Cortical Circuit Development: Intrinsic and Extrinsic Factors Underlying the Connectivity of Inhibitory Neurons

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LAYMAN'S SUMMARY

The cerebral cortex is a brain structure that is involved in a variety of complex tasks, such as language, learning and reasoning. Many different cell types are involved in the execution of these tasks, including excitatory neurons and inhibitory neurons. Communication between these neuron types is important, because inhibitory neurons regulate the activity of the excitatory neurons. However, the excitatory neurons and inhibitory neurons are not born at the same place. While excitatory neurons will reside in locations close to the regions where they were born, the inhibitory neurons are required to move in order to be able to communicate with excitatory neurons. The processes of inhibitory neuron generation, migration and the formation of connections is strictly regulated during different developmental stages.

The inhibitory neurons are generated in a transient embryonic region below the cortex. At different locations within this region, different concentrations of proteins are present. These proteins influence the type of inhibitory neuron is generated. Furthermore, interneurons can also receive some information from their progenitors to become a specific type of interneuron. With maturation, inhibitory neurons also become responsive to signals that can either attract them or repel them from the cerebral cortex.

The cerebral cortex consists of six layers formed by excitatory neurons. Upon arrival in the cortex, the inhibitory neurons undergo a second phase of migration, in which the different kinds of inhibitory neurons populate specific layers of the cortex. Usually, too many inhibitory neurons reach their final destination. During brain development, a fraction of the inhibitory neurons will be instructed to undergo cell death. The remaining inhibitory neurons form connections with excitatory neurons. In this way, a network of excitatory and inhibitory neurons is formed. While making connections with excitatory neurons, the inhibitory neurons also acquire the properties that are necessary for their functions in the cerebral cortex in adulthood.

Disruptions in any of the steps involved in bringing inhibitory neurons to the cerebral cortex could result in disorders such as autism or schizophrenia. Therefore, it is important to understand which mechanisms are involved in the regulation of each developmental step. In this review, I provide an overview on which factors are involved in the generation of inhibitory neurons, migration and integration in cortical

layers. Thereby, I hope to advance our understanding of the origin and the development of the networks in the cerebral cortex and to contribute to our knowledge of several neurodevelopmental disorders.

ABSTRACT

The mammalian cerebral cortex is a brain structure involved in a broad range of sensory processes and more complex cognitive abilities. It is composed of a rich diversity of excitatory projection neurons, inhibitory interneurons and non-neuronal cell types, intertwined into circuits to execute complex functions. GABAergic inhibitory interneurons compose one of the most essential components to the circuitry by providing negative inputs. Cortical interneurons originate from transient structures in the ventral telencephalon called ganglionic eminences (GEs). During embryogenesis, immature cortical interneuron subtypes are generated in the medial (MGE) and caudal ganglionic eminence (CGE) and at a lesser extent in the preoptic area (POA). Exit from the GEs is regulated by repulsive cues, and tangential migration towards the cortex organizes the distribution of interneurons along the developing cortex. By means of radial migration, the cortical interneurons then reach their final destination within the cortical plate to occupy specific cortical layers, where they will integrate into local cortical circuits. Strict guidance of cortical interneurons through all developmental stages is crucial, since abnormal cortical development can result in neurodevelopmental disorders such as autism and schizophrenia. In this review, I will summarize the current knowledge on interneuron genesis, migration and integration into cortical circuits. Finally, I will discuss the factors regulating interneuron maturation through these developmental stages.

Keywords: Cerebral cortex, Interneurons, Development, Genesis, Migration, Synaptogenesis, Circuits

INTRODUCTION

The cerebral cortex is a brain structure underlying a wide range of cognitive and sensory functions that are vital for the survival of the organisms and their interaction with the environment. The cerebral cortex became structurally and functionally more refined and elaborated across evolution and attained its maximal complexity in humans (Molnár et al., 2019). The mouse has been widely used as a model organism to study the genesis, development and function of the cerebral cortex since during evolution there was preservation of conserved sequences of cellular developmental processes and molecular regulatory mechanisms associated with these processes (Molnár et al., 2019). One example is the cortical main cellular composition and its laminar organization (Fang et al., 2022). The mammalian cerebral cortex is mainly formed of excitatory projection neurons, that correspond to 80% of the total neuron numbers and 20% of inhibitory interneurons assembled within the six cortical layers (see **Figure 1**) (Sultan & Shi, 2018).

Interneurons and excitatory neurons are generated during embryogenesis, in the mouse, in distinct neurogenic niches. Later, excitatory and inhibitory neurons are brought together to form cortical cell assemblies responsible for cognitive and sensory processes (Sultan & Shi, 2018). Interneurons are the population that performs the largest displacements to join and interact with excitatory projection neurons during development. The generation, migration and guidance of inhibitory interneurons are therefore limiting and essential steps in corticogenesis and in the establishment of a proper excitation-inhibition balance (Sultan & Shi, 2018). Deviations to this balance have been implicated in developmental brain disorders (Shi et al., 2021; Sultan & Shi, 2018).

Figure 1.

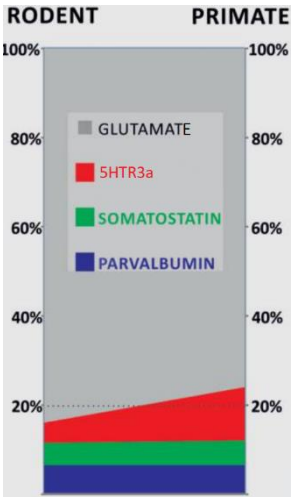

Figure 1. Comparison of excitatory and inhibitory neuron numbers in the rodent and primate cerebral cortex. The relative contribution of somatostatin (SST) and parvalbumin (PV) interneurons compared to the total number of neurons in the rodent and primate cortex is similar. Relatively, primates have a three-fold higher number of 5HTR3a class interneurons compared to rodents. On average, about 80% of the neurons in the cerebral cortex are excitatory glutamatergic projection neurons. Adapted from (Hladnik et al., 2014)

Reconstructing the complex trajectories involved in the allocation of interneurons into final cortical areas and layers has been challenging since: **1)** interneurons are generated at different times within their proliferative domains; **2)** each domain has the potential to generate diverse interneuron subtypes and **3)** there are mechanisms of refinement operating during cortical maturation that might change the balance between interneuron subtypes and final neuronal numbers during the postnatal period. Therefore, this review aims at summarizing and describing the main findings that improved our understanding of the molecular regulation of interneuron generation, migration and integration within cortical circuits.

INTERNEURON GENESIS WITHIN THE GANGLIONIC EMINENCES

Cortical interneurons originate from the ganglionic eminences (GEs) localized in the ventral subpallium, a transient structure from the embryonic brain (Anderson et al., 1997). The ventral subpallium can be subdivided in four main structures: the MGE, the CGE, the lateral ganglionic eminence (LGE) and the POA (see **Figure 2**). Only the MGE, CGE and POA contribute to the generation of cortical interneurons (Kessaris et al., 2014). The LGE generates neurons populating the olfactory bulb and, together with the MGE, will form the basal ganglia (Xu et al., 2004). The GEs are organized in three distinct tissue domains spanning from the ventricles to the most extreme and external edge of the structure: the ventricular zone (VZ), the subventricular zone (SVZ) and the mantle zone (MZ), respectively. Interneuron genesis takes place in the VZ and SVZ and is highly dependent on the gradients of *Sonic Hedgehog* (*Shh*), a morphogen highly abundant in the GE territories (Xu et al., 2005).

