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REVIEW

Cortical interneuron development: a tale of time and space

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ABSTRACT

Cortical interneurons are a diverse group of neurons that project locally and are crucial for regulating information processing and flow throughout the cortex. Recent studies in mice have advanced our understanding of how these neurons are specified, migrate and mature. Here, we evaluate new findings that provide insights into the development of cortical interneurons and that shed light on when their fate is determined, on the influence that regional domains have on their development, and on the role that key transcription factors and other crucial regulatory genes play in these events. We focus on cortical interneurons that are derived from the medial ganglionic eminence, as most studies have examined this interneuron population. We also assess how these data inform our understanding of neuropsychiatric disease and discuss the potential role of cortical interneurons in cell-based therapies.

KEY WORDS: Cell fate, Cortical interneurons, MGE, Parvalbumin, Somatostatin, Transcription factors

Introduction

In mice, GABAergic cortical interneurons (CINs) constitute ∼20% of cortical neurons and are the main source of inhibition in the neocortex. CINs are crucial for regulating information processing and flow along cortical networks (Huang et al., 2007). CINs are a diverse group of mostly locally projecting neurons, which can target the dendrites, cell bodies and axons of other neurons. Moreover, diverse subgroups of CINs are implicated in controlling specific features of cortical circuits and physiology (Marin, 2012). How CINs are generated, acquire their unique properties and functions in the cortex, and contribute to disease are being actively studied. In particular, since many aspects of CIN development are conserved between humans and mice, studies of CINs in mice are proving to be important for understanding human biology and disorders (Fertuzinhos et al., 2009; Hansen et al., 2013; Ma et al., 2013).

CINs are generated by the progenitor zones of three subcortical (subpallial) regions of the brain: the medial ganglionic eminence (MGE, see Glossary, Box 1), the caudal ganglionic eminence (CGE), and the preoptic area (POA) (Gelman et al., 2011; Wonders and Anderson, 2006). The lateral ganglionic eminence (LGE), which primarily generates GABAergic striatal projection neurons, might also generate CINs (Anderson et al., 2001). However, definitive data to support this is lacking, in part because of the lack of LGE-specific Cre driver lines. These various ganglionic eminences (GEs, see Glossary, Box 1) also generate interneurons for other pallial regions (e.g. for the piriform cortex, hippocampus, pallidal amygdala and olfactory bulb), as well as interneurons and projection neurons of the striatum, pallidum and other subpallial nuclei (Potter et al., 2009; Xu et al., 2008). Although most GE-derived neurons are GABAergic, it should be noted that GE can also generate cholinergic and dopaminergic neurons, as well as glia (Batista-Brito et al., 2008; Fragkouli et al., 2005, 2009; Hoch et al., 2015; Kessaris et al., 2006; Petryniak et al., 2007).

The MGE, CGE and POA generate distinct CIN subgroups. The MGE primarily produces parvalbumin $(PV)^+$ and somatostatin $(SST)^+$ CINs (see Glossary, Box 1), whereas the CGE produces $5HT3aR^+$ (HTR3A-expressing) lineages that become either vasoactive intestinal peptide $(VIP)^+$ or $reelin^+$ CINs, with the latter group not expressing SST (Miyoshi et al., 2010; Rudy et al., 2011; Wonders and Anderson, 2006; Xu et al., 2008). Moreover, the POA also contributes ∼10% of CINs; these primarily express PV and SST, and occupy deeper cortical lamina (Gelman et al., 2011). PV, SST, VIP and reelin expression can be used to distinguish the vast majority of CINs, although more specific cell types exist within each cohort. The potential diversity of CINs becomes more complex when factors such as electrophysiological properties, expression of distinct sets of genes, axon and dendrite targeting, as well as overall function, are all considered (Kepecs and Fishell, 2014; Kessaris et al., 2014).

As CIN progenitors exit the GEs they become postmitotic, then tangentially migrate along two major paths to their pallial destinations (Anderson et al., 1997). Once in the neocortex, CINs shift from tangential to radial migration as they invade the cortical plate and sort into specific cortical layers (Miyoshi and Fishell, 2011). As CINs mature, their anatomical, molecular and electrophysiological properties develop as they synapse with other neurons to shape distinct cortical microcircuits (Huang et al., 2007; Kepecs and Fishell, 2014; Kessaris et al., 2014). MGE-derived CINs, for instance, primarily constitute two broad subgroups: those expressing PV and those expressing SST. There are two fast-spiking (see Glossary, Box 1) PV^+ CIN subtypes: basket and chandelier cells. Basket CINs are necessary and sufficient for high-frequency gamma oscillations (see Glossary, Box 1) (Cardin et al., 2009; Sohal et al., 2009). By contrast, axo-axonic or chandelier cells, which target the axon initial segment of pyramidal cells (Somogyi, 1977), have been implicated in gating action potential generation. One particular type of regular-spiking SST^+ CIN, the Martinotti cell, targets its axons to pyramidal neuron dendrites in layer I, and is crucial for sharpening stimuli intensity (Murayama et al., 2009). Single-cell sequencing has revealed that multiple subtypes of SST^+ CIN exist, with differential signatures of molecular markers that might convey distinct properties (Zeisel et al., 2015). Thus, PV^+ and SST^+ CIN connectivity, electrophysiological properties and their molecular makeup are potentially linked to distinct aspects of cortical physiology. In addition, a subset of cortical GABAergic neurons send long-range projections outside the neocortex (Lee et al., 2014; Melzer et al., 2012); their origins and functions are just beginning to be elucidated.

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Box 1. Glossary

Fast-spiking interneurons. Interneurons that respond to synaptic input with minimal delay and with sustained high-frequency spiking activity. They are identified by their expression of parvalbumin.

Gamma oscillations. Neural oscillations occurring between ~30 and 100 Hz.

Ganglionic eminence. Embryonic primordia of the basal ganglia consisting of the lateral, medial and caudal ganglionic eminences.

Globus pallidus. A nucleus derived from the medial ganglionic eminence that regulates movement and other processes.

Late-spiking response. Action potential firing response that discharges with a considerable delay after a stimulus.

Mantle zone. Embryonic neural layer interposed between the subventricular zone and the pia, which is composed of immature neurons, blood vessels and glia.

Medial ganglionic eminence. One of three subdivisions of the ganglionic eminences; it generates somatostatin$^+$ and parvalbumin$^+$ cortical interneurons.

Parvalbumin$^+$ cortical interneurons. Medial ganglionic eminence-derived fast-spiking interneurons that express the calcium-binding protein parvalbumin. These include basket and chandelier cells.

Somatostatin$^+$ cortical interneurons. Medial ganglionic eminence derived non-fast-spiking interneurons that express the neuropeptide somatostatin. These include Martinotti cells.

Subpallium. Also known as the basal ganglia, and distinct from the pallium. The subpallium is ventral to the cerebral cortex. Its mature structures include the striatum, globus pallidus, nucleus accumbens, ventral pallidum, preoptic area, and much of the septum and amygdala.

Subventricular zone. A secondary progenitor zone adjacent to and generated by the ventricular zone.

Ventricular zone. A primary progenitor zone that lines the ventricles.

Although the CGE and POA give rise to a substantial proportion of total CINs, this Review focuses primarily on the development of MGE-derived SST$^+$ and PV$^+$ CINs, as there is currently more information available about these CINs. This is partly because there are fewer genetic tools to study CGE-derived and POA-derived CINs, although recent progress has been made in generating CGE-Cre mouse alleles (Silberberg et al., 2016). Our objective is to evaluate the current understanding of how different subtypes of MGE-derived CINs are formed. We first discuss how MGE progenitors are initially specified. Next, we present models on how MGE-derived CIN subtypes are further specified. Then, we discuss how spatial, temporal and genetic mechanisms regulate cell fate decisions in the MGE. Finally, we discuss the potential roles of CINs in human cell-based therapies. We will not discuss CIN migration and integration into the cortical microcircuit, as these topics have been recently covered elsewhere (see Marín, 2013).

