

REVIEW

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Development and specification of GABAergic cortical interneurons

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Abstract

GABAergic interneurons are inhibitory neurons of the nervous system that play a vital role in neural circuitry and activity. They are so named due to their release of the neurotransmitter gamma-aminobutyric acid (GABA), and occupy different areas of the brain. This review will focus primarily on GABAergic interneurons of the mammalian cerebral cortex from a developmental standpoint. There is a diverse amount of cortical interneuronal subtypes that may be categorized by a number of characteristics; this review will classify them largely by the protein markers they express. The developmental origins of GABAergic interneurons will be discussed, as well as factors that influence the complex migration routes that these interneurons must take in order to ultimately localize in the cerebral cortex where they will integrate with the neural circuitry set in place. This review will also place an emphasis on the transcriptional network of genes that play a role in the specification and maintenance of GABAergic interneuron fate. Gaining an understanding of the different aspects of cortical interneuron development and specification, especially in humans, has many useful clinical applications that may serve to treat various neurological disorders linked to alterations in interneuron populations.

Keywords: GABA, Interneuron, Cortex, Specification, Transcriptional network

Introduction

Interneurons play a vital role in the wiring and circuitry of the developing nervous system of all organisms, both invertebrates and vertebrates alike. Generally speaking, an interneuron is a specialized type of neuron whose primary role is to form a connection between other types of neurons. They are neither motor neurons nor sensory neurons, and also differ from projection neurons in that projection neurons send their signals to more distant locations such as the brain or the spinal cord. Of great importance is that interneurons function to modulate neural circuitry and circuit activity [1-4]. A large majority of interneurons of the central nervous system are of the inhibitory type. In contrast to excitatory neurons, inhibitory cortical interneurons characteristically release the neurotransmitters gamma-aminobutyric acid (GABA) and glycine [5-7]. Cortical interneurons are so named for their localization in the cerebral cortex, which is defined as a

sheet of outer neural tissue, that functions to cover the cerebrum and cerebellum structures in the brain.

This review will place an emphasis on the function and origin of GABAergic cortical interneurons of the developing nervous system. Within the overarching categorization of GABAergic interneurons there are also numerous interneuron subtypes that are largely categorized based on the surface markers they express. Three major cortical interneuron subtypes will be discussed: parvalbumin (PV)-expressing interneurons, a heterogeneous population of somatostatin (SST)-expressing interneurons, and a relatively recently identified population of the ionotropic serotonin receptor 5HT3a (5HT3aR)-expressing interneurons; together, these three subtypes account for approximately 100 percent of the mouse neocortical GABAergic interneuronal population [8]. Although these interneurons home to their respective layers of the cerebral cortex, they are generated in various subpallial locations; the primary origins of these interneuronal progenitors will be extensively discussed as well. The subsequent migratory routes that these interneuronal precursors take to the cerebral cortex are also covered here.

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Of particular interest as of late in this field of research is mapping the network of transcription factors that are responsible for specifying cortical interneurons and specific interneuronal subtype. This review is organized such that the transcription factors are organized and discussed based on the major interneuronal origins in the subpallium. The most arduous task that researchers face is understanding the mechanism by which *each* interneuron subtype is specified as well as the various genes and transcription factors that may be involved; this is not helped by the fact that there are so many subtypes whose features often overlap with one another.

Of utmost importance with regard to cortical circuitry is the balance between excitatory inputs and inhibitory inputs that must be carefully maintained. Disrupting the balance of neural circuits may very well be a contributing factor toward the emergence of neuropsychiatric disorders, such as epilepsy, autism spectrum disorders, and intellectual disabilities, just to name a few [9]. This review focuses on one severe mental illness in particular, schizophrenia. Gaining an understanding of cortical interneurons within the “bigger picture” of neocortical circuitry may provide much needed information behind the etiologies of neurological disorders.

Role of GABAergic cortical interneurons

Given that the population of GABAergic interneurons in the brain is such a heterogeneous one, it is only logical that the many different classes of interneurons will have a myriad of roles to play in the adult nervous system. GABAergic neurons play an inhibitory role and synaptically release the neurotransmitter GABA in order to regulate the firing rate of target neurons. Neurotransmitter release typically acts through postsynaptic GABA_A ionotropic receptors in order to trigger a neuronal signaling pathway.

This research field typically organizes interneuron role/function into three components: (1) afferent input, (2) intrinsic properties of the interneuron, and (3) targets of the interneuron. Generally speaking, interneurons receive input from various sources, including pyramidal cells as well as cells from other cortical and

subcortical regions [10,11]. With regard to output, cortical interneurons engage in feed-forward and feedback inhibition [12-14]. Regardless of the mode of output, the cortical interneuronal network is further complicated by the fact that a single cortical interneuron is capable of making multiple connections with its excitatory neuronal target(s) [15].

Cortical interneuron subtype

It is estimated that there are over 20 different subtypes of GABAergic interneurons in the cortex, and subtypes are also distinguished from one another based upon the calcium-binding proteins they express, which serve as markers (Table 1) [16-24]. Studies performed in both mouse and rat brain tissue have suggested that in particular, the calcium-binding protein known as parvalbumin, and the neuropeptide somatostatin, are two crucial markers in defining the most predominant interneuron subtypes within the cerebral cortex [16,20,22]. Importantly, the PV-expressing interneuron population is independent from the SST-expressing population, in that expression of these markers does not overlap [16,20,22,25]. In addition to PV- and SST-positive GABAergic interneurons, which together comprise approximately 70% of the total GABAergic cortical interneuron population, another subgroup of interneurons that express 5HT3aR were found to comprise approximately 30% of all interneurons [25]. While these three interneuronal subpopulations account for nearly (if not all) 100% of all GABAergic cortical interneurons, it is also important to remember that each of these populations, especially the 5HT3aR-expressing population, is heterogeneous, and therefore expresses other proteins or neuropeptides that contribute to their characterization.

In the recent years there has been a push to create a consistent nomenclature for the varying interneuronal subtypes; a 2005 conference in Petilla, Spain, was held to accomplish this task. A group of researchers known as the Petilla Interneuron Nomenclature Group (PING) convened to formulate a set of terminologies to describe the morphological, molecular, and physiological features of GABAergic cortical interneurons [16]. Morphologically

Table 1 GABAergic cortical interneuron subtypes

Marker	% Total GABA + Population	Morphology	Axonal targeting	Firing pattern	Origin
Parvalbumin (PV)	40	Basket cells	Proximal dendrites/soma	Fast-spiking	Ventral MGE
		Chandelier cells	Axonal initial segment		
Somatostatin (SST)	30	Martinotti cells	Distal dendrites	Bursting	Dorsal MGE
5HT3aR	30	VIP+: Small bipolar	Proximal dendrites	Irregular-spiking,	CGE
		VIP-: Neurogliaform cells	Other GABA neurons	Fast-adapting	
				Late spiking accommodating	

Three markers account for nearly 100 percent of the GABAergic cortical interneuron population: parvalbumin (PV), somatostatin (SST), and 5HT3a receptor (5HT3aR). Outlined in this table are percentage of total GABA-expressing neurons, morphology, axonal targeting, firing pattern, and origin based on the type of marker expressed.

speaking, cortical interneurons are described with regard to their soma, dendrites, axons, and the connections they make. Molecular features include transcription factors, neuropeptides, calcium-binding proteins, and receptors these interneurons express, among many others. Physiological characteristics include firing pattern, action potential measurements, passive or subthreshold parameters, and postsynaptic responses, to name a few [16]. The overarching goal of this conference and the resulting Petilla terminology is to create a uniform set of criteria by which interneurons can be described so as to reduce confusion between the findings by various research groups in this field. While results from the Petilla conference have shown that there are many criteria with which to define and distinguish classes of interneurons, this review will classify interneuron subtypes based on the markers they express, particularly PV, SST, or 5HT3aR, and elaborate upon each of these three groups.