Figure 2

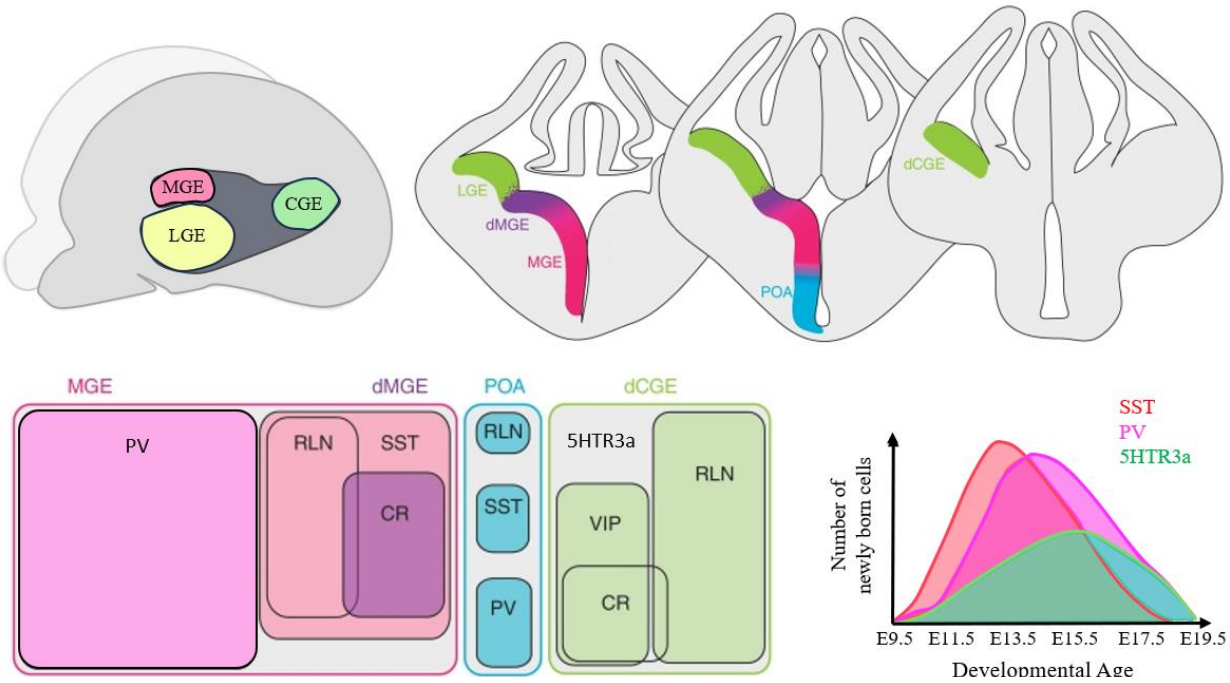

Figure 2. Location and timing of generation of cortical interneurons. The regions giving rise to cortical interneurons (MGE, CGE and POA) are localized in deep transient territories under the cerebral cortex. Depending on *Shh* gradients that vary from the ventral to the dorsal (dMGE), two main interneuron subtypes are generated in this structure, parvalbumin (PV) and somatostatin (STT) interneurons. The CGE and POA generate a large diversity of interneuron subtypes. PV and STT are the first to be generated, at around embryonic day 10 (E10) and CGE-derived interneurons are generated a few days later, at around E14. Adapted from (Williams & Riedemann, 2021) and (Kessaris et al., 2014)

Interneuron progenitors give rise to three major classes of GABAergic interneurons that can be distinguished in the mature cortex by the expression of parvalbumin (PV), somatostatin (SST) or serotonin receptor 3a (5HTR3a), with a relative distribution of 40%, 30% and 30%, respectively (Llorca & Deogracias, 2022). The POA generates a very small fraction of cortical interneurons (less than 5%) (Gelman et al., 2009). Within these classes, several subclasses of interneurons can be discerned by distinct transcriptomic, electrophysiological, synaptic, morphological and functional differences (see **Figures 2 and 3**).

PV interneurons are characterized by their fast-spiking electrophysiological properties, and can be divided into three classes: Basket cells, Chandelier cells (ChCs) and translaminar neurons. Basket cells are the most abundant PV interneuron subtype and target the soma and proximal dendrites of projection neurons and other inhibitory neurons across all cortical layers and areas (Llorca & Deogracias, 2022). Chandelier cells comprise a small group of interneurons, directly controlling axonal signalling by providing inhibitory input at the axon initial segment. Their soma is located in layer VI and the top border of layer II (Llorca & Deogracias, 2022). The soma of translaminar interneurons is most abundant in deep cortical layers, but axonal extensions project through the entire cortex to target projection neurons (Llorca & Deogracias, 2022). SST interneurons can be subdivided into Martinotti cells and non-

Martinotti cells, with a respective proportion of 60% and 40%. Martinotti cells are more abundant in layer II, III and V, whereas non-Martinotti cells mostly reside in layer IV. This is remarkable because these interneuron subtypes are born simultaneously, but occupy different cortical layers, likely due to additional underlying regulatory mechanisms. Martinotti cells have axonal projections in layer I where they inhibit projection neurons, whereas non-Martinotti cells are responsible for local inhibition in the cortical areas where the soma is located (Llorca & Deogracias, 2022). 5HTR3a interneurons generated in the CGE can be subdivided into many different subtypes depending on the expression of other neuropeptides (see **Figure 3**). Many of these interneuron subtypes co-express calretinin (CR) (Llorca & Deogracias, 2022). Interneuron diversity starts being delineated in the GEs shortly after birth. In the last years, we gathered information on the main drivers of such diversity.