Transcriptional mechanisms of CIN specification

The MGE is first morphologically and molecularly apparent in mice on embryonic day (E) 9.5 in the telencephalon. MGE regional identity is specified by the homeobox transcription factors (TFs) NK2 homeobox 1 (NKX2-1) and orthodenticle homeobox 2 (OTX2). In mice null for *Nkx2-1*, the MGE takes on properties of the LGE and CGE (Butt et al., 2008; Sandberg et al., 2016; Sussel et al., 1999), and conditional deletion of *Nkx2-1* from the ventral MGE leads to an expansion of LGE and POA properties (Flandin et al., 2010; Sandberg et al., 2016). Thus, NKX2-1 represses progenitor domains that are adjacent to the MGE. An analysis of OTX2 function in the MGE has shown that it is required for rostroventral, but not caudodorsal, MGE identity. Conditional deletion of *Otx2* leads to the ventral MGE taking on properties of the POA (Hoch et al., 2015). Of note, NKX2-1 and OTX2 repress *CoupTF1* (*Nr2f1*) expression; later in the Review, we discuss the role of COUPTF1, in conjunction with COUPTF2, in promoting the specification of SST$^+$ CINs and in repressing PV$^+$ CINs. Overall, NKX2-1 and OTX2 specify the initial identity and regional pattern of the MGE. Moreover, *Nkx2-1* must be repressed for CINs to reach the neocortex, otherwise they remain in the subpallium (see Glossary, Box 1) (McKinsey et al., 2013; Nóbrega-Pereira et al., 2008; van den Berghe et al., 2013).

Nkx2-1 is genetically upstream of *Lhx6* and *Lhx8*, which encode two LIM homeodomain TFs that control the development of the globus pallidus (GP, see Glossary, Box 1) (Flandin et al., 2011). They also regulate *Shh* expression in MGE-derived CINs, which promotes the establishment of late born CINs, in part by supporting their survival (Flandin et al., 2011). LHX6 and LHX8 function as a complex with their co-factor LDB1. In line with this observation, deletion of *Ldb1* phenocopies many aspects of *Lhx6* and *Lhx8* double mutants (Zhao et al., 2014). Moreover, LHX6 and LHX8 are predicted to form higher order complexes with other LIM homeodomain proteins, including LMO1, LMO3 and ISLET1, which are also expressed in the MGE and in MGE lineages. Although the roles of many of these complexes during MGE development remain to be investigated, evidence from the developing spinal cord indicates that they function in regulating cell fate (Lee et al., 2008; Thor et al., 1999); this could therefore also be the case in the developing forebrain.

In postmitotic neurons, the expression and function of LHX6 and LHX8 become largely restricted to GABAergic and cholinergic neurons, respectively (Fragkouli et al., 2009). Notably, LHX6 is required for the differentiation of almost all PV$^+$ and SST$^+$ CINs (Liodis et al., 2007; Zhao et al., 2008). LHX6 regulates their development in two main ways. First, LHX6 promotes MGE identity in the subventricular zone (SVZ, see Glossary, Box 1) of the cortex, as loss of LHX6 results in ectopic expression of *Sp8* (Vogt et al., 2014), a marker of the CGE and CGE-derived CINs. In the same study, it was shown that *Nkx2-1–Cre* lineages that lack *Lhx6* continue to express SP8 protein in postnatal tissue, with many of these cells occupying cortical layer I, a layer that is devoid of MGE lineage CINs but that contains CGE-derived neurogliaform CINs (Miyoshi et al., 2010). Finally, the electrophysiological properties of transplanted MGE cells from *Lhx6* null mice showed that these mutant cells have a late-spiking response (see Glossary, Box 1) (Vogt et al., 2014), which is a unique characteristic of CGE-derived neurogliaform CINs (Miyoshi et al., 2010). Thus, some *Lhx6* null MGE-derived CINs have molecular, laminar and electrophysiological properties of CGE-derived neurogliaform CINs. Second, LHX6 drives the expression of genes that are required for MGE-derived CIN fate and migration, such as *Arx*, *Mafb*, *Satb1*, *Sox6* and *Cxcr7* (*Ackr3*) (Azim et al., 2009; Batista-Brito et al., 2009; Close et al., 2012; Denaxa et al., 2012; Vogt et al., 2014; Zhao et al., 2008).

Recently, a combined whole-genome epigenetic study provided evidence for how NKX2-1 and LHX6 regulate maturation of the MGE and the generation of MGE-derived CINs (Sandberg et al., 2016). NKX2-1 is primarily associated with transcriptional repression, which is most clearly illustrated by the repression of several genes, TFs and signaling pathways by NKX2-1 in the ventricular zone (VZ, see Glossary, Box 1) of the MGE, including *Fzd5*, *Gli2* and *Bmper*. NKX2-1 also represses transcription via binding to enhancers that are active in the SVZ and mantle zone (see Glossary, Box 1) of the MGE. In this context, transcriptional complexes containing LHX6 are required for activating gene transcription (Sandberg et al., 2016). These results support a model in which MGE development is directed through a combination of stage-specific enhancers that are regulated by unique combinations of TFs. A similar model was recently

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described in two elegant studies describing motor neuron development (Rhee et al., 2016; Velasco et al., 2017).

The idea of LHX6 being the primary driver associated with active expression of MGE lineages is supported by a recent study that used the identification of enhancers with MGE activity, TF ChIP-Seq, and a machine-learning analysis to model likely transcriptional drivers of enhancer activity in the MGE versus the LGE. In this report, LHX6 was the strongest predictor of enhancer activity in the MGE when tested against other known TFs that regulate GE development (Silberberg et al., 2016). Consistent with these data, a previous study showed that forced expression of LHX6 in *Nkx2-1* null mouse MGE cells was sufficient to rescue the generation of SST^+ and PV^+ CINs (Du et al., 2008). Overall, these data provide evidence that, during MGE development, NKX2-1 (and OTX2) represses alternative telencephalic fates, and that NKX2-1 is required for LHX6 expression and the subsequent activation of an LHX6-induced genetic program in the SVZ; this program drives the differentiation of MGE lineages, including that of CINs.

Together, these genetic and biochemical studies highlight mechanisms of how some MGE-specific fates are initially specified. The mechanisms that specify CIN subtypes require further study. We next propose several cellular models for how and when subtype fate decisions are regulated.

Models of CIN subtype specification

The developmental and cellular stages when the fates of SST^+ and PV^+ CINs are specified are beginning to be elucidated and can be summarized by three key models (summarized in Fig. 1). In model 1, the 'mosaic model', separate progenitors in the VZ are committed (or strongly biased) to generate either SST^+ or PV^+ CINs. In model 2, the 'homogenous VZ model', VZ progenitors are multipotent and can generate both subgroups. In model 3, the 'direct versus indirect neurogenesis model', VZ progenitors generate SST^+ CINs (direct neurogenesis), whereas SVZ progenitors generate PV^+ CINs (indirect neurogenesis). Note that VZ progenitors are radial glia stem cells organized as a neuroepithelium (also called apical progenitors), whereas SVZ progenitors are non-epithelial (also known as basal progenitors). We have previously proposed that the SVZ consists of different progenitors (SVZ1 and SVZ2); how their functional properties might differ is uncertain, although SVZ1 is likely to represent a more immature cell type (Petryniak et al., 2007; Yun et al., 2002).