Parvalbumin-expressing interneurons

The PV interneuron group represents approximately 40% of the GABAergic cortical interneuron population [8]. This population of interneurons possesses a fast-spiking pattern, and fire sustained high-frequency trains of brief action potentials [10,16,17,22,26]. Additionally, these interneurons possess the lowest input resistance and the fastest membrane time constant of all interneurons [10,16,17,22,23,27,28].

Two types of PV-interneurons make up the PV interneuron group: basket cells and chandelier cells [16,22]. Far more is understood about basket cells, which are interneurons that make synapses at the soma and proximal dendrite of target neurons, and usually have multipolar morphology [16,22]. Several studies have shown that fast-spiking basket neurons are the dominant inhibitory system in the neocortex, where they mediate the fast inhibition of target neurons, among many other functions [29-35]. As will be discussed in a later section, fast-spiking basket neurons likely play a large role in regulating the delicate balance between excitatory and inhibitory inputs in the cerebral cortex [36,37].

Much less is known about the second subgroup of PV-expressing interneurons, the chandelier cells. Unlike basket neurons, chandelier cells target the axon initial segment of pyramidal neurons [16,22]. Both basket cells and chandelier cells are fast-spiking, but they differ in electrophysiological properties, as reviewed by Woodruff *et al* [38]. Several relatively recent studies have suggested that in contrast to other interneurons, chandelier cells may be excitatory rather than inhibitory due to their depolarizing effects on membrane potential [38-40], although the functions of this subgroup have yet to be elucidated.

One research group has characterized a group of PV-expressing cells that is independent from chandelier and basket neurons in the mouse neocortex [41]. These interneurons were designated multipolar bursting cells, and differ from chandelier and basket cells in both electrophysiology and connectivity [41]. Multipolar bursting neurons possess synapses with pyramidal cells (or other multipolar bursting cells) that demonstrate a paired-pulse facilitation; in contrast, chandelier and basket cells are usually strongly depressing [41]. While this group of interneurons holds promise as a third subgroup within the PV-expressing interneuron type, further investigation is warranted, as no other research groups have characterized these neurons.

Somatostatin-expressing interneurons

The SST-expressing interneuron group is the second-largest interneuron group in the mouse neocortex, representing roughly 30% of the total cortical interneuron population [8]. SST-positive interneurons are known as Martinotti cells, and possess ascending axons that arborize layer I and establish synapses onto the dendritic tufts of pyramidal neurons [22]. Martinotti cells are found throughout cortical layers II-VI, but are most abundant in layer V [14,22,42]. These interneurons function by exhibiting a regular adapting firing pattern but also may initially fire bursts of two or more spikes on slow depolarizing humps when depolarized from hyperpolarized potentials. In contrast to PV-positive interneurons, excitatory inputs onto Martinotti cells are strongly facilitating [43-47]. More details regarding the electrophysiology and firing patterns of SST-expressing Martinotti cells can be found in a review by Rudy *et al* [8].

Results from several studies have suggested that the SST interneuron population is a heterogeneous one. Ma *et al* generated a mouse line designated as X94, whereby GFP expression (encoded for by random insertion of the GFP gene) was controlled by the GAD67 promoter; cells from this line express SST but differ from Martinotti cells in many aspects [48]. These cells were located in layers IV and V that, unlike, Martinotti cells, targeted cells from cortical layer IV [48]. X94 cells also possessed a lower input resistance relative to Martinotti cells, with spikes of a shorter duration and a stuttering firing pattern [48]. This evidence clearly suggests that there are other interneuronal subgroups within the SST subtype than just Martinotti cells. McGarry and colleagues have reported that another transgenic mouse line contains two distinct, SST-positive cells that primarily occupy layers II and III [49]. Like the X94 cells, these two populations of interneurons differ electrophysiologically than Martinotti cells, although additional research must be performed to truly determine their presence, as other

research groups have not been able to duplicate these findings [26,50,51].

It is clear that there are likely additional subpopulations of SST-expressing cortical interneurons. This is bolstered by the observed differences in firing properties, expression of molecular markers, and connectivity of different neurons within this population [8,49,50,52,53]. Additional research in this field is warranted, as the SST-expressing population of GABAergic interneurons is such a large one.

5HT3aR Interneuron group

The third group of GABAergic cortical interneurons was initially characterized in a study by Lee *et al*, and is designated as the 5HT3aR interneuron group [25]. This study utilized both *in situ* hybridization and immunohistochemistry to demonstrate the existence of a population of GABAergic interneurons in the mouse cortex that express the 5HTa3 receptor, but neither PV nor SST; this population accounts for approximately 30% of the GABAergic cortical interneuron population [25]. Due to its relatively recent discovery, this group has yet to be fully characterized, although it is evident that this population is a very heterogeneous one.

Within the 5HT3aR interneuron group are several subsets of interneurons that also express other protein or neuropeptide markers, one of them being vasoactive intestinal peptide (VIP) [22,26,54]. VIP-expressing interneurons are localized in cortical layers II and III, and while they express neither PV nor SST, Lee *et al* confirmed that this subset does indeed express the 5HTa3 receptor and accounts for approximately 40% of the 5HT3aR population [25]. VIP interneurons generally make synapses onto dendrites [25,55,56], and some have been observed to target other interneurons [57,58]. Relative to all cortical interneurons, VIP interneurons possess a very high input resistance and are among the most excitable of interneurons [25,55,56].

There are several types of VIP cortical interneurons that differ in electrophysiological properties, but in general they possess a bipolar, bitufted and multipolar morphology [22,26,54,56]. One VIP subtype in particular is commonly referred to as irregular-spiking neurons [17,25,55,56,59-61]. Irregular spiking interneurons possess a vertically oriented, descending axon that extends to deeper cortical layers, and have an irregular firing pattern that is characterized by action potentials occurring irregularly during depolarizations near threshold [17,25,55,56,59-61]. Additionally, irregular spiking cortical interneurons express the calcium-binding protein calretinin (CR) [56,61], which is a marker that some SST-positive interneurons also possess (and interestingly, also a marker that neither VIP nor SST interneurons express) [25,55,56,62].

There are several other subtypes of VIP-expressing 5HT3aR interneurons present in the cerebral cortex, which are nicely summarized by Rudy *et al* [8]. Briefly, among these are rapid-adapting [63], fast-adapting neurons [25,56] and IS2 [61], as well as a minor population of VIP-positive basket cells with regular, bursting, or irregular-spiking firing patterns [22,26,64].

60% of cortical interneurons in the 5HT3aR-expressing group do not express VIP [25]. Of this VIP-negative 5HT3aR group, nearly 80% express the interneuronal marker reelin [56]. Neurogliaform cells are a type of cortical interneuron that belongs to this category: they are also known as spiderweb cells and express neuropeptide Y (NPY), with multiple dendrites radiating from a round soma [22,65]. Neurogliaform cells are unique relative to other GABAergic cortical interneurons because they are capable of forming synaptic connections with each other *as well as* with other interneuronal types (as opposed to other interneurons that can only make synapses onto homologous neurons), thus solidifying their important role in regulating neural circuitry [66-68]. Furthermore, neurogliaform cells function by activating slow GABA_A and GABA_B receptors in order to provoke long lasting inhibitory postsynaptic potentials onto pyramidal neurons and other interneurons [65,69]. Other subtypes exist within the 5HT3aR-positive, VIP-negative group as well; see the 2010 review by Rudy *et al* [8]. While progress has certainly been made in distinguishing interneuron groups from one another, further research is definitely warranted.

Origin of GABAergic cortical interneurons

Cortical interneurons are born in the ganglionic eminences

Throughout embryogenesis, interneurons are primarily generated in a structure broadly termed the ganglionic eminence (GE) (Figure 1) [70]. The GE is a transitory brain structure located in the ventral area of the telencephalon, and is anatomically present during embryonic development. The GE becomes evident at approximately E11.5 in the developing murine system [71]. In total there are three ganglionic eminences: the medial ganglionic eminence (MGE), the caudal ganglionic eminence (CGE), and the lateral ganglionic eminence (LGE). The names of the different areas within the GE are based on their rostral-caudal location in the telencephalon. As embryonic development continues, the GEs grow and ultimately fuse, at which point they are no longer present in the mature brain. The MGE and CGE are the primary sources of cortical interneurons in the developing nervous system.