Figure 3

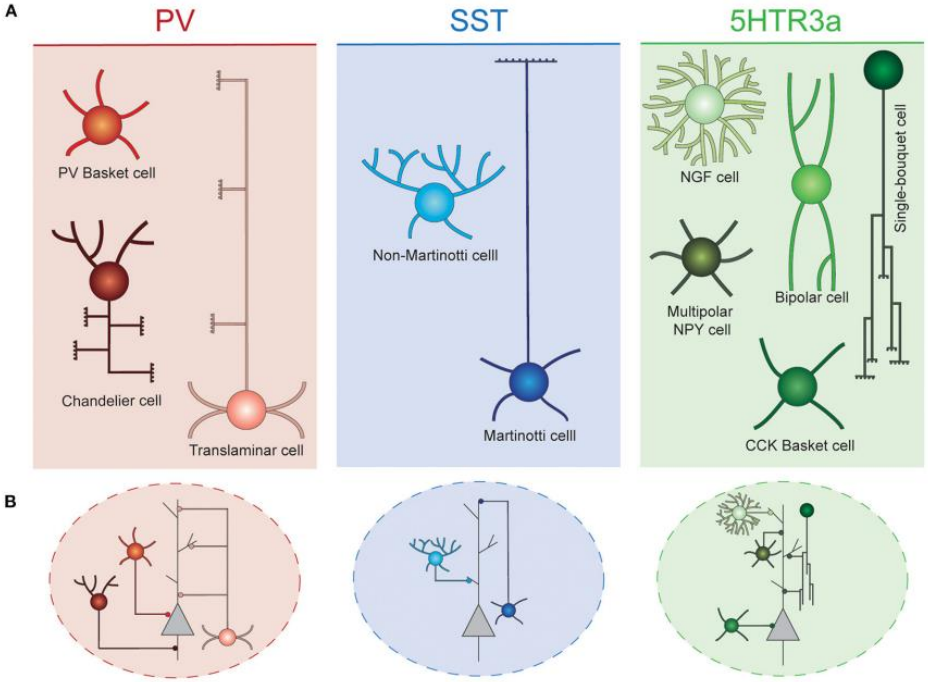

Figure 3. Schematic overview of the main inhibitory neuron classes and their synaptic targeting. A) The three distinct interneuron classes in the adult mammalian cortex are subdivided into different interneuron subtypes. Each subtype has a characteristic morphology, with varying axonal lengths and numbers of dendrites **B)** Each inhibitory neuron subtype is characterized by specific synaptic targeting on apical dendrites, proximal dendrites and/or the soma. Chandelier cells specifically target the axon initial segment (Llorca & Deogracias, 2022).

Factors influencing MGE-derived interneuron specification

- **The localization of progenitors in proliferative regions**

Recent studies indicate that the histological localization of progenitors undergoing neurogenesis within the MGE influences interneuron subtype specification (Tischfield et al., 2017). The VZ of the GEs mainly consists of apical progenitors with either unipolar or bipolar morphologies (see Box 1). The apical progenitors directly generate interneurons or give rise to basal progenitor cells that then migrate to

Box 1. Unipolar and bipolar morphology of apical progenitor neurons. Neurons in the mammalian brain display a high variety of morphologies. The number of neurites connected to the soma is one of the main characteristics that serve to neuron classification. Apical progenitors show either unipolar morphology (bottom image) or bipolar morphology (top image), meaning they display one or two neurites emerging from the soma, respectively (Vanderah et al., 2016). Image adapted from (Llorca & Deogracias, 2022).

the SVZ to finally generate interneurons. In the MGE, direct neurogenesis from apical progenitor cells in the VZ mainly results in the generation of SST interneurons, whereas indirect neurogenesis from basal progenitor cells in the SVZ is the main source of PV interneurons (Petros et al., 2015). Progenitor choices towards direct or indirect neurogenesis are controlled by the Notch signalling pathways interacting with *Shh* (Tischfield et al., 2017).

New technical approaches such as single-cell RNA-sequencing (scRNA-seq) have been used to investigate interneuron diversity onset. There was an intense debate in the last years concerning whether interneuron fate is already determined at birth or acquired at a later stage (Mayer et al., 2018; Mi et al., 2018). Although interneurons exhibit some specific molecular signatures already very early during development, it is still unclear whether progenitors giving rise to interneurons transmit to these cells all the necessary information encoding electrophysiological profiles, morphological features and connectivity programs. Bandler and colleagues used a viral approach to tag interneuron progenitors and the progeny. They found that clones deriving from the same progenitor cell often diverged into different fate trajectories just after cell-cycle exit. It is therefore hypothesized that cell fate is already delineated in these early phases, indicating a crucial role of the combinatorial expression of transcription factors (TFs) (Bandler et al., 2022). This supports the previous observations from an independent laboratory that performed a pioneer study highlighting that early born interneuron subtypes possess already distinct molecular signatures (Mi et al., 2018). Bandler and colleagues' work however unravelled that a GE progenitor is not committed to generate specific interneuron subtypes and there is divergence very early during embryonic development (Bandler et al., 2022).

- **The expression of specific transcription factors across territories of the ganglionic eminences**

Different TFs were also identified as key elements of MGE and CGE interneuron specification (see **Figure 4**). For example, *Nkx2.1* is specifically expressed in the MGE and it gives rise to the entirety of PV and SST interneurons. The conditional knockout of *Nkx2.1* during neurogenesis in the MGE results in a change of interneuron subtype numbers in adulthood, increasing the production of Vasointestinal peptide (VIP) and calretinin (CR) interneurons, probably generated by the CGE and subclasses of 5HTR3a interneurons (Butt et al., 2008). *Lhx6*, a gene downstream of *Nkx2.1*, is also expressed by all MGE-derived PV and SST interneurons and it is another determinant for these interneuron subtypes (Butt et al., 2008). In the last years, it was discovered that *Lhx6* and *Nkx2.1* can however be regulated by alternative mechanisms, such as CCCTC-binding factor (CTCF) and Sp9, respectively, suggesting that several molecular pathways might induce PV and SST fate specification (Elbert et al., 2019; Z. Liu et al., 2019). Another evidence for such complexity in the induction of MGE interneuron fate was the later discovery of other TFs driving SST and PV interneuron fate specification such as *Sox6* (Batista-

Brito et al., 2009) and *Arid1b*, which was found to affect the proliferation of progenitors producing PV interneurons (Jung et al., 2017).

Figure 4

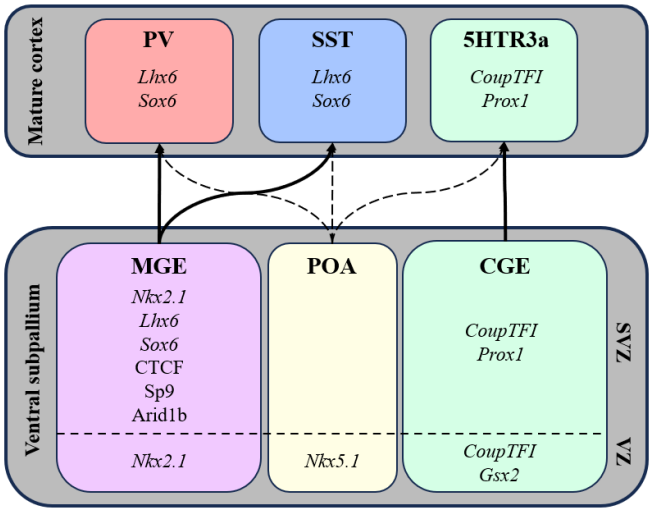

Figure 4. Molecular determinants of interneuron progenitors and maturing interneurons. An overview of the main TFs affecting fate specification of interneurons within the MGE, CGE and POA. Different TFs are expressed during proliferative stages, migration stages and mature stages in the MGE and CGE. Adapted from (Laclef & Métin, 2018).

