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Generation of interneuron diversity in the mouse cerebral cortex

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Abstract

Gamma-aminobutyric acid-containing (GABAergic) interneurons play an important role in the function of the cerebral cortex. Through mostly inhibitory mechanisms, interneurons control hyperexcitability, and synchronize and shape the spatiotemporal dynamics of cortical activity underlying various brain functions. Their influence on cortical function is remarkably diverse, a reflection of the large variety of interneuronal populations that exist in the mammalian cortex. Research over the past few years has rapidly transformed our understanding of their mechanisms underlying the generation of different classes of interneurons. In this review, we summarize recent progress on this process, progress which holds the promise of providing a rational framework for their classification, as well as means to understand their role in cortical processing.

Introduction

The cerebral cortex consists of two main classes of neurons, pyramidal cells and interneurons, which respectively use glutamate and γ-aminobutyric acid (GABA) as main neurotransmitters. In the adult cortex, pyramidal cells are excitatory while GABA-containing (GABAergic) interneurons are typically inhibitory. Increasing evidence suggests that disruption of the excitatory–inhibitory balance maintained by pyramidal cells and interneurons is linked to the etiology of several neurological disorders (Rubenstein & Merzenich, 2003; Dani *et al.*, 2005; Levitt, 2005; Lewis *et al.*, 2005). Conversely, genes associated with such disorders have been shown to influence the development of cortical interneurons (Erbel-Sieler *et al.*, 2004; Flames *et al.*, 2007; Fazzari *et al.*, 2010; Wen *et al.*, 2010). Thus, disruption of GABAergic inputs to pyramidal cells might represent a common pathophysiological mechanism underlying multiple neuropsychiatric conditions.

Interneurons comprise ∼20–30% of the cortical neuronal population and are locally projecting cells that control and synchronize the output of pyramidal neurons. Interestingly, the influence of GABAergic interneurons on pyramidal cells is largely dependent on the subcellular location of their inputs, which varies among different interneuron subtypes. Despite years of research, however, it is still unclear how many different types of cortical interneurons actually exist. This is due, among other reasons, to the difficulties that are inherent to the task of defining what a cortical interneuron is (Ascoli *et al.*, 2008). Despite some reservations, today it is largely accepted that distinct types of interneurons exist; they are defined by a constellation of neurochemical, anatomical and electrophysiological characteristics. Based on this definition, several major classes of interneurons have been identified, although many other types of interneurons are left out of this major classification. This is due, at least in part, to activity-dependent changes in the levels of some neurochemical markers, cross-species differences and the lack of comprehensive analyses of the heterogeneous characteristics of cortical interneurons.

Many years have passed since the initial observations that led to the discovery of the origin of cortical interneurons in the subpallium of rodents (Porteus *et al.*, 1994; De Carlos *et al.*, 1996; Anderson *et al.*, 1997; Tamamaki *et al.*, 1997). Since then, it is becoming clear that understanding the development of cortical GABAergic interneurons may help to shed light on the problem of their diversity. The early description of mice lacking the transcription factor Nkx2-1, for example, made it evident that specific genes control the development of distinct classes of interneurons (Sussel *et al.*, 1999). More recently, analysis of the function of other transcription factors has revealed that each of the properties that contribute to the definition of specific classes of interneurons is controlled by a defined set of genes. For example, acquisition of the fast-spiking characteristics and expression of the calcium-binding protein parvalbumin (PV) seems to be defined by the concerted action of *Nkx2-1*, *Dlx5, Dlx6*, *Lhx6* and *Sox6*, five genes expressed by specific cohorts of cortical interneurons (Liodis *et al.*, 2007; Butt *et al.*, 2008; Zhao *et al.*, 2008; Azim *et al.*, 2009; Batista-Brito *et al.*, 2009; Wang *et al.*, 2010). From this perspective, it is tempting to speculate that deciphering the origin of cortical interneurons may help us to generate a cladistic classification of these cells.