We are currently unaware of any data supporting model 1 in the MGE, although there is still much to learn and it is possible that evidence to support this model could emerge from future studies. By contrast, published data provide evidence that models 2 and 3 can operate in the MGE. For example, a combination of retroviral labeling and lineage tracing of VZ progenitors has shown that individual MGE progenitors can generate both SST^+ and PV^+ CINs (Fig. 1, model 2) (Brown et al., 2011; Harwell et al., 2015; Mayer et al., 2015). This is analogous to the neocortex, where radial glia stem cells can generate multiple types of neurons (Eckler et al., 2015). These conclusions contrast with the evidence that deep (early born) and superficial (later born) cortical projection neurons are generated by distinct neocortical VZ progenitors (Fig. 1, model 1) (Gil-Sanz et al., 2015). Model 3 proposes that SST^+ CINs are generated by direct neurogenesis from the VZ from radial glia (apical progenitors), whereas PV^+ CINs are subsequently generated by the SVZ from secondary basal progenitors (Fig. 1, model 3) (Petros et al., 2015). This hypothesis is based in part on the analysis of mice lacking the cell cycle regulator cyclin D2 (*Ccnd2*), which promotes G1/S progression. In the MGE, *Ccnd2* expression is restricted to the SVZ, and loss of *Ccnd2* results in reduced numbers of PV^+ CINs (Glickstein et al., 2007a,b; Lodato et al., 2011). Consistent with model 3 (Petros et al., 2015), PV^+ CIN generation begins largely after the generation of SST^+ CINs (Cavanagh and Parnavelas, 1988; Inan et al., 2012; Miyoshi et al., 2007; Pla et al., 2006). However, we suggest that at least some SST^+ CINs go through an SVZ progenitor stage and have found that conditional mutagenesis of *CoupTF2* (*Nr2f2*) in the SVZ, via *Dlx1CreERT2*, reduces SST^+ CIN numbers (Hu et al., 2017).

Although these models address when a cell fate or subtype decision is made along an MGE lineage, they do not identify the

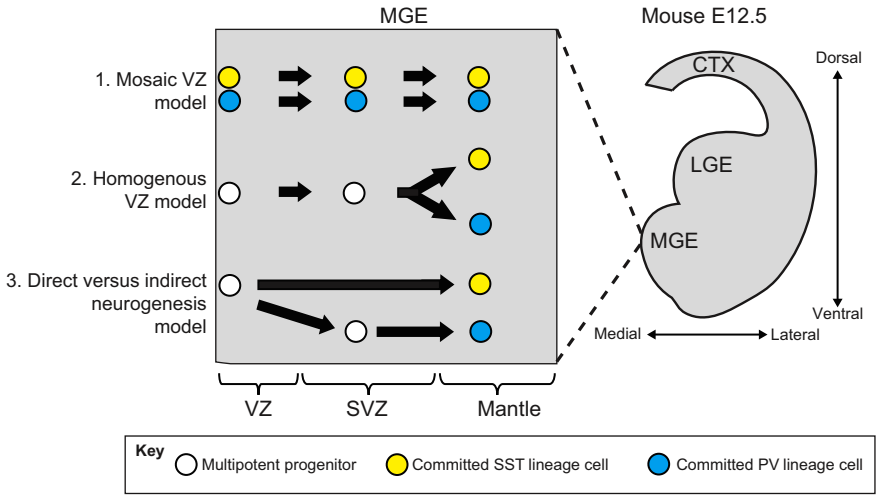

Fig. 1. Cell fate specification models in the medial ganglionic eminence. A coronal section through a developing mouse brain at E12.5 (right). Within the brain, postmitotic neurons in the mantle zone are generated by two major progenitor zones: the ventricular (VZ) and subventricular zone (SVZ) (additional complexity exists, which we do not describe here). The VZ consists of neuroepithelial stem cells, called radial glia, which generate secondary progenitors of the non-epithelial SVZ. Three models can explain how progenitors in the MGE generate SST^+ (yellow) or PV^+ (blue) cortical interneurons (CINs). In model 1 (mosaic VZ model), early VZ progenitors are already committed to generate SST^+ or PV^+ CINs. In model 2 (homogenous VZ model), early VZ progenitors can generate both CIN subgroups (white), with the final decision taking place in the SVZ. In model 3 (direct versus indirect neurogenesis model), the SST^+ subgroup is produced by direct neurogenesis from VZ progenitors, whereas PV^+ CINs are produced by SVZ progenitors. CTX, neocortex; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; PV, parvalbumin; SST, somatostatin.

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factors necessary for these decisions. Namely, which molecules are needed to specify one fate over the other? Are there regional differences that bias the decision? Is there a cell-intrinsic clock that predetermines the fate of a cell depending on mitosis number or developmental stage? We explore these possibilities in the next section.

Regional contributions to CIN cell fate

When thinking about the specification of SST^+ and PV^+ CIN fates, one needs to consider both regional (spatial) and temporal influences (Figs 1 and 2). Factors that are present in one MGE subregion (but absent in another) might bias, or deterministically regulate, the generation of SST^+ and PV^+ CINs. This could occur through the three models mentioned above (Fig. 2A). For instance, in the homogenous VZ model (Fig. 1, model 2), the factors in that MGE subregion might promote the specification of SST^+ CINs. Moreover, one must consider the change in cell fate lineages as developmental time progresses (Fig. 2B).

There is substantial evidence to suggest that regional differences along the rostrocaudal and dorsoventral axes of the MGE contribute to different cell fate decisions. It is known, for example, that the VZ of the MGE is molecularly heterogeneous, with spatial variations in TF expression patterns (Fig. 3) (Flames et al., 2007; Hoch et al., 2015). The transplantation of distinct MGE regions from E13.5 mouse embryos to the neocortex of E13.5 embryos or neonates also provides evidence that different cell types originate from different locations within the MGE (Flames et al., 2007; Inan et al., 2012). A caveat in the MGE transplantation method is that it includes multiple cell types, including pallidal projection neurons (e.g. GP), which express PV and SST. However, strong support that regional subdivisions generate distinct CIN cell fates comes from Cre fate-mapping studies. For instance, *Shh-Cre* fate-mapping experiments in mouse embryos have shown that the ventral MGE and POA generate ∼70% GP neurons, ∼25% striatal PV^+ interneurons and ∼5% PV^+ CINs (and even fewer SST^+ CINs) (Fig. 3, Table S1; region corresponds to MGE5) (Flandin et al., 2010). This provides evidence that more dorsal parts of the MGE are the major sources of CINs. In support of this, loss-of-function and fate-mapping studies involving *Nkx6-2*, which encodes a TF that is expressed in the dorsal MGE (Fig. 3; regions corresponding to MGE0 and MGE1) (Fogarty et al., 2007; Sousa et al., 2009), showed that the dorsal MGE is a major source of CINs that co-express SST and calretinin (CR; calbindin 2). Furthermore, through fate mapping using tamoxifen-dependent CreERT2, distinct MGE regions marked by unique enhancer activity show biases for generating PV^+ and SST^+ CINs, as well as different GP regions (Silberberg et al., 2016).