Factors regulating CGE-derived interneuron specification

CoupTFI is an important TF for CGE-derived interneuron fate specification. By regulating interneuron progenitor divisions, *CoupTFI* controls the number of bipolar VIP+ and CR+ interneurons (Lodato et al., 2011). *Gsx2* and Prox1 are also involved in the subtype specification of CGE-derived interneurons. *Gsx2* promotes the fate specification of CR-expressing interneurons in the VZ, whereas Prox1 is active in the SVZ and also induces the specification of this interneuron subtype (Miyoshi et al., 2015; Xu et al., 2010).

Other factors involved in interneuron subtype specification

Besides factors related to the eminence-of-origin, other factors are involved in fate specification of cortical interneurons during maturation. Mayer and colleagues suggested that the maturation of the progenitors drives a six-fold more variance compared to which eminence a cell originates from, even though early transcriptomic markers at E13.5 were conserved into adulthood (Mayer et al., 2018). It can therefore be proposed that transcriptomic differences within the eminence-of-origin can be the source of initial interneuron divergence, but additional factors are involved in precise subtype diversification. One of the additional modulators of fate specification is temporal patterning, as can be seen in **Figure 2**. Interneurons generated during early neurogenesis (E13) are more likely to diverge into SST interneurons, whereas interneurons generated around E15 often become PV interneurons that are generated during a longer embryonic period (Williams & Riedemann, 2021).

GUIDANCE CUES INVOLVED IN THE MIGRATION OF INHIBITORY NEURONS

After genesis in the GEs, cortical interneurons move away from the birthplace towards the developing cerebral cortex to form cortical circuits. Within the cortex, interneurons receive and send axonal projections onto excitatory projection neurons. Interneuron migration is a limiting step in the formation of the cerebral cortex and is regulated by a wide range of chemo attractive and chemo repulsive cues. Initially, immature interneurons leave the GEs and migrate tangentially towards the pallium, where they distribute along the diverse cortical areas. Regulated by a set of guidance cues, which will be discussed later, each interneuron subtype then localizes in specific cortical layers, where they will form microcircuits and integrate into cortical circuits (see **Figure 5**) (Llorca & Deogracias, 2022).

Figure 5

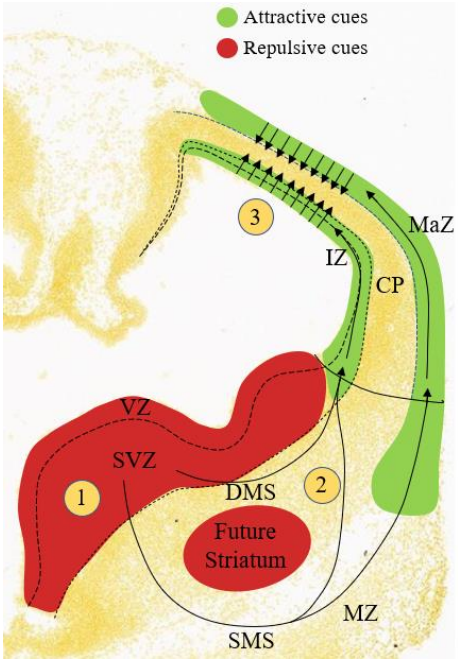

Figure 5. Migration pathways of cortical interneurons. First, cortical interneurons are repelled from the ganglionic eminences (1) and from the future striatum resulting in a deep migratory stream (DMS) and a superficial migratory stream (SMS). Then, tangential migration is stimulated via attractive cues released on the intermediate zone (IZ) migratory stream and marginal zone (MaZ) migratory stream (2). Finally, cortical interneurons exit the tangential migratory stream to radially migrate into the cortical plate (CP) (3). Green delineates regions of attractive cues, whereas red marks regions of repulsion. Figure adapted from the Allen Brain Atlas.

- **<u>Migration away from the GEs</u>**

The initiation of cortical interneuron migration is mainly regulated by repulsive cues belonging to diverse families. These cues can act within the GEs or in the prospective cortex and cause interneurons to migrate via the deep migratory stream (DMS) or superficial migratory stream (SMS) within the GEs, and by the intermediate zone (IZ) stream or marginal zone (MaZ) stream in the cortex. An example of repulsive cues within the GEs is Netrin-1, a guidance molecule that binds to and activates the Unc5 receptor in immature interneurons, promoting interneuron exit from the GEs (Hamasaki et al., 2001). Similarly, Repulsive Guidance Molecule a (RGMa) serves as a repellent for cortical interneurons. Its expression in the SVZ of the GEs prevents their re-entry into the MGE after migration onset (O'Leary et al., 2013).

Eph-receptors, which compose the largest subfamily of receptor protein-tyrosine kinases (RTKs), are also well-established determinants of cortical interneuron migration. By binding Ephrin-isoforms, these receptors affect many cellular processes, including migration. For example, Ephrin-A3 and Ephrin-E5, expressed in the GEs, can bind to Eph4A, a receptor expressed by migrating cortical interneurons (Rudolph et al., 2010). Cortical interneurons expressing Ephrin-A2 interact with Eph4A expressed along the DMS, stimulating migration via this stream (Steinecke et al., 2014). Moreover, interneurons originating from the POA express the ligand Ephrin-B3, which is capable of activating the Eph4A receptor that is responsible for repelling MGE-derived interneurons from the SMS (see **Figure 5**) (Zimmer et al., 2011).

Lastly, growth factors have also been implicated in the initiation of interneuron migration. For example, hepatocyte growth factor/scatter factor (HGF/SF) can drive interneuron exit from the GEs by stimulating interneuron motility (Levitt, 2005).

On the way to the cerebral cortex, interneurons completely avoid the future striatum. This process is regulated by multiple factors, including guidance molecules Sema3A and Sema3F that bind to the neuropilin-2 receptor expressed by cortical interneurons. Lack of expression of this receptor results in a higher number of striatal interneurons at the expense of cortical interneurons (Marín et al., 2001). Intriguingly, chondroitin sulfate expression in the MZ of the future striatum is able to affect this interaction by binding extracellular Sema3A. This suggests a decrease in repulsion from the striatum due to lower ligand concentrations to bind to the neuropilin-2 receptors. Additionally, chondroitin sulfate also carries proteoglycans, which have repulsive properties on cortical interneurons independent of Sema3A (Zimmer et al., 2010). Furthermore, secreted extracellular matrix proteins from the Slit-family can act as repulsive guidance molecules. Slit1 expression in the LGE, and Slit3 expression in the striatum anlage results in repulsive from the respective structures. Although the underlying mechanisms remain to be elucidated, these effects seem to be driven by their interaction with the Robo1 receptor (Andrews et al., 2006). Lastly, aforementioned Ephrin-A3 also is involved in repulsion from the future striatum by interacting with the EphA4 receptor on cortical interneurons (Rudolph et al., 2010).

- **Tangential Migration in the Developing Cortex**

During the early steps of migration within cortical territories, interneurons are guided along two major migratory streams: the IZ migratory stream and the MaZ migratory stream (Nadarajah & Parnavelas, 2002). The IZ migratory stream is an extension of the SVZ and VZ, whereas the MaZ aligns with the MZ. Interestingly, some interneuron subtypes display preference for a specific migratory stream. Lim and colleagues observed that PV translaminar and SST Martinotti cells mainly migrate via the MaZ

migratory stream, whereas other interneuron subtypes seem to prefer to take the IZ migratory stream (Lim et al., 2018). The precise molecular underpinnings of these choices are yet to be discovered.