Several crucial studies during the 1980s demonstrated that contrary to the previous postulation that cortical interneurons originate in the underlying cortical ventricular zone, the majority of GABAergic interneurons are

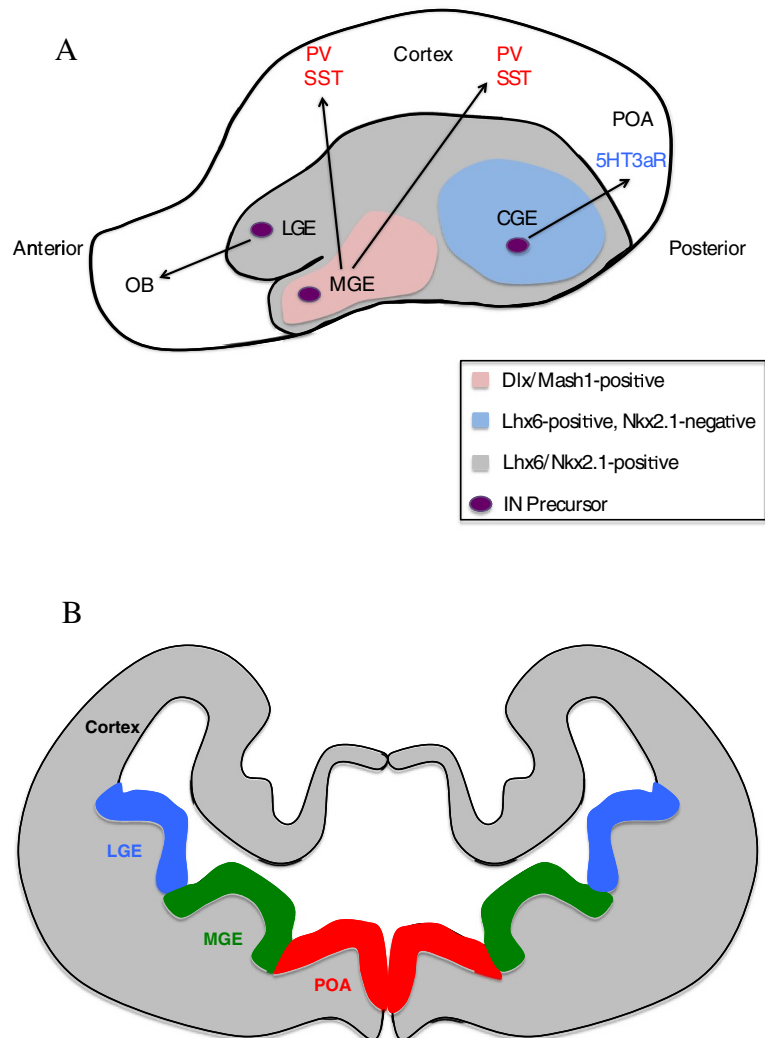


Figure 1 Origin of GABAergic Cortical Interneurons. Anatomy of the embryonic telencephalon at approximately embryonic day 13.5 (E13.5), showing the major origins of GABAergic cortical interneurons. **A** Sagittal (top) view of the telencephalon. The MGE is labeled in pink and represents Lhx6- Nkx2.1-positive areas. MGE-derived interneurons ultimately express either PV or SST in the cerebral cortex. The CGE is labeled in light blue and represents Lhx6-positive, Nkx2.1-negative areas. CGE-derived interneurons ultimately express 5HT3aR in the cortex. The gray-labeled area represents Dlx1/Mash1-expressing areas. The black dotted line represents the migratory route interneuron precursors take to the cortex. **B** Coronal view of the telencephalon. Interneuronal progenitors originating in the LGE are labeled in blue; MGE-derived progenitors are labeled in green, and interneurons from the preoptic area are labeled in red. Abbreviations: CR, calretinin; CGE, caudal ganglionic eminence; IN, interneuron; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; OB, olfactory bulb; PV, parvalbumin; POA, preoptic area; SST, somatostatin.

actually born in the ganglionic eminences. Van Eden and colleagues first showed, utilizing analysis of GABA-positive cells in the developing rodent cerebral cortex, that cells presumed to be GABAergic interneurons seemed to be migrating *away* from the subpallium [72]. This crucial observation spawned several other studies that subsequently discovered that indeed, interneurons must migrate from the subpallium to their final destinations in the cortex. To corroborate Van Eden *et al's* findings, BrdU labeling of cells in the subpallium were found to accumulate in the cerebral cortex throughout the course of neurogenesis; importantly, these BrdU labeled

cells were GABA-positive, implicating these cells as cortical interneurons [73]. Additional studies utilizing fluorescent dye labeling of neurons and an *in vitro* migratory assay with DiI showed that these interneurons display the same migratory pattern from the ganglionic eminence to the mature cerebral cortex [74,75]. Use of retroviruses to track neural cell lineage also contributed the early yet important study that excitatory and inhibitory neurons are actually generated independently from one another and do not share a common lineage [76,77]. Rakic and Lombroso later confirmed that the telencephalon consists of two separate domains: one containing

the GEs that serves as the source of inhibitory, GABAergic interneurons, and a second in which excitatory neurons are generated [78]. The formerly mentioned domain is also termed the subpallial compartment, whereas the latter is referred to as the pallial compartment. Later studies demonstrated that distinct cortical interneuron subtypes are derived from specific regions within the GEs, as will now be discussed.

Medial ganglionic eminence

The medial ganglionic eminence has long been regarded as a primary source of GABAergic cortical interneurons; it is thought to be the site of origin of approximately~50-60% of the cortical interneuron population in mice [63,79,80]. With regard to interneuron subtype, the MGE gives rise to most of the PV- and SST-expressing interneuron population [80]. To break this down, studies have demonstrated that *in vitro*, approximately 65% of MGE-derived interneurons express parvalbumin, with the remainder of the MGE-derived interneuronal population (~35%) expressing somatostatin [81,82]. *In vivo* experiments have confirmed these initial findings [63,81,83-85]. Of note, the SST-positive subset that is derived from the MGE is a heterogeneous population with regard to morphology, electrophysiology, and expression of reelin, NPY, and/or CR [50,56].

It remains to be elucidated how PV-expressing and SST-expressing GABAergic cortical interneurons are spatially segregated within the MGE itself, and to what extent this spatial segregation occurs. Flames *et al* have suggested that the MGE may actually consist of several progenitor domains, each of which may serve as an origin for unique classes of interneurons [84].

Caudal ganglionic eminence

The CGE itself is unique in that it is somewhat of a “hybrid” of the MGE and LGE: similar to the MGE, the ventral-most CGE expresses transcription factor *Nkx2.1*, and the dorsal region of the CGE expresses the transcription factor *Gsh2*, which is required for proper patterning of the LGE [86]. The caudal ganglionic eminence has been shown to be the second-greatest contributor of interneuron progenitors, producing approximately 30-40% of all cortical interneurons [87-89]. While this is a substantial percentage, the CGE proves to be a difficult place of origin to objectively study due to the challenge of consistently defining this region. Fate mapping CGE-derived interneurons and subsequently determining the exact proportion these interneurons make up within the whole cortical interneuron population has therefore proven to be quite problematic. Nery *et al* were the first to show, via *in utero* transplantation analyses, that a certain percentage of interneurons destined for the cortex indeed originates in the CGE [89].

Other studies have utilized both *in vitro* and *in vivo* experiments to confirm this initial discovery, and have further added that CGE-derived interneurons are bipolar or double-bouquet in morphology [63,79]. These interneurons express CR (not SST) and/or VIP [63,79]. Recently, Miyoshi and colleagues utilized genetic fate mapping approach to corroborate the finding that the CGE is indeed a source of cortical interneurons [56].