Although it has been obvious for more than a century that many different classes of interneurons exists, for the purposes of this review we have adopted a conservative grouping of GABAergic interneurons into four major classes: (1) fast-spiking, PV-containing basket and chandelier cells; (2) somatostatin (SST)-containing interneurons, which typically display intrinsic burst spiking or adapting

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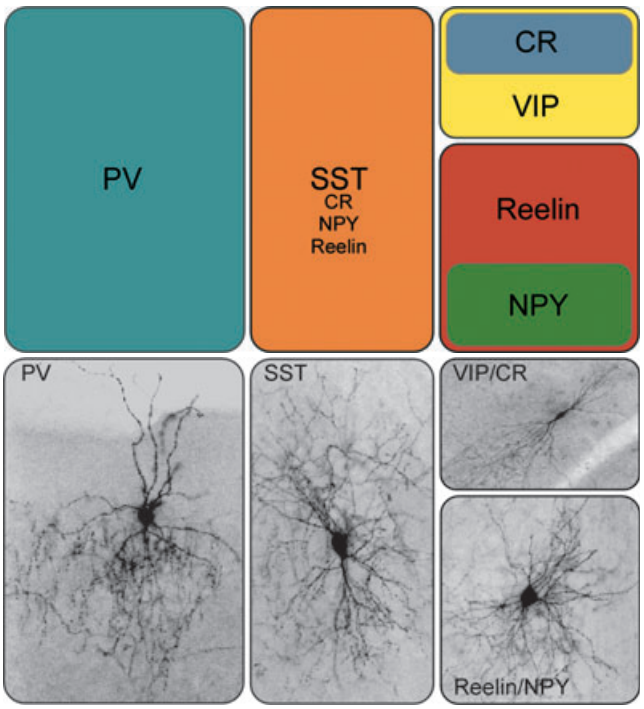

FIG. 1. Four major groups of cortical interneurons can be distinguished in the mouse neocortex. (1) Fast-spiking, PV-containing basket and chandelier cells. To date there are no other markers that subdivide this large population of interneurons. (2) SST-containing interneurons, which typically display intrinsic-burst spiking or adapting non-fast-spiking electrophysiological profiles. Many of these neurons have the morphology of Martinotti cells. This population of SST-containing cells is very heterogeneous and includes several classes of interneurons that may also express reelin, CR and/or NPY. (3) Rapidly adapting interneurons with bipolar or double-bouquet morphologies. These cells very frequently express VIP, and many of them also contain CR. (4) Rapidly adapting interneurons with multipolar morphologies. Most of these cells express reelin but not SST, and many also express NPY.

non-fast-spiking electrophysiological profiles and many of which have long axons that extend into layer I; (3) rapidly adapting interneurons with bipolar or double-bouquet morphologies, which frequently express calretinin (CR) and/or vasointestinal peptide (VIP); and (4) rapidly adapting interneurons with multipolar morphologies and that express neuropeptide Y (NPY) and/or reelin, but not SST (Fig. 1). Recent progress on the origin of interneurons suggests that these different classes of cells originate from three main sources in the developing subpallium: the medial ganglionic eminence (MGE), the caudal ganglionic eminence (CGE) and the preoptic area (POA), and reach the cortex following different migratory routes (Fig. 2). Here we review our current view on this process, which is largely based on studies in the mouse. The origin of some populations of GABAergic interneurons in the developing pallium of monkeys and human embryos will not be the addressed in this article, as this topic has recently been reviewed elsewhere (Jones, 2009). Similarly, we will not review here the literature concerning the contribution of LGE-derived interneurons to the olfactory bulb.

