *et al*. (2014) Cytomegalovirus-induced brain malformations in fetuses. *J Neuropatholgy* **73**, 143–158.
122 Grosse SD, Ross DS and Dollard SC (2008) Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss : a quantitative assessment. *J Clin Virol* **41**, 57–62.

123 Van Den Pol AN, Mocarski E, Saederup N, Vieira J and Meier TJ (1999) Cytomegalovirus cell tropism, replication, and gene transfer in brain. *J Neurosci* **19**, 10948–10965.
124 Kawasaki H, Kosugi I, Sakao-suzuki M, Meguro S, Arai Y and Tsutsui Y (2015) Cytomegalovirus initiates infection selectively from high-level b 1 integrin e expressing cells in the brain. *Am J Pathol* **185**, 1304–1323.
125 Shinmura Y, Kosugi I, Aiba-Masago S, Baba S, Ren Yong L and Tsutsui Y (1997) Disordered migration and loss of virus-infected neuronal cells in developing mouse brains infected with murine cytomegalovirus. *Acta Neuropathol* **93**, 551–557.
126 Li R and Tsutsui Y (2000) Growth retardation and microcephaly induced in mice by placental infection with murine cytomegalovirus. *Teratology* **62**, 79–85.
127 Luo MH, Hannemann H, Kulkarni AS, Schwartz PH, Dowd JMO and Fortunato EA (2010) Human cytomegalovirus infection causes premature and abnormal differentiation of human neural progenitor cells. *J Virol* **84**, 3528–3541.
128 Mutnal MB, Cheeran MC, Hu S and Lokensgard JR (2011) Murine cytomegalovirus infection of neural stem cells alters neurogenesis in the developing brain. *PLoS ONE* **6**, e16211.
129 Li X, Liu X, Yang B, Fu Y, Zhao F, Shen Z, Miao L and Rayner S (2015) Human cytomegalovirus infection dysregulates the localization and stability of NICD1 and Jag1 in neural progenitor cells. *J Virol* **89**, 6792–6804.
130 Stinski MF and Isomura H (2008) Role of the cytomegalovirus major immediate early enhancer in acute infection and reactivation from latency. *Med Microbiol Immunol* **197**, 223–231.
131 Liu X, Yang B, Huang S, Wu C, Li X, Cheng S, Jiang X, Hu F, Ming Y, Nevels M *et al.* (2017) Human cytomegalovirus IE1 downregulates Hes1 in neural progenitor cells as a potential E3 ubiquitin ligase. *PLoS Pathog* **13**, 1–28.
132 Angelova M, Zwezdaryk K, Ferris M, Shan B, Morris CA and Sullivan DE (2012) Human cytomegalovirus infection dysregulates the canonical Wnt/β-catenin signaling pathway. *PLOS Pathog* **8**, e1002959.
133 Kapoor A, He R, Venkatadri R, Forman M and Arav-boger R (2013) Wnt modulating agents inhibit human cytomegalovirus replication. *Antimicrob Agents Chemother* **57**, 2761–2767.
134 Dick GWA, Kitchen SF and Haddow AJ (1952) Zika virus. I. Isolations and serological specificity. *Transl R Soc Trop Med Hyg* **46**, 509–520.
135 Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Guzman H, Tesh RB and Weaver SC (2012) Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. *Plos Negleted Trop. Dis* **6**, e1477.
136 Yuan L, Huang XY, Liu ZY, Zhang F, Zhu XL, Yu JY, Ji X, Xu YP, Li G, Li C *et al.* (2017) A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. *Science* **358**, 933–936.
137 Driggers RW, Ho C-Y, Korhonen EM, Kuivanen S, Jääskeläinen AJ, Smura T, Rosenberg A, Hill DA, DeBiasi RL, Vezina G *et al.* (2017) Zika virus infection with prolonged maternal Viremia and fetal brain abnormalities. *N Engl J Med* **37**, 51.
138 Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, Kolenc M, Resman Rus K, Vesnaver Vipotnik T, Fabjan Vodušek V *et al.* (2016) Zika virus associated with microcephaly. *N Engl J Med* **374**, 951–958.
139 Tang H, Hammack C, Ogden SC, Wen Z and Qian X (2016) Zika virus infect human cortical neural precursors and attenuates their growth. *Cell Stem Cell* **18**, 587–590.
140 Wu K, Zuo G, Li X, Ye Q, Deng Y and Huang X (2016) Vertical transmission of Zika virus targeting the radial glial cells affects cortex development of offspring mice. *Cell Res* **26**, 645–654.
141 Chavali PL, Stojic L, Meredith LW, Joseph N, Nahorski MS, Sanford TJ, Sweeney TR, Krishna BA, Hosmillo M, Firth AE *et al.* (2017) Neurodevelopmental protein Musashi-1 interacts with the Zika genome and promotes viral replication. *Science* **357**, 83–88.
142 Souza BSF, Sampaio GLA, Pereira CS, Campos GS, Sardi SI, Freitas LAR, Figueira CP, Paredes BD, Nonaka CKV, Azevedo CM *et al.* (2016) Zika virus infection induces mitosis abnormalities and apoptotic cell death of human neural progenitor cells. *Sci Rep* **6**, 39775.
143 Garcez PP, Loiola EC, Madeiro R, Higa LM, Trindade P, Delvecchio R, Nascimento JM, Brindeiro R, Tanuri A and Rehen SK (2016) Zika virus impairs growth in human neurospheres and brain organoids. *Science* **352**, 816–818.
144 Liang Q, Luo Z, Zeng J, Chen W, Foo S, Lee S, Ge J, Wang S, Goldman SA, Zlokovic BV *et al.* (2016) Zika Virus NS4A and NS4B proteins deregulate Akt-mTOR signaling in human fetal neural stem cells to inhibit neurogenesis and induce autophagy. *Stem Cell* **19**, 663–671.
145 Gabriel E, Ramani A, Karow U, Kro M, Gabriel E, Ramani A, Karow U, Gottardo M, Natarajan K, Gooi LM *et al.* (2017) Recent Zika virus isolates induce premature differentiation of neural progenitors in human brain organoids. *Cell Stem Cell* **20**, 397–406.
146 Shao Q, Herrlinger S, Zhu Y-N, Yang M, Goodfellow F, Stice SL, Qi X-P, Brindley MA and Chen J-F