Findings from several studies suggest that 5HT3aR-expressing cortical interneurons are actually largely CGE-derived, as demonstrated by EGFP visualization in the *5HT3aR-BAC^{EGFP}* mouse [90-92]. Lee *et al* combined the *Nkx2.1-BAC^{cre}* and the cre-dependent red *R26R^{tdRFP}* reporter with *5HT3aR-BAC^{EGFP}* in order to exclude the MGE as a possible source of this population of interneurons [25]. Overlap of cells labeled in red and cells labeled in green was not observed, and since the *Nkx2.1-BAC^{cre}* line labels MGE-derived cortical interneurons, the MGE can thus be discounted as a source of 5HT3aR interneurons [25]. Additionally, the *Mash1-BAC^{CreER}*; *R26R^{tdRFP}* mouse line, which is CGE-specific, displayed significant and near complete overlap with 5HT3aR-expressing cells, confirming the CGE as the major source of 5HT3aR-positive cortical interneurons [25].

Embryonic preoptic area (POA)

A very recent study by Gelman *et al* has demonstrated that in addition to the ganglionic eminences, the embryonic preoptic area (POA) should also be considered a source of cortical GABAergic interneurons [93]. The POA is a region of the hypothalamus, and results from this study suggest that this area contributes approximately 10% of all GABAergic interneurons in the murine cerebral cortex.

Lateral ganglionic eminence

While it is largely agreed upon that the MGE and CGE serve as the primary source of cortical interneurons in the developing rodent nervous system, the possibility of the LGE as a third source has also been heavily debated. Results from several studies have allowed the conclusion that the LGE is at most a minor contributor of interneurons [85,87,94]. However, observations from a few studies do suggest otherwise: Sussel and colleagues reported that *Nkx2.1* mutants, in which normal MGE tissue fails to form, show a 50% reduction in cortical interneuron numbers relative to wild-type [95]. If the MGE was the origin of the majority of cortical interneurons, only a 50% reduction implies that there are clearly other areas of the brain responsible for generating interneurons. More convincing evidence has shown that at E15.5, the LGE-like region in *Nkx2.1* mutants demonstrates strong cellular migration to the developing cortex [87,88]. BrdU labeling of neural progenitors also supports the notion

of a cellular migratory route from the LGE to the cortex during embryogenesis, although only a portion of the BrdU labeled cells were also GABA-positive [87]. Additionally, Jimenez and colleagues discovered that when the MGE is removed in explants taken from rat embryos, cellular migration from the LGE to the cortex continued to be observed, suggesting that the migrating cells are *not* MGE cells merely passing through the LGE [96].

Specification of cortical interneurons

There has been a recent push in the study of GABAergic interneurons to understand and create a transcriptional network that regulates GABAergic interneuron development, migration to the cortex, and ultimately maturation to the appropriate adult phenotype. To understand the complexity of the transcriptional network and identify other candidate genes involved in the production and patterning of interneurons in the mammalian cortex, it

is most logical to separate the various transcription factors based on the three primary origins of cortical interneurons: the medial ganglionic eminence, the caudal ganglionic eminence, and the embryonic preoptic area (Figure 2).

Specification of MGE-derived GABAergic cortical interneurons

There is an extensively studied transcriptional network that plays a role in regulating proper development and specification of MGE-derived GABAergic cortical interneurons (Figure 2). While transcription factors such as the *Dlx* homeobox genes, *Lhx6*, and *Sox6* are crucial toward specification of the PV-positive and SST-positive subset of interneurons derived from the MGE, the major transcription factor that must be taken into account is *Nkx2.1* [97-102], whose expression is localized and confined within the MGE [103,104]. *Nkx2.1* expression

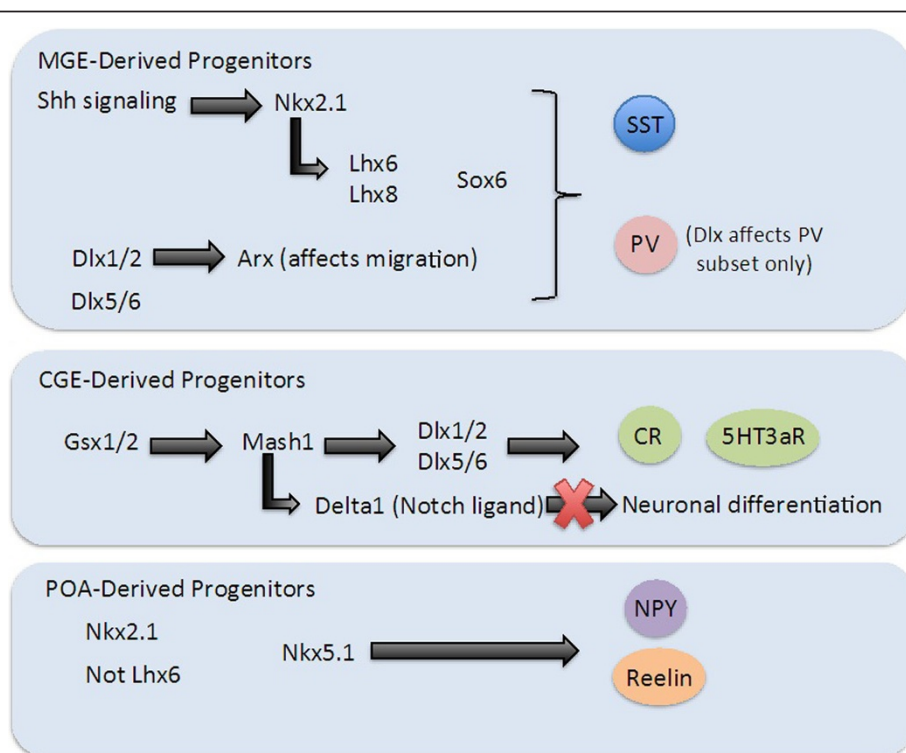


Figure 2 Specification of GABAergic Cortical Interneurons. With regard to the specification of MGE-derived interneuronal progenitors, several transcription factors play a role. Shh signaling activates *Nkx2.1*, which is the key transcription factor in specifying PV- and SST-positive interneurons from this region. *Lhx6* and *Lhx8* are transcription factors that lie downstream of *Nkx2.1*; they also aid in the specification of PV and SST interneurons (see text). *Sox6* lies downstream of both *Nkx2.1* and *Lhx6/8*. The *Dlx* homeobox family of genes play a key role in specification of CGE-derived cortical interneurons, although they also function to maintain the PV-expressing subset of MGE-derived interneurons (*Dlx5* in particular). *Arx* is a homeobox transcription factor whose expression is directly affected by *Dlx* genes; *Arx* seems to play a role in the migration of interneurons to the cortex. *Gsx1* and *Gsx2* are both required for the specification of cortical interneurons that originate in the CGE. *Mash1* is a downstream transcription factor whose absence results in reduced cortical interneuron numbers; it is required for proper function of the Notch ligand *Delta1*, which, in the Notch signaling pathway, serves to repress neuronal differentiation. The *Dlx* genes lie further downstream and play a crucial role in CGE-derived interneuron specification. The molecular mechanisms behind POA interneuron specification are unclear, although *Nkx2.1* is expressed by interneurons derived from this area. *Lhx6* is not expressed by these interneurons. *Nkx5.1* was shown to affect the specification of NPY and Reelin interneurons.

dictates the generation of both PV- and SST-expressing MGE progenitors, and maintenance of Nkx2.1 expression is activated by Sonic hedgehog (Shh) signaling [105]. More specifically, the *level* of Shh signaling within MGE interneuronal progenitor cells seems to be a determinant of what marker these neurons will express, either PV or SST: Xu *et al* have shown that high levels of Shh signaling preferentially give rise to SST-expressing interneurons, which in turn results in reduced production of PV-expressing interneurons [106]. Complete absence or conditional loss of Nkx2.1 results in reduction of PV- and SST-expressing interneurons, demonstrating its importance for MGE-derived interneuronal specification [99,100,102].