The MGE is the main origin of cortical interneurons

Converging evidence indicates that the MGE is the origin of ~50–60% of the population of cortical interneurons in the mouse. In particular, the MGE gives rise to the large majority of PV-containing and SST-containing interneurons (Fig. 3). This later group is rather

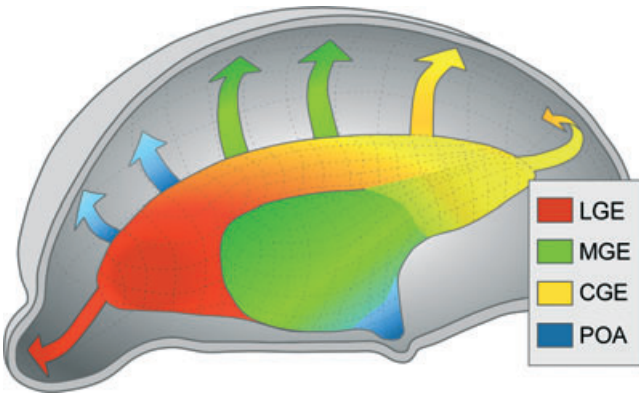

FIG. 2. Cortical interneurons are born in the subpallium and migrate tangentially to the cortex. The schema represents an E13.5 embryo brain hemisection. The arrows show representative migratory routes. POA-derived interneurons have a bias to invade the cortex through its rostral region, while CGE-derived interneurons primarily reach the cortex by its caudal pole. For simplicity, the septum and the thalamus are not depicted in the schema.

heterogeneous, including cells that also contain reelin, NPY and/or CR and have distinct electrophysiological properties and morphologies (Xu *et al.*, 2006; Miyoshi *et al.*, 2010). Both PV- and SST-containing interneurons greatly depend on Nkx2-1 for their normal generation. The analysis of *Nkx2-1* mutants has already revealed that this transcription factor is required for the generation of more than half of the GABAergic cells populating the cortex (Sussel *et al.*, 1999), but it has only become clear recently that this correspond to these specific classes of interneurons. Thus, both *in vitro* experiments (Xu *et al.*, 2004; Wonders *et al.*, 2008) and *in vivo* transplantation analyses (Wichterle *et al.*, 2001; Butt *et al.*, 2005; Cobos *et al.*, 2005; Flames *et al.*, 2007; Wonders *et al.*, 2008) have revealed that the majority of cortical interneurons derived from the MGE are PV-containing (~65%) while the remaining cells (~35%) express SST. These studies have recently been confirmed by genetic fate-mapping studies that took advantage of the existence of genes with patterns of expression that are largely confined to the MGE, such as *Nkx2-1* and *Lhx6* (Fogarty *et al.*, 2007; Xu *et al.*, 2008), as well as by the analysis of null or conditional mutants for these genes (Liodis *et al.*, 2007; Butt *et al.*, 2008; Zhao *et al.*, 2008).

A question that remains open is to what extent progenitor cells that give rise to PV- and SST-containing interneurons are spatially segregated within the MGE. The analysis of the expression pattern of several dozens of transcription factors within the ventricular zone of the MGE has led to the proposal that this region may consist of up to five distinct progenitor domains, designated pMGE1 to pMGE5, which it has been hypothesized give rise to different classes of neurons (Flames *et al.*, 2007). Consistently, several lines of evidence suggest that the dorsal (pMGE1-2) and ventral (pMGE3-5) regions of the MGE have a tendency to preferentially give rise to SST- and PV-containing interneurons, respectively (Flames *et al.*, 2007; Fogarty *et al.*, 2007; Wonders *et al.*, 2008). Furthermore, recent fate-mapping analyses have suggested that the progenitor cells giving rise to PV-containing GABAergic neurons populating the basal ganglia might also be spatially segregated from those producing PV-containing GABAergic interneurons for the cortex (Nóbrega-Pereira *et al.*, 2008; Flandin *et al.*, 2010). Thus, while pMGE5 seems to originate most PV-containing GABAergic neurons in the globus pallidus, it seems to produce very few PV-containing cortical interneurons. In turn, very few GP neurons seem to be generated from pMGE3-4, which therefore may primarily generate cortical interneurons. In sum, although