We recently provided further evidence that distinct MGE regions are biased towards generating different CIN subtypes (Hu et al.,

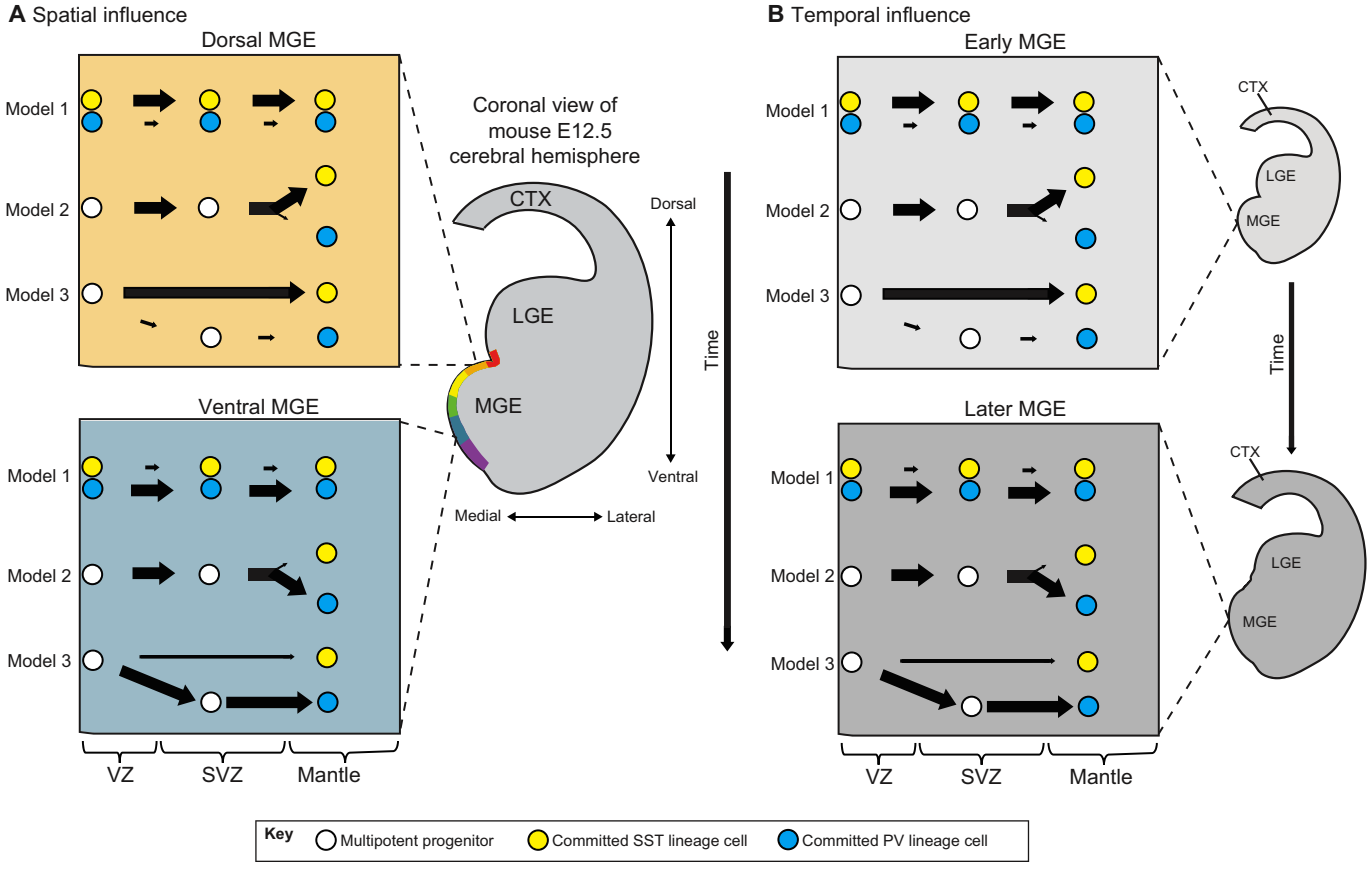

Fig. 2. Spatial and temporal influences on cell fate specification in the MGE. (A) In the three models shown, different MGE regions along the dorsoventral or rostrocaudal axis (colored in the MGE VZ) bias MGE progenitors to generate one cell fate (thick arrows) over another (thin arrows). This bias can occur in each of the three cell specification models described in Fig. 1. The dorsal MGE (orange) biases the production of SST^+ CINs (Flames et al., 2007; Fogarty et al., 2007; Sousa et al., 2009; Silberberg et al., 2016), whereas the ventral MGE (blue) biases the production of PV^+ CINs (Flames et al., 2007; Inan et al., 2012; Silberberg et al., 2016). (B) Developmental time also biases MGE progenitors to generate more of one cell fate over another. Again, this bias can affect all three cell specification models. Early MGE progenitors from E11.5 give rise to mostly SST^+ CINs (Hu et al., 2017), whereas later MGE progenitors from E14.5 give rise to mostly PV^+ CINs (Xu et al., 2010; Hu et al., 2017). Abbreviations as Fig. 1.

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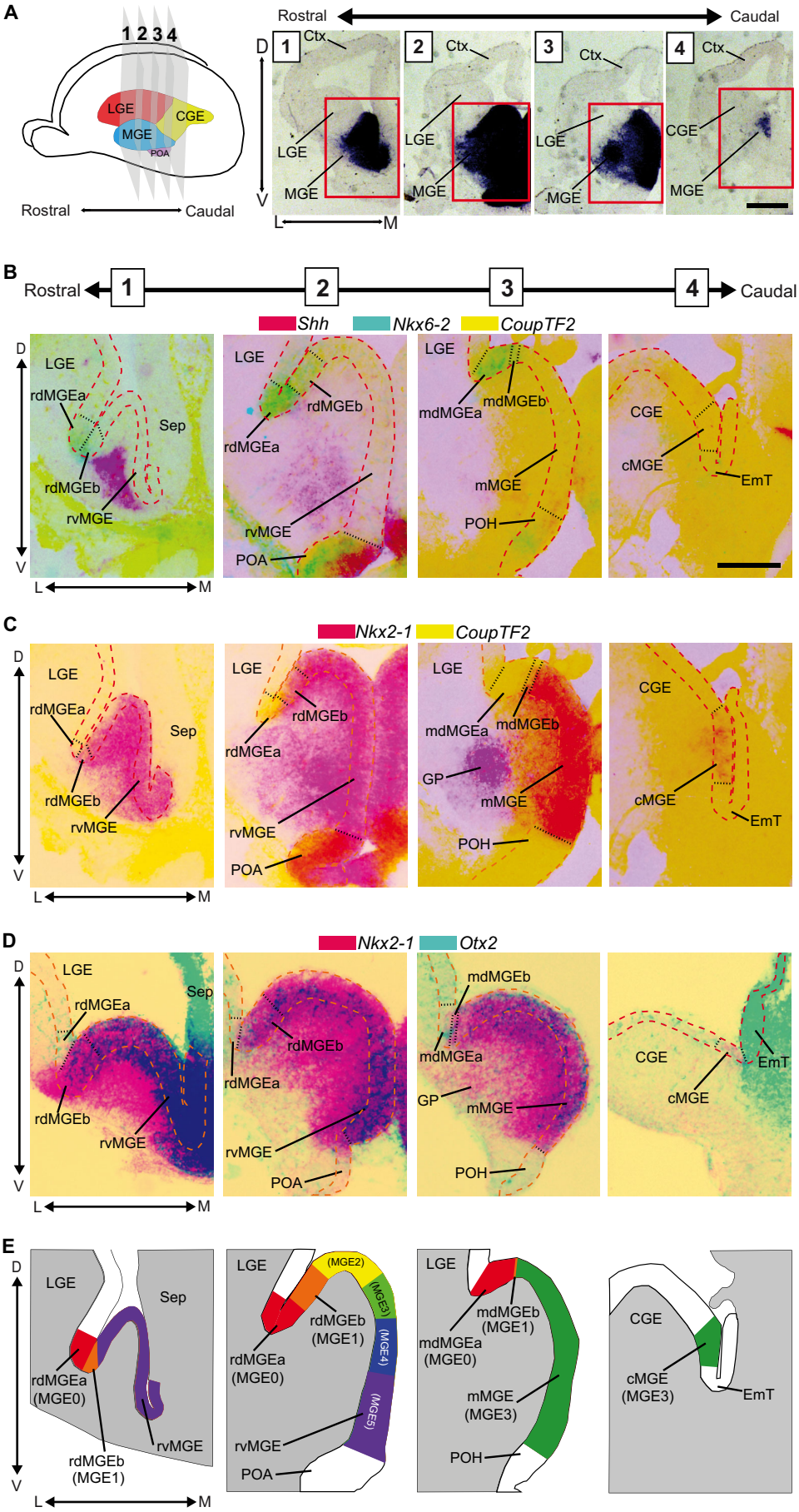