A second transcription factor whose role is crucial to MGE-derived interneuronal specification, and whose expression is also confined to the MGE, is Lhx6 [99,100,102]. Lhx6 was discovered to be a target of Nkx2.1 [107]. Mutational analyses with regard to Lhx6 have demonstrated its importance in determining the fate of both PV- and SST-positive interneurons: in the absence of Lhx6, MGE-derived neural progenitors are still able to migrate properly to the pallium, but most of these interneurons fail to express either PV or SST; interestingly, an increase in NPY expression is observed [99,100,102]. Additionally, Lhx6-deficient interneurons are unable to properly integrate into their respective cortical layers; this observation suggests that factors downstream of Lhx6 contribute to the process of cortical integration [102]. Despite these findings, the PV- and SST-expressing population of cortical interneurons is not completely eliminated in *Lhx* mutants, implying that PV-positive and SST-positive interneurons are not solely derived from the MGE [99,100,102]. Alternatively, transcription factors other than Nkx2.1 and Lhx6 may be important for the specification of MGE-derived, PV and SST interneurons; this may partially compensate for the loss of Nkx2.1 and Lhx6. Additional studies should be performed to discern other origins of these subsets of cortical interneurons.

It is also important to take into account additional transcription factors that lie downstream of both Nkx2.1 and Lhx6 so as to obtain a better understanding of the specification of MGE-derived interneurons. Recent studies have done just that, and several transcription factors are suggested to act in conjunction with either Nkx2.1 or Lhx6. One such transcription factor is Sox6. Sox6 is an HMG-box-containing transcription factor that is expressed by MGE-derived GABAergic cortical interneurons; mice lacking *Sox6* do not possess PV-positive interneurons and have significant reductions of SST-positive interneurons [97,98]. Interestingly, proper Lhx6 functioning is required for maintenance of Sox6 expression in neurons that are actively migrating toward the cortex,

but not in MGE-derived interneuronal progenitors [98,108].

Another transcription factor that works in conjunction with Lhx6 is Lhx8, which lies downstream of Nkx2.1 and is co-expressed with Lhx6 in MGE-derived neuronal progenitors [95,109]. While Lhx8-positive cells are not specified to become GABAergic cortical interneurons, mutational analyses of mice lacking both Lhx6 and Lhx8 provide some insight toward the Lhx8's role in cortical interneuron specification. *Lhx6/8* double mutants exhibit significantly reduced MGE-derived interneuron production and defective migration [108]. However, this phenotype is not observed in mice that are mutant for Lhx8 only [108].

The *Dlx* family of homeobox genes, specifically *Dlx1*, 2, 5, and 6, also play a role in the specification of MGE interneuronal progenitors, and are expressed in most subpallial neural progenitor cells [110,111]. The *Dlx* genes will be discussed more extensively in the following section, seeing as they play a larger role in the specification of CGE-derived cortical interneurons. *Dlx5* in particular is expressed in the PV-positive mature interneuronal subset [101]. Wang *et al* utilized transplantation experiments to demonstrate that loss of *Dlx5* or both *Dlx5* and 6 in mice manifests as a significant reduction in PV-expressing interneuron numbers, alteration in dendritic morphology, and epilepsy [101].

Specification of CGE-derived GABAergic cortical interneurons

As was previously mentioned, approximately 30% of GABAergic cortical interneurons originate from the CGE. While it was previously thought that the gene expression profile of the CGE was merely an extension of that of the LGE [80,84,110,111], more recent work has suggested that the CGE possesses a unique transcriptional network of its own, making it a bona fide source of cortical interneurons, separate from any other source [111-113].

Of great importance in the specification of CGE-derived interneurons are the homeobox transcription factors known as *Gsx1* and *Gsx2*, both of which are required for the specification of interneuronal progenitors in this region [106]. Xu *et al* have shown through conditional loss and gain of *Gsx2* function that *Gsx2* has a hand in the generation of CR-expressing bipolar cortical interneurons [106].

Investigation of genes downstream of *Gsx1* and *Gsx2* resulted in the discovery of *Mash1*, a basic-helix-loop-helix transcription factor also involved in the interneuron specification process. *Mash1* mutants demonstrate significant neuronal loss early in development, as well as reduced cortical interneuron numbers [114]. *Mash1* was found to be required to express the Notch

ligand Delta1, whose function within the Notch signaling pathway serves to repress neuronal differentiation [114-116]. Thus, loss of Mash1 results in the premature differentiation of cells within the subventricular zone (SVZ) expressing the Dlx genes [114,115].

As was mentioned in the previous section, the Dlx family of genes are key players in the specification of CGE-derived interneurons. The Dlx genes are located downstream of both Gsx2 and Mash1 [117-120]. With regard to interneuron specification, four Dlx genes – Dlx1, Dlx2, Dlx5, and Dlx6 – are expressed in the developing forebrain, and are central to the specification process [121]. Temporal expression of these four genes follows a Dlx2, Dlx1, Dlx5, and Dlx6 sequence [122,123]. Gsx2 and Mash1 neural progenitor cells have been shown to simultaneously express Dlx1/2 [110,115,124]. Loss of Dlx1/2 function results in the failure of Dlx5/6 expression [110,115,124]. Importantly, these *Dlx1/2* double mutants exhibit incorrect specification of the LGE/CGE, with inappropriate expression of ventral cortex markers [110,111]. A detailed analysis of the transcriptional network within the *Dlx1/2* double mutants has resulted in the investigation of almost 100 transcription factors that may play a role, both dependently and independently of the Dlx genes, in CGE-derived cortical interneuron specification [110,111]. An outline of several candidate transcription factors is nicely reviewed by Gelman *et al* [125].

Specification of embryonic POA-derived GABAergic cortical interneurons

While the embryonic POA is similar to the MGE in that it expresses the transcription factor Nkx2.1, many POA cells do not express the transcription factor Lhx6 [84]. A study by Gelman *et al* has elegantly showed via fate mapping with a Cre line expressed from transcription factor Nkx5.1 that the POA serves as a source of GABAergic interneurons expressing NPY and/or reelin [126]. Interestingly, none of the other calcium-binding proteins, such as PV, SST, CR or VIP, were expressed in these POA-derived cortical interneurons [126]. It is possible that this population of NPY- and/or reelin-expressing cells may stem from both the CGE and the POA, but additional investigations should be carried out to confirm these speculations. Studies should also be performed to discover the transcription factors and the roles they play in specification of POA-derived cells.

Influence of non-autonomous cell factors on GABAergic interneuron identity

Non-cell autonomous factors and the role they possess in conferring GABAergic cortical interneuron identity must also be taken into account. Lodato *et al* have shown that certain excitatory neurons are able to control

the distribution of GABAergic interneurons within the cortex [127]. Deletion of subcerebral projection neurons and subsequent replacement with callosal projection neurons results in the abnormal lamination of cortical interneurons, along with abnormal GABAergic inhibition [127]. Certain factors may also affect particular subsets of interneurons. Orthodenticle homeobox 2 (Otx2) is a homeoprotein whose expression is required to both open and close a critical period of neural plasticity in the visual cortex of PV-expressing interneurons in mice [128,129]. It remains to be clarified whether other factors affect the specification of other interneuronal subsets in a non-cell-autonomous manner.

Differences in cortical interneuron origin and specification between rodents and primates

Studies in both primates and humans have determined that differences do exist between rodents and primates with regard to the origins and migratory routes of GABAergic interneurons. This will be briefly discussed, but for more detail refer to the review by Petanjek *et al* [130].