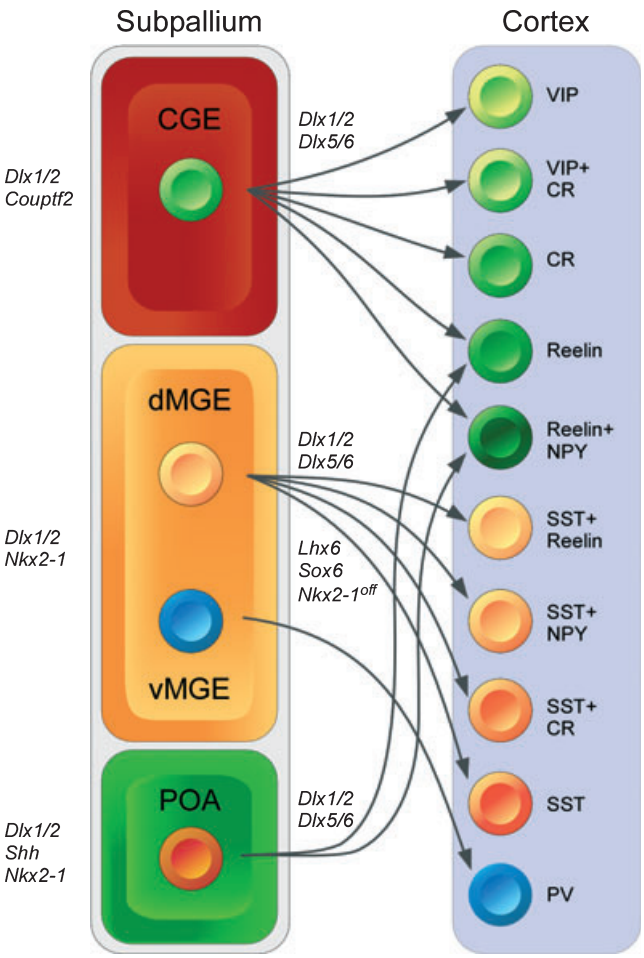

FIG. 3. Cortical interneuron diversity largely emerges from spatially segregated progenitor cells with distinct transcriptional profiles. The schema shows the main sources of cortical interneurons, CGE, MGE and POA, which contain progenitor cells that can be distinguished by their expression of transcription factors and other proteins. Thus, CGE cells express both Dlx1/2 and Couptf2, MGE cells express Dlx1/2 and Nkx2-1, and POA cells express Dlx1/2, Nkx2-1 and Shh. Furthermore, each of these regions seems to contain distinct progenitor domains (not shown in the schema), characterized by the expression of different transcription factors (Flames *et al.*, 2007). Each progenitor region produces a particular group of interneurons, although some interneuron classes may emerge from different progenitor domains. This is the case for multipolar reelin/NPY-containing interneurons, which derive from both CGE and POA. It is possible, however, that these cells derive from a progenitor domain that bridges the two structures and that is characterized by the expression of Couptf2 (Kanatani *et al.*, 2008). Only the mechanisms involved in the generation of MGE cells are beginning to be elucidated. Thus, down-regulation of Nkx2-1 and expression of Lhx6 and Sox6 are necessary for the proper specification of MGE-derived interneurons.

progenitor domains in the telencephalon do not seem to segregate as sharply as in the spinal cord, increasing evidence suggest that the generation of distinct classes of GABAergic interneurons in the subpallium is tightly linked to the existence of distinct classes of progenitor cells (Fig. 3).