Fig. 3. Progenitor domains in the E12.5 mouse MGE. (A) Schema (left) depicting a lateral view of an E12.5 telencephalon and highlighting the locations of four coronal planes along the rostrocaudal axis. *Nkx2-1 in situ* hybridization (ISH) in these coronal sections from mouse E12.5 wild-type brain is shown (right). Red boxes denote corresponding locations magnified in B-D. (B-D) ISH for the indicated genes on a rostral to caudal series of coronal sections from mouse E12.5 wild-type brains. Each row comprises images of ISHs performed on adjacent sections of the same brain (B and C are also from the same brain). Sections within a column are from approximately the same level and plane of section. Red dashed lines delineate the VZ. Progenitor domain labels are based on terms used by Hu et al. (2017) and Flames et al. (2007). Black dotted lines delineate the proposed VZ domains derived from the combinatorial patterns of TF expression. Note that *CoupTF2* is expressed in caudorostral and dorsoventral gradients (B,C), opposite to that of *Otx2* (D). We identify (B,C) an MGE subdomain (rdMGEa, mdMGEa, MGE0) that is *Nkx6-2*$^{+}$ *CoupTF2*$^{+}$ *Nkx2-1*$^{-}$, which was not proposed by Flames et al. (2007). (E) Schema depicting the locations of the progenitor domains. CGE, caudal ganglionic eminence; cMGE, caudal medial ganglionic eminence; Ctx, neocortex; D, dorsal; EmT, eminentia thalami; GP, globus pallidus; L, lateral; LGE, lateral ganglionic eminence; M, medial; MGE, medial ganglionic eminence; mMGE, middle medial ganglionic eminence; mdMGE, middle dorsal medial ganglionic eminence; POA, preoptic area; POH, preoptic-hypothalamus; rdMGE, rostral dorsal medial ganglionic eminence; rvMGE, rostral ventral medial ganglionic eminence; Sep, septum; V, ventral. Scale bars: 1 mm in A; 500 µm in B.

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2017). It had previously been shown that expression of the nuclear hormone receptor TFs CoupTF1 and CoupTF2 is restricted to a continuous arc within the MGE VZ (Fig. 3, Table S1; regions MGE0 and MGE1) in rostral and middle sections, and the MGE in the caudal section. This arc extends from the small *Nkx6-2*$^{+}$ rostral/dorsal zone (Fogarty et al., 2007) to a large *Nkx6-2*$^{-}$ caudal zone (Hu et al., 2017). In addition, *CoupTF2* expression is maintained in adult SST^{+} CINs within layer V (Cai et al., 2013). Our recent study showed that conditional deletion of *CoupTF2* in the MGE and POA, via *Nkx2-1–Cre*, reduces SST^{+} CIN numbers and increases PV^{+} CIN numbers (Hu et al., 2017), revealing a role for this TF in controlling the SST^{+}/PV^{+} ratio. *CoupTF1* and *CoupTF2* appear to have overlapping functions in SST^{+} and PV^{+} CIN development as *CoupTF1*$^{+/-}$;*CoupTF2*$^{-/-}$ mutants have a quantitatively stronger phenotype than *CoupTF2*$^{-/-}$ mutants (Hu et al., 2017). Furthermore, it was shown that the transplantation of caudal MGE progenitors that express *CoupTF1* and *CoupTF2* in neonatal neocortices yields more SST^{+} CINs than transplanted rostral MGE progenitors (note that rostral regions are mostly devoid of *CoupTF1* and *CoupTF2* expression), when transplanted in neocortices of the same age (Hu et al., 2017). In addition, increasing *CoupTF2* expression in MGE cells by lentiviral transduction increases the number of SST^{+} CINs and reduces the number of PV^{+} CINs. There is evidence that *CoupTF2* establishes SST^{+} fate by promoting *Sox6* expression in MGE progenitors (Hu et al., 2017). This is consistent with prior evidence that *Sox6* promotes SST^{+} fate and CIN maturation (Azim et al., 2009; Batista-Brito et al., 2009; Vogt et al., 2014). Thus, this study demonstrates that a TF with region-specific expression within the MGE participates in the mechanisms that direct cell fate choice between SST^{+} and PV^{+} CINs.

Like *CoupTF2*, the expression of *Npas1*, which encodes the TF neuronal PAS domain protein 1, in the MGE is biased towards a caudodorsal domain, and is largely excluded from PV^{+} CINs (Stanco et al., 2014). *Npas1* constitutive null mouse mutants exhibit increased proliferation, ERK signaling and *Arx* expression in MGE and CGE progenitors. Notably, *Npas1* null mutants generate an excess of CINs, which would normally express *Npas1*, including SST^{+} (MGE-derived) and CGE-derived VIP^{+} CINs, without affecting PV^{+} CIN numbers. Interestingly, *Npas1* expression in migrating CINs is greatly reduced in *CoupTF2* mutants (Hu et al., 2017). Thus, evidence suggests that *CoupTF1* and *CoupTF2* lie genetically upstream of *Sox6* and *Npas1*.

From these studies, we can conclude that spatially restricted TF expression within the MGE contributes to the SST^{+} versus PV^{+} fate decision. Given that the ratio of SST^{+} and PV^{+} CINs generated varies with embryonic age, further studies should explore whether there are temporal variations in the regional expression of these TFs and other molecules.

Temporal contributions to CIN cell fate

There is evidence that developmental timing also influences the specification of MGE-derived CIN subtypes. For instance, factors that are present early but are absent or reduced later may influence an MGE region to produce more SST^{+} CINs at a given time by promoting the SST^{+} lineage through any of the three models (Fig. 2B). For example, in the homogenous VZ model (model 2, Fig. 2B), factors at one time point may promote the division of progenitors into one particular identity but that same progenitor may produce another identity later because of the absence of those factors.

Like cortical projection neurons, early born MGE-derived CINs occupy deeper cortical layers, whereas later born MGE CINs reside in superficial cortical layers, providing evidence that MGE progenitors express regulators of temporal identity that contribute to laminar specification (Cavanagh and Parnavelas, 1988; Inan et al., 2012; Miyoshi et al., 2007; Pla et al., 2006). MGE neurons 'born' at E11 predominantly become SST^{+} CINs; thus SST^{+} CINs (residing mostly in cortical layer VI) are generated before PV^{+} CINs (Hu et al., 2017). Moreover, MGE neurons born at E14 predominantly become PV^{+} CINs (most reside in the superficial layers of the cortex); thus, many PV^{+} CINs are later born (Xu et al., 2010; Hu et al., 2017). In addition, chandelier cells, a subtype of PV^{+} CINs, are born after PV^{+} basket cells (Inan et al., 2012; Taniguchi et al., 2013).