A few studies have shed light on the fact that the majority of primate GABAergic interneurons, in contrast to rodent cortical interneurons, may not actually originate solely in the GEs [131,132]. In fact, cortical interneurons in primates have also been shown to have their origins in the proliferative zones of the dorsal telencephalon [131,133-135]. Letinic and colleagues utilized retroviral labeling in organotypic slice cultures to demonstrate that there are two independent lineages of cortical interneurons in the fetal human forebrain [131]. However, whereas it was previously mentioned that the GE is the primary source of rodent interneurons, this study demonstrated that in a Dlx1/2-positive, Mash1-negative lineage of cortical interneurons in the fetal human forebrain, only 35% of the interneuron population in the proliferative ventricular zone and subventricular zone originates from the GE [131]. To support these findings, the same results were reported in the macaque monkey (*Macaca rhesus*, *Macaca fascicularis*) [134].

In addition to differing locations of interneuron origin between species, it is also important to realize that the transcription factors expressed by rodent interneurons and interneuronal precursors may not necessarily overlap with the transcriptional network that governs the development of human GABAergic interneurons. Research to better characterize human interneurons is underway. One such study investigated the expression of transcription factors Nkx2.1, Dlx1/2, Lhx6 and Mash1 in human fetal forebrains during the first half of gestation [136]. All transcription factors were expressed in both the GEs and the ventricular/subventricular zones, and expression was maintained up to 20 gestational weeks. Collectively the data suggest that cortical interneuron populations

exist in multiple locations, both ventrally (as described in rodents) and dorsally in the VZ/SVZ [136]. The possibilities that the production of interneurons may follow a different time-course based on origin, or that different areas of production may contribute to the heterogeneity of the cortical interneuron population, should also be taken into account. Findings from a previous study utilizing cryosections and *in vitro* data also support the existence of multiple sources of cortical interneuron progenitors in the developing human brain [137]. The greater complexity characterizing progenitor populations most likely reflects the higher brain functioning characteristic of humans compared to other organisms.

Migration to the cerebral cortex

Once generated and specified in their respective origins within the ventral telencephalon, GABAergic cortical interneurons face the task of migrating to their ultimate destinations within the cerebral cortex [138]. It has been observed that GABAergic interneurons first begin a tangential route of migration at E12.5 in rodents, a time point that also happens to correspond with the early stages of neurogenesis [80,139,140]. At E12.5 in the mouse, an early population of interneurons reaches the cortex, migrating at the level of the preplate, while a second, larger proportion of interneurons migrates through the intermediate zone [139,141,142] (IZ). At a later time point of corticogenesis (E14-15), three migratory routes, called tangential migratory streams, are observed in the cortex: the marginal zone (MZ), subplate (SP), and the lower intermediate zone (IZ)/subventricular zone (SVZ) [87,142,143]. Migration is, for the most part, complete by birth, with exception of the RMS; the migration route that neurons in the RMS take to reach the olfactory bulb will not be discussed in this review. Like the processes of interneuron generation and specification, migration from the subpallial origins to the cerebral cortex is a complicated undertaking, involving the activity of various motogens, chemotactic factors, transcription factors, as well as neurotransmitters [144,145]. Each will now be briefly elaborated upon.

Motogens

Motogens are secreted factors that influence newly specified interneurons in their ability to migrate [141]. One such example of a motogen is Hepatocyte Growth Factor (HGF), which was discovered to regulate the migratory abilities of subpallial-derived cortical interneurons. HGF has been found to be required for interneuron migration, and encourages interneurons to migrate away from their sites of origin [146]. *mu*-PAR nulls (*mu*-PAR is a required component of the HGF pathway) demonstrate significant deficits in interneuron migration from the GE to the cortex [146,147]. In their 2003 study Powell

et al also presented the finding that HGF loss of function has an effect on some, but not all, subsets of interneurons [147].

In addition to HGF, the neurotrophin family of genes serve as motogens for migratory cortical interneurons. Various developmental studies have demonstrated that the cortex is positive for neurotrophin expression [148-151], and that the neurotrophin receptors TrkB and TrkC (tyrosine kinase receptors) are expressed by interneurons [152,153]. One member of the neurotrophins is known as Brain-Derived Neurotrophic Factor (BDNF) [154]. Loss of proper BDNF signaling has been shown to result in a downregulation of cortical interneuron markers [155-157].

Lastly, the neurotrophin glial cell line-derived neurotrophic factor (GDNF), which is expressed in cortical interneuron migratory routes [158], acts as a motogen for GABAergic interneurons. A 2002 study demonstrated that members of the glial derived neurotrophic factor family bind to specific types of receptors known as GFR α 1-4 [159]. Loss of GFR α 1 in mice manifests in improper migration from the MGE and an inability to reach the cortex compared to wild type [159]. A more recent study proposed, using *GFR α 1* null mice, that GFR α 1 signaling may serve to guide the development of a population of PV-expressing interneurons destined for the cortex [160].

Chemorepellants

Whereas motogens affect the ability of interneurons to migrate, chemorepellants and chemoattractants serve to provide migratory cells with the information about which *direction* to migrate. Conceivably, chemorepellants serve as a type of guidance cue that will direct migrating interneurons *away* from a certain area. Wichterle and colleagues have shown through cell culture studies that in the telencephalon, the GEs exert a repulsive force on interneurons, allowing the postulation that chemorepellants are primarily expressed in the subpallium [161].

One such example of a chemorepellant is the family of ligands known as the semaphorins (Sema) [162]. The semaphorins are able to exert their repulsive forces upon interneurons because interneurons express neuropilins (Nrp1 and Nrp2) and plexin coreceptors, both of which recognize the semaphorins that are expressed within the LGE [162]. A 2003 study demonstrated that two semaphorins in particular, Sema 3A and 3E, regulate the migratory capacity of GABAergic interneurons toward the cortex [163]. Additionally, Zimmer *et al* have shown that the chondroitin sulfate proteoglycan known as chondroitin-4-sulfate acts in concert with Sema 3A to repel migrating cortical interneurons within the LGE,

further defining the boundary of the migratory route of interneurons [164].

Slit1 is a second chemorepellant whose expression is found in the ventricular zone and the subventricular zone of the GEs, as well as the embryonic POA [165-168]. Slit1 is able to exert its chemorepulsive effects due to the expression of its receptor, Roundabout (Robo1), on migrating cortical interneurons [165-168]. Analysis of the expression patterns of both Slit and Robo proteins are indicative that interneurons are repelled from their sites of origin in the GEs [169-172].

The last type of chemorepellant that will be discussed is Ephrin and its Ephrin receptor tyrosine kinases, which are repulsive cues for MGE-derived interneurons, as demonstrated both *in vitro* and *in vivo* [173,174]. Ephrin A5 in particular is expressed in the ventricular zone of the GE, whereas its receptor, EphA4, is expressed by calbindin-expressing MGE-derived interneurons [173]. Interestingly, siRNA knockdown of the EphA4 receptor resulted in the inability of ephrin A3 to exert its repulsive effects upon interneurons within the MGE [174].

Chemoattractants

While inhibitory signals exhibited by chemorepellants are undoubtedly essential in defining the tangential migratory route cortical interneurons undertake, chemoattractive factors are just as important in aiding the migration process. Whereas chemorepellants are localized in the subpallium, chemoattractive molecules are present in the pallium. One such chemoattractant is the chemokine CXCL12, which carries out signaling through its receptors CXCR4 and CXCR7. Interneurons derived from the MGE are found to express both of these receptors [175]. The expression pattern of CXCL12 varies throughout development: its expression remains high in the marginal zone and subventricular zone until time point E14.5, but during later stages of corticogenesis its expression is significantly reduced in the subventricular zone (expression in the marginal zone remains unchanged) [176]. Li *et al* have described CXCL12's function: it exerts its attractant force on MGE-derived interneurons, guiding them to the previously mentioned tangential migratory streams; these cells remain there until intracortical migrations are received [177].