The mechanisms underlying the generation of PV- and SST-containing interneurons are beginning to be elucidated. As mentioned above, the generation of both types of interneurons requires the maintenance of Nkx2-1 expression in MGE progenitors, a process that involves Shh signaling (Xu *et al.*, 2005). Interestingly, the level of Shh signaling induced in MGE progenitors seem to dictate the type of interneuron produced, as is the case in the spinal cord (Jessell, 2000). Thus, high levels of Shh signaling favor the generation of SST-containing neurons at the expense of PV-containing neurons (Xu *et al.*, 2010). This is consistent with previous findings that reported high levels of Shh effectors, such as *Gli1*, *Gli2* or *Hhip1*, in the dorsal MGE (Wonders *et al.*, 2008). What is paradoxical in this system is that the highest level of Shh activation within the ventral telencephalon occurs in the dorsal MGE, far away from the source of the signal in the POA. This is in sharp contrast with the situation in the spinal cord, and so future studies should aim to elucidate the mechanisms responsible for this difference.

The fate of the large majority of PV- and SST-containing interneurons depends on *Lhx6*, a direct target of Nkx2-1 (Du *et al.*, 2008). In the absence of *Lhx6*, MGE-derived interneurons reach the pallium but most of them fail to express PV or SST (Liodis *et al.*, 2007; Zhao *et al.*, 2008). In addition, Lhx6-deficient interneurons have problems allocating into their appropriate target layers in the cortex, suggesting that targets downstream of this transcription factor are also involved in this process. Interestingly, a small population of GABAergic interneurons continues to express PV and SST in the cortex of *Lhx6* mutants (Liodis *et al.*, 2007; Zhao *et al.*, 2008), which suggest that some of these interneurons are generated outside the MGE (see below).

Recent studies have began to identify transcription factors that act downstream of Nkx2-1 and Lhx6 in the specification of MGE-derived interneurons. One of these proteins, the Sry-related HMG-box-containing transcription factor Sox6, is expressed by most, if not all, MGE-derived cortical interneurons as soon as they become postmitotic, and continues to be expressed in the adult cortex. Genetic analysis has revealed that Sox6 functions downstream of Lhx6 in MGE-derived interneurons (Batista-Brito *et al.*, 2009). Analysis of *Sox6* null and conditional mutant mice revealed that this transcription factor is required for the development of PV-containing and, to a lesser extent, SST-containing interneurons (Azim *et al.*, 2009; Batista-Brito *et al.*, 2009). The function of Sox6 seems related to the final steps of the differentiation of these interneurons (Batista-Brito *et al.*, 2009), although a more direct role in the specification of these cortical interneuron subtypes has also been suggested (Azim *et al.*, 2009).

In addition to the spatial segregation of interneuron progenitors, there is an important relationship between time of neurogenesis and allocation of MGE-derived cells into specific layers of the cortex (Miller, 1985; Fairén *et al.*, 1986; Nery *et al.*, 2002; Valcanis & Tan, 2003). Although the mechanisms underlying this process are unclear (Hammond *et al.*, 2006; Pla *et al.*, 2006), recent genetic fate-mapping analyses have shown that some types of MGE-derived neurons are preferentially generated at specific times during neurogenesis (Miyoshi *et al.*, 2007), which may explain their relatively restricted laminar distribution in the cortex.

The caudal ganglionic eminence produces several additional types of interneurons

Although it was initially thought that the contribution of the CGE to the population of cortical interneurons was relatively minor, recent data suggest that the CGE may produce between 30 and 40% of all cortical interneurons. Fate mapping the contribution of the CGE to the complement of cortical interneurons has been problematic because of the difficulties in consistently defining this region. Thus, while Nkx2-1 has been a key gene for the identification of the MGE and its derivatives, the definition of the CGE has been largely based on anatomical references, which complicates the comparison between different studies. The similarities in gene expression patterns between the LGE and the CGE led to the suggestion that the CGE may indeed contains a caudal extension of the LGE progenitor domains (Wonders

& Anderson, 2006; Flames *et al.*, 2007; Long *et al.*, 2009). Although this may actually be the case for some of the LGE progenitor domains (in particular for pLGE3, which probably originates most GABAergic projection neurons populating the striatum and amygdala), recent studies have shown that the CGE indeed contains progenitor domains with a unique molecular profile (Kanatani *et al.*, 2008; Willi-Monnerat *et al.*, 2008). In particular, the transcription factor Couptf2 is rich in progenitor cells within the CGE, and experimental evidence suggest that this protein is required for the migration of CGE-derived interneurons to the cortex (Kanatani *et al.*, 2008). Interestingly, progenitor domains in the CGE seem to be longitudinally continuous with some of the domains previously defined in the LGE and MGE (compare fig. 2A in Kanatani *et al.*, 2008 with fig. 9 in Flames *et al.*, 2007), which suggests the number of distinct progenitor domains within the subpallium is larger than initially expected.