The temporal cues that influence the identity of MGE-derived CINs are beginning to be identified. For example, it has been reported that the conditional deletion of *Nkx2-1* at E10 leads to increased production of striatal medium spiny neurons at the expense of SST^{+} and PV^{+} CINs (Butt et al., 2008). Furthermore, deletion of *Nkx2-1* at E12 leads to increased production of CGE-derived CINs at the expense of SST^{+} and PV^{+} CINs. Through fate-mapping experiments with EdU, a thymidine analog that is incorporated during S-phase of the cell cycle, it was shown that conditional deletion of *CoupTF2* changes the fate of MGE-derived neurons as a function of when the cells leave the cell cycle (so-called 'birthdating' analyses) (Hu et al., 2017). This study found that an increased number of cells born at ∼E11.5 become PV^{+} GP projection neurons in the absence of *CoupTF2*. Likewise, there is an increase in the number of cells born at ∼E14.5 that contribute to PV^{+} interneurons of the somatosensory cortex, piriform cortex and striatum. Progenitor regions of the MGE that express *CoupTF2* exhibit increased neurogenesis specifically at E11 in *CoupTF2* mutants. Conversely, there are decreases in the number of cells born at ∼E12.5 that become SST^{+} interneurons in the somatosensory cortex and piriform cortex. Furthermore, the timed inactivation of *CoupTF2* at E12.5 within the SVZ of the MGE, using *Dlx1CreERT2*, leads to a reduction in SST^{+} migrating cells. Together, these results indicate that *CoupTF2* acts as a temporal identity cue that promotes the E12.5 SST^{+} CIN lineage and inhibits the E11.5 PV^{+} GP and E14.5 PV^{+} CIN lineages (Fig. 4) (Hu et al., 2017).

Recent fate-mapping experiments using an enhancer element that is active in the E11.5 dorsal MGE (regions corresponding to MGE0 and MGE1; Fig. 3) show that this MGE region gives rise to rostral GP neurons and CINs, supporting a model in which a distinct MGE region can generate rostral GP neurons and CINs (Silberberg et al., 2016). We propose that *CoupTF1* and *CoupTF2* function analogously to their *Drosophila* homolog, *svp*, which controls the temporal specification of neurons in the eye and ventral CNS (Mlodzik et al., 1990). Thus, restricted *CoupTF1* and *CoupTF2* expression within subregions of the MGE integrate temporal and spatial cues that coordinate the generation of SST^{+} CINs (Fig. 4). However, in contrast to the developing *Drosophila* eye and ventral CNS, MGE-derived CINs are not yet mapped in such detail. In this regard, the role of time and mitosis in regulating the specification of MGE-derived CIN subtypes is incompletely known and requires further investigation. In addition, further work is required to establish the transcription network that regulates temporal specification.

TFs and signaling molecules that regulate CIN fate

As we have highlighted above, multiple TFs influence the development of SST^{+} and/or PV^{+} CINs and control their ratios (Fig. 5). These include ARX, COUPTF2, DLX1/2/5/6, LHX6/8, LMO3, NPAS1, SATB1, SOX6 and PGC1A (PPARGC1A) (Au et al., 2013; Batista-Brito et al., 2009; Close et al., 2012; Cobos et al., 2005; Denaxa et al., 2012; Hu et al., 2017; Lucas et al., 2010; Stanco et al., 2014; Vogt et al., 2014; Wang et al., 2010). Some TFs

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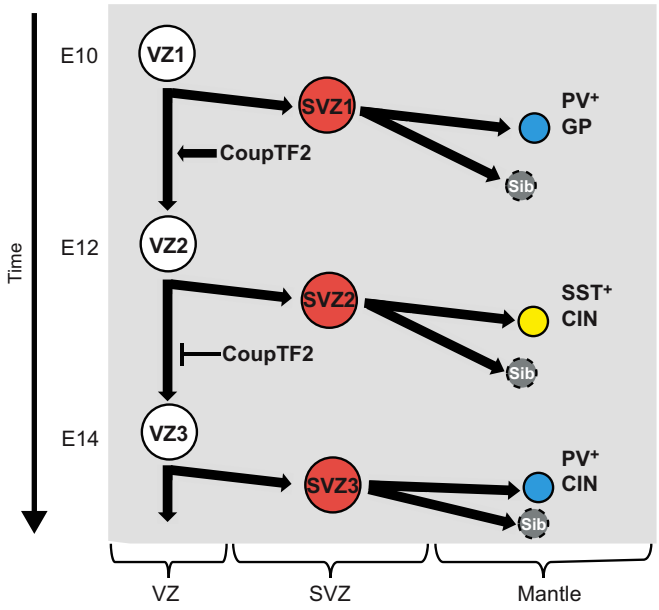

Fig. 4. Temporal specification in the MGE lineage. In this schematic, a mouse MGE VZ progenitor (white) undergoes a series of asymmetric divisions to generate V1, V2 and V3 progenitors, analogous to cell production in the invertebrate nerve cord (Kohwi and Doe, 2013). Each VZ division regenerates a VZ progenitor (white) and generates an SVZ progenitor (red). Each SVZ progenitor divides to produce a neuron and a sibling cell (which could be another SVZ progenitor, a neuron, a glia, or a dead cell). As shown here, the VZ progenitor 1 (VZ1) lineage generates a PV^+ GP neuron (blue), the VZ2 lineage generates an SST^+ CIN (yellow), and the VZ3 lineage generates a PV^+ CIN (blue). In this model, *CoupTF2* promotes the E12.5 VZ2 sublineage that gives rise to SST^+ CINs, while inhibiting the E14.5 VZ3 sublineage that produces PV^+ CINs (Hu et al., 2017). Sib, sibling daughter cell.

are expressed in both SST^+ and PV^+ CINs, including DLX5, LHX6, MAFB, SATB1 and SOX6 (Azim et al., 2009; Batista-Brito et al., 2009; Close et al., 2012; Cobos et al., 2006; Denaxa et al., 2012; Fogarty et al., 2007; Liodis et al., 2007; Wang et al., 2010). By contrast, COUPTF2, DLX1 and NPAS1 are not expressed in PV^+ CINs but are expressed in SST^+ CINs (Cobos et al., 2005; Cai et al., 2013; Stanco et al., 2014). However, *Dlx1* is transiently expressed in the embryonic precursors of PV^+ CINs (Pla et al., 2017). Currently, it is unclear how these TFs combinatorially participate in the spatial and temporal specification of MGE-derived CINs. However, there is evidence that some enhancer elements can be preferentially active in SST^+ CINs (compared with in PV^+ CINs). Notably, enhancer 799 is bound *in vivo* in the GEs by multiple TFs, including NKX2-1, LHX6, COUPTF1, DLX1, DLX2, DLX5 and ARX (Silberberg et al., 2016); thus, there is ample opportunity for TF interactions to drive cell type-specific gene expression through combinatorial binding to enhancer elements that are active in the MGE.

We are unaware of any TF that is expressed in PV^+ but not SST^+ CINs during development. Perhaps, the PV^+ identity is the default state that is modified by the expression of *CoupTF2*, *Dlx1*, *Npas1* and *Satb1*. Nonetheless, there is an active hunt for TFs, other genes and/or cellular events that determine PV^+ fate. In that regard, there is evidence that *Arx* and *Lmo3* are sufficient to promote PV^+ CIN fate (Au et al., 2013; Vogt et al., 2014). There are also two major types of PV^+ CINs – early generated basket neurons and the later generated chandelier neurons (Inan et al., 2012; Taniguchi et al., 2013) – providing further evidence for the role of timing in cell type specification. Since PV expression in CINs begins postnatally, and there are no known markers that specifically mark PV^+ cell types at earlier ages, it has been difficult to study the mechanisms that differentially control the differentiation of these two types of PV^+ CINs.