Many factors have been discovered to guide tangential migration of interneurons. Firstly, interactions between ligands and their receptors regulate interneuron migration by either providing attractive or repulsive cues. These interactions include proteins from families of guidance molecules, growth factors, adhesion molecules, TFs and kinases. Secondly, neurotransmitters also serve as guidance cues during the development of the cerebral cortex (Petros & Anderson, 2013).

1. Ligand-receptor interactions

Guidance molecules are also fundamental in the regulation of tangential migration in the cortex. Here, Netrin-1 interacts with α3β1 integrin to promote interneuron migration towards the cerebral cortex. This interaction mainly occurs along both migratory streams, where Netrin-1 is secreted (Stanco et al., 2009). Likewise, stromal cell-derived factor 1 (SDF-1) is a chemokine expressed by excitatory projection neurons and the developing meninges and also interacts with cortical interneurons during tangential migration. By binding to its receptors Cxcr4 and Cxcr7, this chemokine attracts migrating interneurons towards the pallium (Wang et al., 2011). However, recent research indicated that more complex mechanisms are involved in interneuron guidance mediated by SDF-1. Both cortical interneurons and subpopulations of oligodendrocytes express Cxcr4 and Cxcr7 that bind and are activated by SDF-1. In contrast with cortical interneurons, oligodendrocyte precursor cells (OPCs) migrate along blood vessels. These cells promote unidirectional contact repulsion, steering cortical interneurons away from the vasculature and hence prevent interneurons from interacting with endothelial cells that also express SDF-1. Thereby, cortical interneurons are stimulated to progress moving in the migratory streams to reach their final destinations (Lepiemme et al., 2022). Furthermore, proteins from the Eph-receptor family contribute to tangential migration. Ephrin-A5 and Ascl1, which are expressed by cortical interneurons can bind to the EphB2 receptor that is expressed along the IZ migratory stream. This interaction provides repulsive cues, confining the interneurons to the migratory stream (Y. H. Liu et al., 2017).

Secondly, different families of growth factors help to guide cortical interneuron migration to the cerebral cortex. For instance, epidermal growth factor Neuregulin-1 (Nrg1) has been strongly associated with interneuron guidance by interacting with its receptor ErbB4, which is expressed by a subset of cortical interneurons, mainly PV interneurons (Flames et al., 2004). Neuregulin isoforms are expressed by both excitatory projection neurons and other migrating cortical interneurons. Thereby, isoforms expressed by distant excitatory projection neurons provide long-range cues, whereas isoforms expressed by nearby migrating cortical interneurons provide short-range guidance cues (Bartolini et al., 2017; Flames et al., 2004). However, *in vitro* and *in vivo* research by Li and colleagues provides evidence that Neuregulin-

ErbB4 interactions in the cortex serve as a repellent instead of an attractant (Li et al., 2012). As ErbB4-expressing interneurons avoid regions with high Neuregulin isoform expression, these researchers have provided evidence for the repulsive nature of Neuregulin-ErbB4 interaction (Li et al., 2012). Other growth factors implicated in interneuron guidance are brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin-4 (NT4). BDNF and NT4 are known to stimulate tangential migration by binding the TrkB receptor, whereas GDNF accomplishes its chemo attractive properties by binding GFRα1 (Yang et al., 2022).

Proteins of the FLRT-family, known for their function as adhesion molecules in the cortex, also perform repulsion. This is regulated by metalloproteases that cleave the extracellular domains of these transmembrane proteins. Cleaved domains of FLRT2 and FLRT3 subsequently provide repulsion by binding the Unc5 receptor. As the expression of these domains is high alongside the IZ migratory stream, neurons are confined to this stream (Fleitas et al., 2021). Another adhesion molecule, N-cadherin, affects tangential migration of interneurons that express both CR and SST. The molecular underpinnings of this subtype-specific effect are yet unknown, but co-expressed Nkx6.2 has been implicated to play an important role (László et al., 2020).

Additionally, TFs such as CoupTFI and CoupTFII modulate interneuron migration. Interestingly, CoupTFI expression in interneurons stimulates migration towards the cortex and the POA, whereas CoupTFII expression specifically modulates migration via the IZ migratory stream (Tripodi et al., 2004). CoupTFs have been suggested to regulate migration by either 1) regulating short-range cues such as extracellular matrix and/or adhesive molecules to prevent random dispersion or 2) control diffusible guidance molecules and/or receptors to promote migration (Tripodi et al., 2004).

Finally, interaction between cyclin-dependent kinase 5 (CDK5) and its activator p35 have also been implicated in tangential migration. P35-knockout mice displayed delays in tangential migration, ultimately resulting in altered cortical lamination (Rakić et al., 2009).

2. Neurotransmitters

As mentioned before, neurotransmitters such as glutamate, dopamine, serotonin and GABA itself also play an important role in interneuron guidance by inducing calcium currents that are able to stimulate downstream effectors, impacting on the machinery of movement of cortical interneurons (Murthy et al., 2014; Uhlén et al., 2015).

Glutamate signalling occurs via multiple glutamate receptors, including NMDA-receptors (Bortone & Polleux, 2009). Activation of NMDA is supposed to increase the expression of endothelial proteases, notably the matrix metalloproteinase-9 (MMP-9) and tissue-plasminogen activator (t-PA) in small blood vessels along the migratory streams. Although the underlying mechanisms are yet to be elucidated, these

proteins stimulate migration of cortical interneurons (Léger et al., 2020). There is evidence that glutamate might also act upon migration via non-NMDA receptors, but the molecular mechanisms are yet to be explored (Bortone & Polleux, 2009).

Interneuron motility is also stimulated by binding non-synaptically secreted GABA by different GABA receptor subtypes. For example, $GABA_A$ receptors, expressed by both progenitor cells and immature interneurons, can promote interneuron motility (Owens et al., 1999). $GABA_B$ receptor is expressed by nearly all interneurons originating from the MGE. Interestingly, the blockade of this receptor resulted in an accumulation of cortical interneurons within the VZ and SVZ, thus implicating its involvement in migration (López-Bendito et al., 2003).

Serotonin release by serotonergic raphe fibers located in the IZ and MaZ migratory streams can affect cortical interneuron migration of CGE-derived, but not MGE-derived neurons, by multiple mechanisms. The activation of 5HTR3a receptors on interneurons leads to an increase in calcium gradients that increase motility (Murthy et al., 2014) but the activation of 5HT6a receptors inhibits cortical interneuron migration in a dose-dependent manner. These effects are regulated by the cyclic adenosine monophosphate (cAMP) pathway, which can be stimulated by an increase in calcium gradient but can be inhibited by 5HT6a receptor activation (Riccio et al., 2009).

D2 dopamine receptor activation on interneurons has been observed to stimulate the migration of cortical interneurons by stimulating the synthesis of ligands of the TrkB receptor. These neurotrophins, including BDNF, promote interneuron motility (Ohira, 2019).