The first evidence supporting the origin of cortical interneurons in the CGE derives from pioneer *in utero* transplantation studies carried out in the Fishell laboratory (Nery *et al.*, 2002). In these experiments, they found that the CGE gives rise to a robust population of cells that migrate into the cortex and differentiate to GABAergic interneurons. These early observations have been subsequently confirmed and extended by other studies, both *in vitro* and *in vivo*, which have demonstrated that the CGE is the main origin of interneurons with bipolar and double-bouquet morphologies, many of which express CR (but not SST) and/or VIP (Xu *et al.*, 2004; Butt *et al.*, 2005). These results are also consistent with the fate mapping of neurons derived from *Nkx2-1* and *Lhx6* lineages, which did not report labelling of interneurons with bipolar or double-bouquet morphologies (Fogarty *et al.*, 2007; Xu *et al.*, 2008).

The inherent difficulty of delineating the entire population of CGE progenitors, along with the possibility that some MGE-derived cells may indeed migrate through the CGE, have complicated the identification of the entire complement of interneurons produced in the CGE. A recent fate-mapping study, however, has taken advantage of a *Mash1-CreER* driver line that is preferentially expressed in the LGE and CGE to report the existence of an additional population of CGE-derived interneurons that express reelin but not SST (Miyoshi *et al.*, 2010), and have a multipolar morphology and the electrophysiological features of rapidly adapting interneurons.

The mechanisms underlying the specification of CGE-derived interneurons are poorly understood. As mentioned above, it is very likely that Couptf2 might be partially responsible for conferring migratory capabilities on CGE-derived cells (Kanatani *et al.*, 2008), in a role analogous to those of Nkx2-1 and Lhx6. It is not known, however, what transcription factors are responsible for controlling the expression of CR, VIP or reelin in these cells, or their diverse morphology. Moreover, the mechanisms controlling the final allocation of CGE-derived interneurons into specific layers of the cortex are also likely to be different from those regulating the distribution of MGE-derived cells, as CGE-derived interneurons tend to occupy superficial layers of the cortex independently of their time of neurogenesis (Miyoshi *et al.*, 2010). Nevertheless, most CGE-derived interneurons are produced at relatively late stages of neurogenesis in the subpallium (i.e. ~E15.5), and neurons born at this stage in both the MGE and CGE primarily colonize superficial layers of the cortex (Miyoshi *et al.*, 2010).

The preoptic area is a novel source of cortical interneurons

The results summarized above indicate that the large majority of cortical interneurons derive from the MGE and the CGE. A recent study, however, indicates that a proportion of interneurons may derive from a third source, the embryonic POA (Gelman *et al.*, 2009; Fig. 3). The POA is the region located immediately in front of the optic recess, just ventral to the MGE. As in this later structure, all progenitor cells in the POA express Nkx2-1. In contrast, many of the cells that emerge from this structure, at least from its ventral domain (pPOA2), do not seem to express *Lhx6*, a feature that may distinguish POA- and MGE-derived cells (Flames *et al.*, 2007). Because Nkx2-1 is expressed by POA progenitors, it is conceivable that the analysis of the derivatives of *Nkx2-1-Cre* mice includes cells not only derived from the MGE but also from other structures that express this gene, such as the POA. To circumvent this problem, we took advantage of the fact that the transcription factor *Nkx5-1* is expressed by a rather small population of cells in the POA, but not in the MGE or any other structure in the telencephalon. Fate-mapping this population with *Nkx5-1-Cre* revealed that the POA is the origin of a small population of multipolar GABAergic cells with an electrophysiological profile of rapidly adapting interneurons (Gelman *et al.*, 2009). Interestingly, these cells express NPY and/or reelin (D. M. Gelman and O. Marín, unpublished observations) but none of the other markers of cortical interneurons, such as PV, SST, CR or VIP (Gelman *et al.*, 2009). As such, these cells closely resemble those recently identified as deriving from the CGE (Miyoshi *et al.*, 2010), suggesting that both the POA and the CGE may contribute to this population of cortical interneurons. We have estimated that the Nkx5-1 lineage within the POA may contribute up to 4% of the entire population of cortical GABAergic interneurons.