The previously mentioned gene NRG1, which is a susceptibility gene in schizophrenia, also serves as a chemoattractant in the interneuronal migration process. NRG1 was discovered to be essential for interneurons to leave the MGE, traverse through the LGE and into the cortical wall [178]. Flames *et al* more specifically demonstrated that different isoforms of NRG1 possess unique migratory roles [178]. When interneurons are exposed to an exogenous source of NRG1, neurons extend new neurites in the direction of the source [179], suggesting

endogenous NRG1 present during development serves the same purpose. Reduction or loss of NRG1 in the forebrain prevents GABAergic interneurons from leaving the MGE [178]. Research has also been performed on the NRG receptor ErbB4, which is expressed on migratory interneurons [180]. In mature, conditional *ErbB4* mutants, a reduced number of cortical interneurons is observed [178].

Transcription factors

While both motogenic and chemotactic factors have been recognized as classic influences on interneuron migration to the cortex, relatively recent studies have cited the roles of transcription factors in migration. One such transcription factor is the LIM homeodomain transcription factor Lhx6. MGE-derived interneurons that are actively migrating to the cerebral cortex express Lhx6 [143,181]. Moreover, Lhx6 is also expressed in most PV- and SST-positive cortical interneurons in mice [83]. Utilization of *Lhx6* knockdown using RNAi hindered the migration of cortical interneurons, lending strong support to the postulation that the Lhx6 gene somehow plays a role in migratory capability of interneurons [182]. Recent studies have also shown that Lhx6 may operate by promoting the expression of receptors such as ErbB4 (receptor for NRG1), CXCR4 and CXCR7 (receptors for chemokine CXCL12) [102].

While Nkx2.1 is known to be a key transcription factor for the specification of MGE-derived GABAergic interneurons [99,107], it is also suggested to play a role in migration of these interneurons toward the cortex. Nobrega-Pereira and colleagues have shown that proper migration of MGE-derived interneurons to the cortex requires downregulation of Nkx2.1 expression [183]. Further confirming this observation is the finding that ectopic expression of Nkx2.1 in migrating MGE interneuron progenitors results in the inability of Sema3A and Sema3F to exert their repulsive effects [183]. Additional studies should be performed to further elucidate the mechanism by which Nkx2.1 acts in the migration process.

The Dlx family of homeobox genes is involved in migration of interneurons to the cortex [124,184]. More specifically, Dlx1 and Dlx2 may repress the genes PAK3 and MAP2 in order to restrain neurite outgrowth [184]. PAK3 is a gene involved in regulating and maintaining cytoskeletal dynamics, and whose expression is low in migrating interneurons; *Dlx1/2* mutants show aberrant, increased PAK3 expression, with an inability to migrate to the cortex [184]. Reducing these aberrant levels of PAK3 restores the ability of these interneurons to migrate tangentially to the cortex [184]. Additionally, results from another study have shown that Dlx1 and Dlx2 may play a role in repression of Nrp2, the receptor

for semaphorins [107], suggesting the *Dlx* genes have multiple modes of action to regulate migration.

Lastly, the homeobox transcription factor known as *Arx* is located downstream of the *Dlx* genes, and *Dlx* function has been shown to directly affect *Arx* expression: *Dlx1/2* double mutants show a down-regulation of *Arx* expression [185]. In the absence of *Arx*, MGE-derived interneuron progenitors are unable to migrate toward the cortex, resulting in reduced numbers of interneurons in the cortex [186,187]. Additionally, mice possessing conditional *Arx* mutations also have reduced cortical interneuron numbers and have epilepsy [188], demonstrating the importance of this transcription factor in interneuron specification within the MGE.

Neurotransmitters

While their role in migration toward the cerebral cortex may seem unconventional, evidence is emerging that neurotransmitters do indeed aid GABAergic interneurons in their movement toward the cortex. The two major neurotransmitters that will be elaborated upon are GABA and dopamine. Migrating interneurons express the GABA_A and GABA_B, two main receptors for GABA [189-191]. Reducing GABA activity via neutralizing antibodies results in an accumulation of interneurons at the corticostriatal junction, and prevents their entry into the cortical wall [189]. A more recent study also showed that migrating interneurons have a higher affinity for GABA, relative to non-migrating interneurons that are localized in the MGE [191].

Like the GABA receptors, migrating cortical interneurons also express D₁ and D₂, which are the receptors for dopamine [192,193]. D₁ and D₂ receptors, when activated, are known to have opposite functions from one another [192]. Generation of individual knockouts further confirms the inverse function of these receptors: *D1* nulls possess a decreased ability to migrate, allowing the conclusion that D₁ normally functions to promote cortical interneuron migration. On the other hand, *D2* knockouts possess increased migratory capability, suggesting that its role is to inhibit migration of interneurons [192]. It is clear that additional studies must be performed to further elucidate the roles that neurotransmitters such as GABA and dopamine play in the migratory process, as the mechanisms by which they operate are still unknown.

Interestingly enough, while there are clearly many factors that influence the migratory route of GABAergic interneurons to the cortex, Sahara *et al* have demonstrated that the proportion of cortical interneurons, relative to excitatory neurons, stays the same from the beginning of neurogenesis until adulthood [194]. Data from this study suggests that approximately 1 in 5 interneurons migrating tangentially toward the cerebral

cortex in mice are GAD67-positive, indicating they are inhibitory GABAergic interneurons [194].

It is important to note that once GABAergic interneurons successfully reach the cortex, a process referred to as “intracortical migration” must be carried out, whereby interneurons undergo different migratory routes within the cortex to reach their ultimate destinations. This process, as well as interneuron lamination, is beyond the scope of this review and will not be discussed. For a detailed discussion of these processes, refer to the review by Faux *et al* [195].

To date, the molecular mechanisms that regulate the termination of interneuron migration in the cortex are largely unknown. However, Bortone and Polleux have shown that the potassium-chloride cotransporter KCC2 plays an integral role in terminating interneuron migration [196]. When interneurons are actively migrating, ambient GABA and glutamate initially stimulate the motility through activation of GABA_A and AMPA/NMDA receptors. However, once interneurons reach the cortex, upregulation of KCC2 results in a hyperpolarization of membrane potential, thereby serving as a stop signal that interneurons are able to sense [196]. Further investigations should be performed to further elucidate the mechanisms underlying termination of migration.

GABAergic dysfunction and neuropsychiatric disorders

As can be imagined, there is a delicate balance between excitatory and inhibitory inputs that must be carefully maintained with regard to cortical circuits. It is thus conceivable that a number of neuropsychiatric disorders may stem from an alteration or disruption in the balance of excitation vs. inhibition in the cortical circuitry. Additionally, a number of studies have shown that the lack of proper cortical interneuron specification may play a significant role in the development of neurological disorders. This may entail a deviation from either the course of interneuron development, or aberrant transcriptional regulation in the cortical interneuron specification process. Schizophrenia, a severe mental illness, will be utilized as an example of cortical circuitry gone awry. Understanding the effects of both GABAergic neurotransmission, alterations in inhibitory cortical circuits, and how they may be responsible for the clinical features observed in schizophrenia are paramount to this field of research.

Schizophrenia is a mental disorder that is characterized by a variety of symptoms, with cognitive deficits being recognized as both the core and enduring features of this illness [197]. Hallmark features of schizophrenia include auditory hallucinations, paranoid or bizarre delusions, disorganized speech and thinking, and social withdrawal. Additionally, working memory and attention are characteristically impaired in schizophrenic patients

[197]. Onset of symptoms occurs in young adulthood. While environmental influences are widely suggested to play a contributory role in development of this illness, genetics and familial predisposition play a very significant role: a meta-analytic review on cognitive performance between relatives of schizophrenic patients and healthy control subjects demonstrated that the same cognitive deficits found in patients with schizophrenia are also found in non-affected relatives [198].

It was initially postulated that schizophrenic patients demonstrating GABAergic interneuron deficits had a significantly reduced number of interneurons relative to non-schizophrenic subjects [199]. While this may still hold true, this field of research is seeing a gradual shift toward the belief that GABAergic dysfunction in schizophrenia may be a result of disruption or imbalance of inhibitory neurocircuitry, rather than a sheer reduction in neuron number [9].