- **<u>Radial Migration during Cortical Interneuron Development</u>**

During mid-embryogenesis, tangentially migrating cortical interneurons enter the cortical plate by radial migration. Although the precise mechanisms leading to the shift from tangential to radial migration are yet to be revealed, perturbations of multiple genes and proteins have been observed to result in an incorrect lamination of interneurons in the cortical plate.

For example, loss of SDF-1/Cxcr7 or SDF-1/Cxcr4 signalling resulted in a change in cortical interneuron distribution, with lower interneuron numbers in superficial cortical layers compared to deeper cortical layers (Bartolini et al., 2017). Although both are considered important for radial migration, Cxcr4 and Cxcr7 operate via distinct intracellular signalling pathways (Wang et al., 2011).

Neuregulin 3 (Nrg3) is expressed by projection neurons as soon as they migrate to the cortical plate and also serves as a chemoattractive cue by binding to ErbB4 (Bartolini et al., 2017). Perturbing this signalling led to an accumulation of PV interneurons in superficial cortical layers without alterations in the total number of interneurons (Bartolini et al., 2017). Although Nrg3 and SDF-1 signalling can occur

simultaneously, it has been shown that MGE-derived interneurons are more responsive to SDF-1 (See **Figure 6**) (Bartolini et al., 2017).

Figure 6

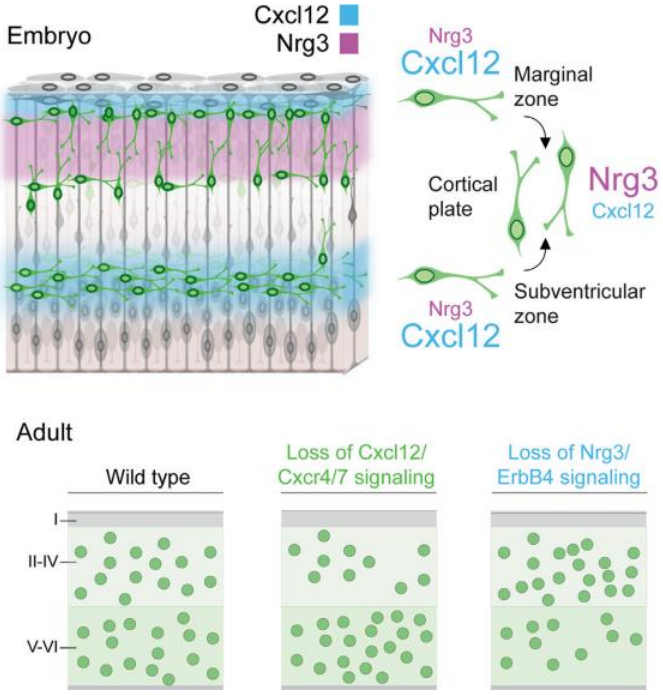

Figure 6. SDF-1 (Cxcl12) and Neuroregulin-3 (Nrg3) signalling is essential for the proper laminar distribution of cortical interneurons. Interneurons reach the cerebral cortex by tangential migration. Radial migration into the cortical plate is then necessary to distribute interneurons in appropriate cortical layers. Loss of SDF-1 or Nrg3 results in aberrations in cortical layer interneuron numbers. Adapted from (Bartolini et al., 2017b).

Proteins involved in gap junction adhesion have also been implicated in radial migration. For instance, Connexin43 (Cx43), a protein that provides gap junction adhesion between migrating interneurons and radial glial cell processes, contributes to the switch from tangential to radial migration. This effect does not depend on the channel itself, but on the adhesion properties of Cx43 (Elias et al., 2010).

Lastly, the primary cilium formation on interneurons is crucial for proper cortical interneuron migration. Firstly, this cellular structure is crucial for *Shh* signal transduction. *Shh* in turn serves as a guidance cue for MGE-derived interneurons to exit tangential migratory routes (Baudoin et al., 2012). Secondly, the primary cilium contains a higher concentration of receptors that are of importance for radial migration, including Cxcr4, Cxcr7 and ErbB4 (Métin & Pedraza, 2014).

FACTORS MEDIATING INTERNEURON CORTICAL LAMINATION

After invading the cortical plate, interneurons distribute along the different cortical layers. Interneuron distribution within cortical layers seems to depend on the subtype and is modulated by different factors. MGE-derived interneurons mainly populate deeper cortical layers, whereas CGE-derived interneurons populate preferentially superficial cortical layers (Mayer et al., 2018). One of the regulators of cortical interneuron lamination is the guidance molecule Sema3A, which is mainly expressed in deep cortical

layers. PlexinA4 receptors, which are abundantly expressed by CGE-derived interneurons, perform chemo repulsion when bound to Sema3A. Therefore, these neurons are repelled from the deep cortical layers, and hence localize in more superficial layers (Limoni et al., 2021).

Recent research also indicated that Reelin is involved in the fine-tuning of interneuron cortical lamination. This secreted extracellular matrix glycoprotein can provide repulsive cues that are crucial for cortical interneuron lamination by binding and activating α3β1 integrin on cortical interneurons. During perinatal stages, Reelin is expressed by Cajal-Retzius cells in the cerebral cortex and GABAergic interneurons and is suggested to be involved in the regulation of cortical lamination of layers II to VI. Later, Reelin-expression is limited to GABAergic interneurons and is crucial to prevent ectopic invasion of cortical layer I (Vilchez-Acosta et al., 2022).

Additionally, radial glia and projection neurons have also been implicated in the proper lamination of cortical interneurons, as loss of a projection neuron subpopulation disrupted CGE-derived cortical interneuron lamination. Therefore, genes important for projection neurons such as Satb2, Fezf2 and Ctip2 are indirectly implicated in the proper lamination of cortical interneurons (Wester et al., 2019).

Lastly, interneuron cortical lamination could be influenced by cell intrinsic mechanisms, as interneuron subtype generation also shows time-dependence. For example, the expression of the KCC2 potassium-chloride transporter during postnatal stages was shown to decrease interneuron motility. Indeed, KCC2 acts as a STOP signal for interneuron migration. During the perinatal period, cortical lamination does not seem to be disturbed in a KCC2 conditional KO mouse model. Nonetheless, during postnatal periods, the brains of KCC2 conditional KO mice show aberrant cortical lamination, including excess of SST neurons in layer V and a reduction in the numbers of PV neurons in layers II, III and VI (Zavalin et al., 2022).

ESTABLISHMENT OF BRAIN CIRCUITRY

The organisation of interneurons into functional cortical circuits requires a few more steps. Initially, a supernumerary number of interneurons reach the cortex and establish synaptic connections locally. To ensure a proper excitatory-inhibitory balance in the cortical circuits, strictly regulated programmed cell death apoptosis occurs in early postnatal days. Simultaneously, the interneurons acquire their final electrophysiological properties and connect to other excitatory and/or inhibitory neurons within the cortex, ultimately followed by refinement of synaptic connections. By these connections, interneurons start generating and participating in circuit-related processes, such as rhythmic oscillations and distinct activity patterns (Williams & Riedemann, 2021).