Is this small population of reelin/NPY-containing cells interneurons the only contribution of the POA to the complement of cortical GABAergic interneurons? Ongoing studies in our laboratory suggest that this is not the case. For example, fate-mapping analysis of a different population of POA cells with *Dbx1-Cre* mice indicates that this region may also give rise to some PV- and SST-containing cortical interneurons (D. M. Gelman, A. Griveau, C. Varela, R. Pla, A. Teissier, A. Pierani and O. Marín, unpublished observations). This result would be consistent with the hypothesis outlined above, that a small fraction of PV- and SST-containing interneurons develop independently of Lhx6 function, and initial estimations suggest that they may represent another ~5% of the cortical interneurons. Although further studies would be required to determine the entire contribution of the POA to the generation of cortical interneuron diversity, our results so far suggest that this region may generate ~8–10% of the cortical GABAergic interneurons.

As for the CGE, our knowledge of the mechanisms controlling the development of POA-derived interneurons is very limited. Interestingly, our results suggest that this small progenitor region gives rise to a small but very diverse population of interneurons, including at least PV-, SST- and reelin/NPY-containing cells. This suggests that the mechanisms controlling cell-fate specification may have features which are common to MGE and CGE.

Concluding remarks

Recent studies have made important progress in our understanding of the origin of cortical interneurons. It seems that most, if not all, cortical interneurons are derived from three progenitor regions in the embryonic subpallium: MGE, CGE and POA (Fig. 3). The MGE generates most interneurons, including fast-spiking PV-containing basket and chandelier cells and several classes of SST-containing interneurons, many of which display the morphology of Martinotti cells (Kawaguchi & Kubota, 1996). The CGE primarily produces

interneurons with bipolar and double-bouquet morphologies, many of which express CR (but not SST) and/or VIP. In addition, a population of rapidly adapting, multipolar neurons that express reelin and/or NPY, but no SST, PV or CR, emerges from the CGE and, to a minor extent, from the POA. Finally, the POA also seems to be the origin of a small fraction of PV- and SST-containing function whose development does not depend on Lhx6 function. Altogether, the projected contributions of MGE (∼60%), CGE (∼30%) and POA (∼10%) progenitor cells seems to account for the entire population of cortical GABAergic interneurons. It cannot be discounted, however, that other subpallial sources may also contribute a minor proportion of cortical interneurons. It has been suggested that the septum, for example, is involved in the generation of cortical interneurons (Taglialatela *et al.*, 2004), although *in vitro* experiments suggest that explants obtained from the embryonic septum has very limited migratory capability (Hirata *et al.*, 2009). Similarly, it cannot be discounted that some progenitor cells in the LGE, especially at late stages of neurogenesis, may contribute to the complement of cortical interneurons (Wonders & Anderson, 2006). Future studies should aim at increasing our understanding of the mechanisms controlling cell fate specification in each of these progenitor domains.

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Abbreviations

CGE, caudal ganglionic eminence; CR, calretinin; GABA, γ-aminobutyric acid; GABAergic, GABA-containing; MGE, medial ganglionic eminence; NPY, neuropeptide Y; POA, preoptic area; PV, parvalbumin; SST, somatostatin; VIP, vasointestinal peptide.

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