A common trend observed in independently performed studies has shown that only certain interneuronal subtypes seem to be affected in schizophrenia. Schizophrenic patients showed a marked reduction of GAD67 mRNA levels in PV-expressing interneurons of the prefrontal cortex, while GAD67 mRNA levels did not differ in CR-positive interneurons of schizophrenics and healthy controls [200,201]. A number of studies have postulated that the population of PV-expressing GABAergic interneurons in people with schizophrenia may not be functioning at full capacity, and this may contribute to the cognitive deficits observed with this illness. An inability of PV-positive interneurons to function properly may result in disruption of inhibitory input onto pyramidal neurons, and impairment of synchronization in the gamma range [202,203]. This theory is corroborated by the observation that schizophrenic patients, when asked to do working memory tasks, display abnormal gamma frequency oscillations in the prefrontal cortex relative to healthy, non-schizophrenic subjects [204-207].

With the knowledge that the parvalbumin-expressing subtype of GABAergic interneurons in particular is largely affected in schizophrenia, it is sensible to seek out factors that play a role in the development of the PV-positive subtype. One such protein is the receptor tyrosine protein kinase ErbB4, which is a receptor for the trophic factor Neuregulin 1 (NRG1). Research was initially focused on NRG1, which was first identified as a susceptibility gene for schizophrenia in an Icelandic population, and then confirmed as a susceptibility gene in an unrelated Scottish population [208]. NRG1 plays a variety of roles during neural development, including modulation of neuronal migration, synaptogenesis, gliogenesis, myelination, and neurotransmission [209]. In particular, NRG1 stimulates GABA release from

interneurons, which inhibits pyramidal cells in the prefrontal cortex [210]. It can be imagined that disruption of NRG1 function can have greatly affect the balance between excitatory and inhibitory input. The possible mechanisms by which altered function of NRG1 and its receptor ErbB4 contribute to schizophrenia have been reviewed by Mei and Xiong [211].

With regard to schizophrenia, attention is shifted to NRG1's receptor, ErbB4: this is largely due to the fact that ErbB4 is a receptor preferentially expressed by interneurons migrating tangentially from the ventral to the dorsal telencephalon [180] and by both embryonic and postnatal PV-expressing interneurons with chandelier and basket cell morphology [212,213]. Importantly, *in vitro* and *in vivo* gain- and loss-of-function experiments prove that ErbB4 promotes the formation of axo-axonic inhibitory synapses over pyramidal neurons in a cell-autonomous manner [212]. More evidence suggests that ErbB4 exerts its effects on PV-positive interneurons: PV-*ErbB4*^{-/-} mice exhibit a schizophrenia-like phenotype much like that of *NRG1*-null and *ErbB4*-null mutants; these mice are hyperactive and show impaired working memory [210]. Deletion of ErbB4 in PV-positive interneurons in these mice also results in fewer synapses being made onto pyramidal neurons [210], thus demonstrating the importance of this transmembrane receptor (as well as Neuregulin 1) in affecting the proper development of at least one subset of GABAergic interneurons.

An additional gene whose disruption predisposes to schizophrenia was first identified in 2000 in a large Scottish family, and named Disrupted-In-Schizophrenia 1 (*DISC1*) [214]. Utilization of *DISC1* genetically engineered mice served as a model for mental illnesses such as schizophrenia, and analysis of these mice showed that dominant-negative *DISC1* mice display behavioral abnormalities and a depression-like deficit [215]. Hikida *et al* also importantly show that *DISC1* plays a role in the development of PV-expressing cortical interneurons: dominant-negative *DISC1* mice possess pyramidal cells with reduced PV immunoreactivity in the cortex [215]. Another study using knockdown of *DISC1* has generated the same results regarding decreased PV immunoreactivity [216]. *DISC1* knockdown in prefrontal cortex pyramidal neurons during the pre- and perinatal stages results in abnormal postnatal mesocortical dopaminergic maturation, as well as behavioral abnormalities linked to disrupted cortical circuitry during adulthood [216]. A recent review by Porteus *et al* offers a detailed summary of the progress that several research groups have made in understanding the role *DISC1* protein plays in neurosignaling and neurodevelopment since its initial discovery [217]. While the specific role that *DISC1* plays in maintaining cortical interneuron development has yet to be elucidated, it is

clear that it is needed to allow proper development of PV-expressing interneurons.

Dysbindin is another schizophrenia susceptibility gene, which plays a role in dopamine receptor trafficking [218]. Multipoint linkage analysis in an Irish population showing genetic variation in the 6p22.3 gene DTNBP1 (dystrobrevin-binding protein 1, the human ortholog of dysbindin) was found to be associated with schizophrenia, thereby spurring a number of investigations of this gene [219]. Findings from a subsequent study indicated that reduction in DTNBP1, frequently observed in schizophrenia, was linked to glutamatergic alterations in intrinsic hippocampal formation connections [220]. Another study corroborated the finding of dysbindin reduction: schizophrenic patients show decreased levels of dysbindin mRNA in multiple layers of the dorsolateral prefrontal cortex relative to healthy subjects [221]. Importantly, *Dtnbp1*-knockout mice possess cortical and striatal PV-expressing, fast-spiking interneurons with a significant reduction in excitability [218]. This therefore results in decreased inhibitory input to pyramidal neurons in layer V of the prefrontal cortex [218].

While it was initially believed that DISC1 and dysbindin both served as independent susceptibility genes to schizophrenia, a 2011 study investigated whether both DISC1 and dysbindin proteins converged onto a common pathway. Co-aggregation of the two proteins in postmortem brains of patients with mental disease, but not that of healthy patients, was observed, demonstrating that DISC1 and dysbindin do indeed directly interact with each other on a molecular level [222]. It is clear that there are many genetic components implicated in the development of schizophrenia, each of which serve to somehow tip the excitatory-inhibitory balance within the neural circuitry. It is also clear how important of a role GABAergic interneurons play in maintaining this balance. It is important, however, to remember that this is merely the tip of the iceberg – there are many other neuropsychiatric disorders such as epilepsy, autism spectrum disorders, and various intellectual disabilities, many of which are reviewed extensively in a review by the Marin research group [9], that possess some sort of alteration or disruption of balance within the developing nervous system.

Summary

The population of GABAergic interneurons in the cerebral cortex is a clearly a diverse one, comprised of many different subtypes and functions. While each interneuronal subtype is characteristically unique with regard to function, electrophysiology, immunohistochemical profile, axonal targeting and firing pattern, the overlapping features between particular subtypes makes the method of categorizing each subset of GABAergic interneurons

quite challenging. Most recent undertakings in the study of cortical interneurons have been concerned with constructing the transcriptional network of genes that are involved in the specification of these interneurons, in pre-migratory stages within the subpallium as well as during the migratory phase of interneuron precursors. Additional investigations must be performed in order to understand the specific transcription factors and signaling pathways involved in the specification of interneuronal fate. More specifically, studies must be undertaken to understand how the 5HT3aR-expressing interneuron lineage is specified before migration of these interneuronal progenitors to the cerebral cortex, as it is such a large proportion of the interneuron population. Additionally, not enough is known about the differential specification of PV- and SST-positive subgroups within the Nkx2.1-expressing lineage of interneuronal progenitors. The emergence of cutting edge genetic technologies should be utilized to target specific interneuronal subtypes and understand what key players will determine their fate and function. On a broader level, investigations must also be carried out to understand the differences in origin and specification of rodent vs. human GABAergic interneurons. Understanding the mechanisms behind human GABAergic interneuron specification may enable a large step forward in treating various neurological disorders linked to alterations/dysfunctions in interneuron populations. An increased understanding of the mechanism(s) by which GABAergic interneurons are able to integrate properly and seamlessly into the cortex after migration is complete is also warranted.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

Both CK and WL contributed to writing of the manuscript. All authors read and approved the final manuscript.

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