- **Apoptosis of supernumerary cortical interneurons**

During the first two postnatal weeks, both inhibitory interneurons and excitatory projection neurons undergo programmed cell death named apoptosis. During this period, the total cortical interneuron number reduces 20-30% (Wong & Marín, 2019). The exact rate in which apoptosis occurs is both area-specific and cortical layer-specific and is regulated by either intrinsic or extrinsic cues. In the case of extrinsic cues, different families of death receptors can be bound by external death ligands, including FAS/FAS-ligand interactions (Zhong et al., 2020). Activation of these receptors results in cleavage of pro-caspase-8, resulting in active caspase-8. This protease is able to cleave procaspase-3 and procaspase-7 and thereby activate caspase-3 and/or caspase-7, which are known to induce cell death. Intrinsic cell death is initiated by the activation of pro-apoptotic proteins Bax and Bak, which permeabilize the membrane of mitochondria. As a result, cytochrome C is released from mitochondria, which activates caspase-9. Caspase-9 can in turn activate caspase-3 and caspase-7 by cleaving the procaspases-3 and -7 (see **Figure 7**).

Figure 7

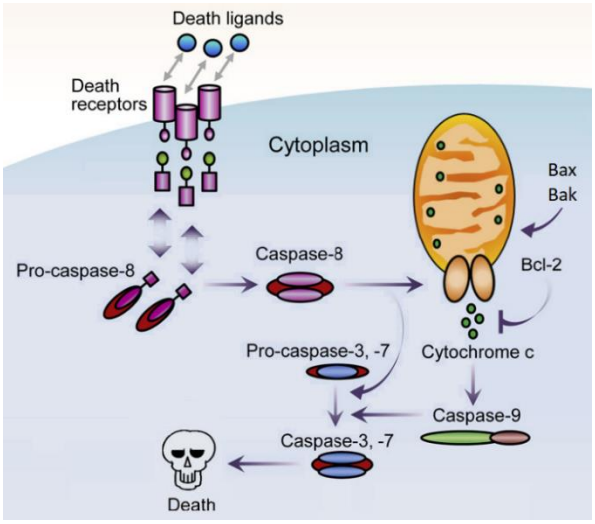

Figure 7. Schematic overview of apoptosis by intrinsic and extrinsic cues. Intrinsic cues for apoptosis result in cytochrome C release from mitochondria. This stimulates caspase-9 activation, which can cleave pro-caspase-3 and -7 into caspase-3 and -7. Thereby, cell death can be induced. Extrinsic cues involve ligands binding to death receptors. Activation of these receptors results in the activation of caspase-8 by cleaving pro-caspase-8. Caspase-8 can promote cytochrome C release from mitochondria, as well as cleave pro-caspase-3 and -7. Thereby it is also able to induce cell death in interneurons. Adapted from (Zhong et al., 2020).

Although the precise molecular underpinnings of intrinsic cell death are yet unclear, it is speculated that interneurons have an intrinsic timer that drives interneuron death when reaching certain maturation stages in the cortex, which can be counteracted by cues that promote interneuron survival (Wong & Marín, 2019). Since it is important to establish a proper excitatory-inhibitory balance, projection neurons are crucial for the regulation of cortical interneuron survival. Research by Wong and colleagues revealed that Phosphate Tensin Homologue (PTEN), a factor that is fundamental to apoptotic processes during a temporal window during postnatal development, is downregulated in cortical interneurons after projection neuron activity (Wong et al., 2018). PTEN normally serves as an inhibitor of the PI3K/Akt signalling pathway, which has been implicated in cortical interneuron apoptosis, especially SST interneurons (Vogt et al., 2015). Thereby, projection neuron activity antagonizes the pro-apoptotic effects of PTEN and promotes interneuron survival (Wong et al., 2018).

Besides glutamatergic signalling from the projection neurons, also other neurotransmitters have been implicated in interneuron survival in the cerebral cortex. For example, bipolar cells require serotoninergic signalling for survival during this period (Wong et al., 2022). GABA signalling from the interneurons onto projection neurons has also been found crucial for MGE- but not CGE-derived subtypes, as it ultimately leads to network synchrony. These activity patterns also block apoptotic factors within the interneurons (Duan et al., 2020).

Lastly, some repellent guidance factors and morphogens mentioned before such as Netrin-1 and *Shh*, respectively, play a role in interneuron survival. Interneurons exhibiting a drop in the levels of these factors initiate the process of apoptosis (Wong & Marín, 2019). Additionally, Bcl2, localized at the outer membrane of mitochondria, is capable of inhibiting pro-apoptotic proteins Bax and Bak, thereby preventing the initiation of the apoptotic pathways (Williams & Riedemann, 2021).

- **Postnatal connectivity and maturation**

During early postnatal stages, cortical interneurons establish synaptic connections with projection neurons and other interneurons in the cerebral cortex, while mature stages are being completed (Williams & Riedemann, 2021). Indeed, a FACS-array analysis of the murine cortex just after birth revealed a wide change of expression in genes associated with the maturation of distinct interneuron subtypes. Amongst the top genes were genes important for GABA synthesis and genes that define subtypes such as SST and 5HTR3a. Ontology analysis on the remaining top genes revealed upregulation in genes important for synaptic connections and electrophysiological properties, while genes related to cell cycle and cell division were downregulated. (Fukumoto et al., 2018). This is followed by cortical PV expression during the second postnatal week. By the end of this week, cortical interneuron subtypes are stabilized and active and passive membrane properties are established (Williams & Riedemann, 2021).

Simultaneously, synaptogenesis in the murine cerebral cortex starts taking place, peaking around postnatal day 10 (P10). RNA-sequencing at P5, P8 and P10 revealed genes important for the establishment of specific connections between cortical interneurons and excitatory projection neurons. In a study by Favuzzi and colleagues, genes underlying interneuron connectivity to specific subcellular compartments of projection neurons were found (Favuzzi et al., 2019). For instance, the innervation at distal dendrites of excitatory projection neurons by SST interneurons is associated with the expression of genes such as Cbln4, Igsf21 and CD59a. The synaptic connections formed by PV interneurons at the soma and proximal dendrites has been suggested to be regulated by Lgals1, Lgi2 and Tmem91, amongst other genes. In turn, Hapln1, Thsd7a and Fgf13 likely contribute to the synaptic connections between ChCs and the axon initial segment of excitatory projection neurons (Favuzzi et al., 2019).

- **Refinement of cortical circuit connectivity and interneuron functions in cortical circuits**

During the second postnatal week, neuronal activity can drive the rearrangement of synaptic connections. Some synapses will be strengthened and others weakened. A hallmark of interneuron maturation is the expression of the chloride extruder KCC2, resulting in the switch from excitatory to inhibitory signalling in GABAergic interneurons. Thereby, cortical refinement becomes dependent on experience-driven activity during a temporal window of extended plasticity, in which neurons compete for synaptic connections (Kiss et al., 2014). Between the third and fourth postnatal week, the synaptic connections are established and the cortical interneurons acquire their final electrophysiological properties to operate in cortical circuits (Williams & Riedemann, 2021).