(2017) The African Zika Virus MR-766 is more virulent and causes more severe brain damage than current Asian lineage and dengue virus. *Development* **144**, 4114–4124.

147 Li C, Xu D, Ye Q, Hong S, Jiang Y, Liu X, Zhang N, Shi L and Qin C (2016) Zika virus disrupts neural progenitor development and leads to microcephaly in mice. *Cell Stem Cell* **19**, 120–126.

148 Yoon K, Song G, Qian X, Pan J, Xu D, Rho H, Kim N, Habela C, Zheng L, Jacob F *et al.* (2017) Zika-virus-encoded NS2A disrupts mammalian cortical neurogenesis by degrading adherens article Zika-virus-encoded NS2A disrupts mammalian cortical neurogenesis by degrading adherens junction proteins. *Stem Cell* **21** 349–358.

149 Lancaster MA, Renner M, Martin C-A, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, Knoblich JA *et al.* (2013) Cerebral organoids model human brain development and microcephaly. *Nature* **501**, 373–379.

150 Lancaster MA, Corsini NS, Wolfinger S, Gustafson EH, Phillips AW, Burkard TR, Otani T, Livesey FJ and Knoblich JA (2017) Guided self-organization and cortical plate formation in human brain organoids. *Nat Biotechnol* **35**, 659–666.

151 Qian X, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, Yao B, Hamersky GR, Jacob F, Zhong C *et al.* (2016) Brain-region-specific organoids using mini-bioreactors for modeling ZIKV exposure. *Cell* **165**, 1238–1254.