Efforts are also underway to study the TFs that control the development of specific PV^+ and SST^+ CIN subgroups. As noted above, *Nkx6-2* expression is tightly restricted to progenitors of the dorsal MGE, where it regulates the numbers of SST^+ CINs that express CR (Fogarty et al., 2007; Sousa et al., 2009). *CoupTF2* expression is highly enriched in layer V SST^+ CINs, and thus perhaps participates in regulating the development of this subtype of SST^+ CIN. PV expression potentially requires synaptic activity and/or signaling events; this emphasizes the need to explore cellular events outside of the nucleus that control gene expression. Indeed, mutations in genes encoding membrane and signaling proteins, including *Cntnap2* and *Pten*, lead to an imbalance in SST^+ versus PV^+ CIN ratios (Fig. 5) (Peñagarikano et al., 2011; Vogt et al., 2015). In particular, the deletion of *Pten* (which encodes an inhibitor of the AKT/mTOR signaling pathway) in the MGE reduces the number of MGE-derived CINs; although both CIN subgroups are affected, SST^+ CINs are the most greatly reduced. These data suggest that growth factor signaling pathways, such as those repressed by *Pten*, might differentially regulate PV^+ and SST^+ CIN development and maturation. Other genes may also impinge upon this pathway, including those encoding the receptor tyrosine kinase receptors MET and ERBB4 (Martins et al., 2011; Neddens and Buonanno, 2010) (Fig. 5). In addition, it has been shown that loss-of-function mutations in the neurexin family member *Cntnap2* decrease PV expression (Peñagarikano et al., 2011). Although the signaling mechanisms that are regulated by *Cntnap2* in CINs are yet to be elucidated, it should be noted that many members of the neurexin family have important roles in cell-cell communication at the synapse and between axons and myelin (Bemben et al., 2015; Zoupi et al., 2011).

New molecular players and mechanisms have also emerged from studies of projection neuron specification (Molyneaux et al., 2015; Zhang et al., 2016). These mechanisms have yet to be demonstrated in CIN specification but should also be considered. One is the role of long non-coding RNAs (lncRNAs). lncRNAs are >200 nucleotide RNAs that do not encode proteins and are prevalent in the brain (Molyneaux et al., 2015). Through RNA-Seq and the purification of pyramidal cell subclasses, numerous mouse lncRNAs have been shown to have cell type-restricted and temporally restricted expression patterns (Molyneaux et al., 2015). Another mechanism is alternative splicing (Conboy, 2016); mutations in the PTBP1 and RBFOX splicing factors regulate neurogenesis and cell fate decisions in the neocortex (Zhang et al., 2016). Future work is needed to investigate if and how alternative splicing and lncRNAs might regulate the PV^+ versus SST^+ lineage choice.

In summary, multiple TFs and signaling proteins participate in the specification of SST^+ and PV^+ CINs (Fig. 5). Further research needs to identify other molecular components that function in these processes and to elucidate how they work together to specify the fate and maturation of CINs. Knowledge of these components will help geneticists studying human neuropsychiatric disorders and stem cell researchers attempting to program stem cells into specific neuronal subtypes.

CIN dysfunction in neuropsychiatric disease: insights into potential therapies

CINs regulate cortical networks in part by creating a balance of excitatory and inhibitory activity. Consequently, CIN defects can lead to pathological hyperexcitable circuits, which can contribute to disorders such as epilepsy. Clinical studies have provided evidence

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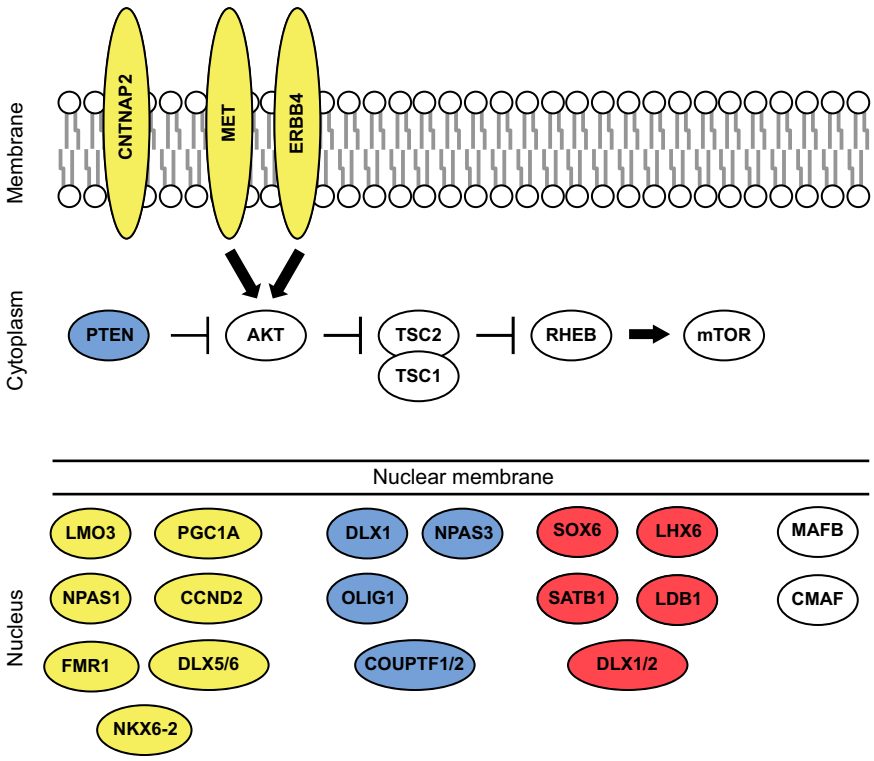

Fig. 5. Loss-of-function mutants that influence the ratio of PV$^+$/SST$^+$ CINs. Multiple factors have been shown to influence the production, maturation and/or survival of CIN subgroups that express SST or PV. These include TFs, as well as cell signaling and membrane proteins. Yellow denotes factors that when lost result in a greater number of SST$^+$ than PV$^+$ CINs; blue denotes factors that when lost result in greater PV$^+$ than SST$^+$ CIN numbers. The loss of factors shown in red results in a relatively even loss of both CIN subgroups. Other factors, as shown in white, although expressed in these CINs and in progenitors, do not have a known function in establishing proper numbers of either subgroup.

for cortical and hippocampal interneuron defects in patients with schizophrenia (SCZ), bipolar disorder and autism spectrum disorder (ASD). For instance, in human SCZ patients there is reduced expression of GAD67 (GAD1) and PV in CINs (Akbarian et al., 1995; Gonzalez-Burgos et al., 2015), as well as reduced PV and SST expression in the hippocampus (Wang et al., 2011; Konradi et al., 2011). How CIN dysfunction can mechanistically contribute to these disorders is not clear. However, studies on mouse models involving ASD and SCZ risk genes that regulate CIN development, along with interneuron transplantation and stem cell experiments, are providing insights into how certain symptoms of these disorders could arise (Marin, 2012). Moreover, given the heterogeneity in symptoms observed in these disorders, it is likely that their symptoms could arise through defects in multiple cell types, individually or in combination. For instance, there is evidence for reduced excitatory inputs into PV$^+$ CINs in an SCZ mouse model (Rotaru et al., 2012).