Each interneuron subtype serves a different function in the cortical circuitry. Therefore, each subtype displays differences in their firing properties and innervations. For example, PV interneurons are known as fast-spiking cells due to the expression of the Kv3.1 potassium channel. PV interneurons from layers I to III mostly receive inputs from neighbouring projection neurons to provide feedback inhibition, whereas PV interneurons from layers IV to VI receive strong inputs from the thalamus, providing feed-forward inhibition (Williams & Riedemann, 2021). SST interneurons also primarily receive input from neighbouring projection neurons. SST Martinotti cells often display continuous firing patterns, whereas non-Martinotti cells resemble fast-spiking interneurons (Williams & Riedemann, 2021). CGE-derived interneuron subtypes receive inputs from pyramidal neurons, thalamic projections and/or other interneurons. These interneurons display either regular spiking patterns due to Kv3.1 potassium channel expression or irregular spiking patterns with initial bursts followed irregularly spaced action potentials (Guet-McCreight et al., 2020).

Due to their electrophysiological properties and subtype-specific synaptic targets, these GABAergic neurons are not only crucial for basic inhibitory signalling, but also regulate temporal coordination of the firing within local circuitries (Fishell & Kepecs, 2020). During activity, PV interneurons are the main provider of high gamma frequency oscillations in upper cortical layers and suppressors of beta oscillations in deeper cortical layers. SST interneurons serve as a modulator of these oscillations in certain brain regions, thereby being involved in functions revolving around habituation and adaptation as well as learning and memory (see Box 2) (Williams & Riedemann, 2021).

Box 2. The functions of alpha, beta, gamma, delta and theta oscillations in the cerebral cortex. By performing an electroencephalogram, five different frequency oscillations can be distinguished: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-35 Hz) and gamma (above 35 Hz). Delta and theta waves are mostly limited to sleep stages. Alpha waves are mostly recorded during wakeful relaxation, but have also been implicated in information processing in various cognitive tasks involving working memory or top-down influences on perceptual processes. Beta waves are mostly involved in information processing at a cognitive level, whereas gamma-activity is mostly involved in perceptual processing (Miller, 2007).

DISCUSSION

Although many underlying mechanisms remain to be elucidated, it is evident that the effort made in the last 30 years was essential to improve our understanding of the interneuron dynamics in cortical circuits. We acquired the understanding of how cortical interneurons are generated in the MGE, CGE and POA in the ventral telencephalon (Kessaris et al., 2014) and that both the location and timing of interneuron genesis are crucial for fate determination. Although interneurons possess specific molecular signatures immediately after birth, it is still unclear from where the vast diversity of interneuron subtypes emerges. The current theory postulates that this initial diversity is the scaffold for more complex forms of diversity that shape after maturation (Bandler et al., 2022).

After genesis, interneurons are repelled from the GEs by repulsive cues. A broad selection of attractive and repulsive cues then helps to guide cortical interneurons towards their final destinations (Llorca & Deogracias, 2022). However, it is still unclear whether these molecules converge into a common cytoskeleton organizer or whether they affect motility *via* independent pathways. It is also still an open question whether all this diversity of signals is necessary for the complete integration of interneurons into cortical circuits or whether there is redundancy that ultimately ensure the arrival of interneurons at the final destination. Interestingly, research in PlexinA1-knockout mice revealed decreased proliferative abilities in progenitors from the GEs of approximately 30% (W. D. Andrews et al., 2016). As this percentage broadly resembles the percentage of cortical interneurons undergoing apoptosis, this mouse model could be used to study cortical development without supernumerary interneuron numbers arriving in the cerebral cortex.

Upon reaching their final destination, a substantial number of interneurons is eliminated by apoptosis (Williams & Riedemann, 2021). From an evolutionary perspective, the excessive generation and migration of interneurons appears inefficient, as it requires energy that could also be utilized for alternative biological processes. To this day, it is unclear whether the evolutionary benefits of excessive interneuron genesis and migration are limited to ensuring enough interneurons reach the cerebral cortex to establish a proper excitation-inhibition balance or whether additional processes are involved. Lastly, transplantation of interneuron progenitors revealed that interneuron apoptosis is timed by the expression of intrinsic maturation programs and not by the developmental state of the cerebral cortex itself. However, the underlying mechanisms driving intrinsic apoptosis remain unclear (Southwell et al., 2012). Now that scRNA-seq technologies are developing, we will hopefully soon be able to capture the maturation genes responsible for the initiation of intrinsic apoptosis.

As cortical development impairments are involved in autism, schizophrenia and epilepsy in humans, it is crucial to broaden our knowledge on the interneuron dynamics in the cerebral cortex using the mouse or human systems such as brain organoids or brain tissue from human foetuses (Shi et al., 2021). Mice and humans do not only show much overlap in structural elements, but recent research also predicts

similar regulatory genes to be involved in fate specification, migration and maturation (Shi et al., 2021). Although murine cerebral cortex development is representative for the human cerebral cortex, it is important to realize the main differences. Firstly, interneuron subtype proportions are different. CR interneurons represent less than 4% of the total number of cortical neurons in rodents, whereas this percentage exceeds 12% in some regions of the human cerebral cortex. In contrast, the relative number of other interneuron subtypes are comparable between rodents and primates (Hladnik et al., 2014; Shi et al., 2021). This three-fold difference in CGE-derived interneurons is expected to impact in the different modes of signal processing and cognitive abilities that humans possess (Hladnik et al., 2014).

Lastly, the genesis of immature cortical interneurons in humans is not only limited to the GEs. Recent research has discovered that progenitors in the human cerebral cortex are also capable of producing cortical interneurons (Delgado et al., 2022). This elicits an interesting question, as the choice for cortical interneuron genesis over projection neuron genesis is regulated by morphogens that are abundant in the ventral GEs, such as *Shh*. The discovery that cortical progenitors can also produce cortical interneurons therefore suggests the existence of *Shh* sources in the cerebral cortex. Intriguingly, Memi and colleagues found an increasing expression of *Shh* in the cerebral cortex during gestational weeks 10 to 40. Moreover, cortical radial glial cells were found to express PTCH1, *BOC*, *GAS1* and *CDON*, genes that are crucial for *Shh* signal transduction (Memi et al., 2018). Interestingly, *BOC* is strongly expressed in the human cerebral cortex, but not in the murine cortex, suggesting that this gene and underlying signalling pathways might be involved in *Shh* signalling in the human developing cortex (Memi et al., 2018). Moreover, *in vitro* studies in human radial glial cells revealed that exogenous treatment with *Shh* was able to induce an intracellular switch to interneuron fates (Radonjić et al., 2016). However, various methods of *Shh* administration in this *in vitro* study displayed varying distributions of each of the three interneuron classes (Radonjić et al., 2016). As recent research revealed that all cortical-generated interneurons in humans were transcriptionally similar to CGE-derived cortical interneurons (Delgado et al., 2022), it is clear that additional mechanisms are necessary for the fate determination of cortically produced interneurons. Taken together, an understanding of the underlying mechanisms of *Shh* in cortically derived interneurons is essential to progress our understanding of cortical interneuron development and their implication in developmental disorders.

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