Recent success in the identification of genes that predispose to ASD has increased the tractability of studies of this complex disorder (Sanders et al., 2015). ASD manifests within the first two years of life and is characterized by social and language deficits, as well as by restricted and/or repetitive behaviors. One hypothesis poses that neural system dysfunction occurs in ASD due to alteration of the excitation/inhibition ratio in key brain regions, such as the cerebral cortex (Rubenstein and Merzenich, 2003). It is likely that failure of homeostatic mechanisms that maintain excitation/inhibition balance could also contribute to ASD (Mullins et al., 2016). Research is thus underway to understand the function of genes that are significantly associated with ASD in brain development and function, particularly using mouse mutants (Marín, 2012). Several ASD/intellectual disability risk genes have roles in regulating CIN subtypes. Mutations in these genes in the mouse MGE can increase or decrease CIN numbers, alter CIN morphology, and modify their inhibitory activity (Han et al., 2012; Hoffman et al., 2016; Karayannis et al., 2014; Peñagarikano et al., 2011; Vogt et al., 2014). In addition, induced pluripotent stem cells (iPSCs) from humans with idiopathic ASD overproduce CINs because of an accelerated cell cycle and increased differentiation, in part through increased *FOXG1* expression (Mariani et al., 2015). It has also been demonstrated that several genes that are implicated in ASD regulate CIN function in mice and, in particular, appear to affect PV$^+$ CIN density, although other CIN subtypes might have been insufficiently investigated (Gogolla et al., 2009; Martins et al., 2011; Selby et al., 2007; Takano, 2015) (Table S2). In addition, recent studies of human postmortem brain tissue have reported that PV$^+$ CIN numbers are decreased in individuals with ASD (Hashemi et al., 2016). Although this reduction in PV$^+$ CIN numbers is unlikely to underlie the entirety of ASD symptoms, it is possible that these defects could have important neural implications. PV$^+$ CINs control gamma oscillations (Cardin et al., 2009; Sohal et al., 2009), which are associated with various cognitive processes (Sohal, 2016). Furthermore, CIN defects are well known to predispose to epilepsy, a common phenotype in ASD (Marin, 2012). These observations suggest that alterations to PV$^+$ CIN numbers or function (or to PV expression) could be a recurring symptom in many forms of ASD.

SCZ is characterized by positive (delusions and hallucinations) and negative (social withdrawal and cognitive deficits) symptoms. One hypothesis proposes that some of these symptoms are caused by a reduction in excitatory input into inhibitory neurons (Gonzalez-Burgos and Lewis, 2012). The reduced activation of CINs could lead to the disinhibition of excitatory neurons and hence to excessive excitation in brain regions implicated in SCZ, such as the prefrontal cortex (PFC), striatum and hippocampus. This hypothesis is partly based on the observed reduction in excitatory synapses on PV$^+$ interneurons in mutant mice in which genes associated with SCZ have been conditionally deleted in PV$^+$ CINs, such as *Erbb4*, *Nrg1* and *Dtnbp1* (Chen et al., 2008; del Pino et al., 2013; Talbot et al., 2004). In these studies, mutant mice exhibit increased locomotor activity and defective brain wave synchrony across

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multiple brain regions. Notably, mice that are heterozygous for *Dlx5* and *Dlx6*, two TF genes that are expressed in CINs, have behavioral and electrophysiological phenotypes reminiscent of SCZ, including changes in gamma rhythms (Cho et al., 2015). Many of these phenotypes can be rescued with a GABA agonist. Individuals with SCZ also reproducibly have decreased levels of *GAD1* in their PFC (Akbarian et al., 1995), together with reduced expression of *LHX6*, *PV* (*PVALB*) and *SST* in CINs (Volk et al., 2012). By contrast, increased levels of *CXCR4* and *CXCR7* have been found in the CINs of the PFC of SCZ individuals (Volk et al., 2015).

Altogether, these findings highlight that defects in interneuron function, and genes that regulate interneuron development, are implicated in ASD and SCZ, suggesting that therapies which restore interneuron signaling might ameliorate some ASD and SCZ symptoms. In addition, an idea gaining traction for epilepsy therapy is the introduction of healthy interneurons via cell transplantation, as we discuss below.

CINs in potential human cell-based therapies

Pioneering studies have found that when mouse embryonic MGE cells are transplanted into a host neocortex of a later age, the MGE cells still follow their intrinsic timeline of migration (both tangential and radial), survival, cell fate and maturation, and incorporate into their resident microcircuit (Alvarez-Dolado et al., 2006). This observation suggests that the environment in which the MGE cells are migrating is permissive for a long period. More importantly, transplanted MGE cells have an intrinsic clock, allowing them to function in a cell-autonomous manner in host brains (Alvarez-Dolado et al., 2006; Southwell et al., 2014). An example of this comes from studies in which embryonic MGE cells were transplanted into an adult mouse brain or spinal cord and were still able to migrate away from the injection site, assume proper cell fates, and connect and function properly within the host circuitry (Bráz et al., 2012; Tong et al., 2014). These observations suggest that the cortical environment is permissible at multiple ages, even into adulthood. Owing to these features, CIN transplantation has been proposed as a potential cell-based therapy to treat particular disorders, in which the nervous system has increased excitation, by replacing defective interneurons with functional ones (Southwell et al., 2014). This approach has been successful in mouse models of epilepsy (Hunt et al., 2013), where a loss of inhibition can be the major driver of the disorder. Other disorders such as ASD and SCZ might also benefit from this potential therapy (Gilani et al., 2014), particularly if transplants into specific structures (such as the PFC or hippocampus) are sufficient to ameliorate symptoms.

A recent approach has also highlighted the potential to screen for human disease mutations by screening the *in vivo* development of transplanted mouse MGE cells in which an endogenous gene is replaced by a human disease allele that harbors a single missense mutation (Vogt et al., 2015). This study revealed that human *PTEN* mutant ASD alleles are hypofunctional compared with the wild-type human gene, in terms of regulating PV^+ CIN numbers. Not only can this complementation assay identify mutant alleles that contribute to the disorder, but it also offers mechanistic insights into how certain genetic mutations can lead to specific phenotypes.

Studies are also underway to program human embryonic stem cells and human iPSCs into functional GABAergic CINs (Nicholas et al., 2013). Recent advances in our understanding of the mechanisms of CIN development, such as those described above, have been essential to these efforts. Generating defined mixtures, and/or specific subgroups, of *in vitro* programmed human CINs holds promise as a potential treatment for a range of neural diseases. However, there are several hurdles that the field must first overcome. First, achieving a pure population of a human CIN subtype remains to be accomplished. Next, the efficiency of CIN generation needs to be improved. Furthermore, the recipient's diseased CNS may impair the survival, differentiation and/or function of the transplanted CINs. Ideal treatment cases would be focal disorders of excessive local excitation, where CINs could rebalance the excitation/inhibition ratio. However, this type of approach is currently only a tangible and testable option, and future studies will determine whether this type of treatment is indeed feasible.

Conclusions

To better understand neuropsychiatric disorders and to engineer specific CIN subtypes from stem cells, the genetic mechanisms controlling the development of CINs must be elucidated. Although tens of genes identified in mouse studies have been shown to be crucial in CIN development, many aspects of the genomic, cellular and biochemical mechanisms underlying CIN formation remain unknown. Single-cell RNA-Seq will enable a more thorough analysis of the combinatorial expression of genes, and should enable the discovery of novel key regulators. High-resolution lineage-tracing methods, in conjunction with conditional mutagenesis, will improve the spatial and temporal precision needed to define at the single-cell level when and where genes impact CIN development. The application of genomic methods is also needed to define the relevant regulatory elements, epigenomic regulators and transcriptional circuits that influence CINs. Progress in all of these approaches will together provide a fuller picture of CIN specification. Given that many of the TFs that are active in CIN progenitors continue to be expressed throughout adulthood, this progress will also provide insights into the mechanisms that drive the later steps of CIN maturation, function and dysfunction.

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Competing interests

J.L.R. is cofounder, stockholder, and currently on the scientific board of Neurona, a company studying the potential therapeutic use of interneuron transplantation.

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Supplementary information

Supplementary information available online at
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