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The development of MGE-derived cortical interneurons: An Lhx6 tale

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ABSTRACT The cerebral cortex contains two main neuronal cell populations: the excitatory pyramidal neurons and the inhibitory interneurons, which constitute 20-30% of all cortical neurons. Cortical inter- neurons are characterized by a remarkable morphological, molecular and functional diversity. A swathe of research activity over the last 20 years has sought to determine how cortical interneurons acquire their mature cellular and functional features, and has identified a number of transcription factors that func- tion at different stages of interneuron development. Here, we review all current knowledge concerning the multiple functions of the "master regulator" - LIM-Homeodomain transcription factor Lhx6 - a gene expressed in the medial ganglionic eminence of the basal telencephalon that controls the development of somatostatin and parvalbumin expressing interneurons.

KEYWORDS: Lhx6, medial ganglionic eminence, cortical interneurons, parvalbumin, somatostatin, brain development

Introduction

GABAergic interneurons comprise 20-30% of all neurons in the cortex and are essential for cortical circuit function. They have multiple roles, from maintaining excitation/inhibition balance and synchronizing brain activity, to refining cortical processing in unique and multiple ways. Their functional diversity is enabled through their remarkable heterogeneity at the molecular, morpho- logical and electrophysiological level. This diversity begins during embryonic development.

In mammals, most cortical and hippocampal interneurons are born in three distinct regions of the basal telencephalon: the medial ganglionic eminence (MGE), the caudal ganglionic eminence (CGE) and the preoptic area (POA) (Wonders and Anderson 2006; Kessaris et al. 2014; Lim et al. 2018). Each of these regions gives rise to distinct cohorts of interneurons of the cortex and hippocampus. The MGE is the largest source of interneurons for the cortex, generating around 60% of the total population. This includes two major classes: a) interneurons that are characterized by the expression of the calcium binding protein parvalbumin (PV), which exhibit fast-spiking firing properties, including basket, Chandelier and translaminar interneurons; and b) interneurons that are characterized by the expression of the neuropeptide somatostatin (SST) and the preferable dendritic targeting of their synapses. SST-expressing interneurons can be further subdivided into Martinotti, non-Martinotti and long-range GABAergic projection neurons.

Tremendous efforts have been made in the last 20 years to identify molecular mechanisms controlling interneuron develop- ment, after Anderson and colleagues discovered the origin of cortical interneurons in the embryonic subpallium (Anderson et al., 1997). Although our knowledge is still limited, details about the genetic cascades of transcription factors regulating MGE derived interneuron specification, migration and differentiation/maturation have begun to emerge. At the core of these gene networks is the LIM-homeodomain transcription factor Lhx6. In this review, we describe all current knowledge of the multiple functions of LHX6 at different stages of cortical interneuron development.

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The LHX6/LHX8 group of LIM/homeodomain proteins

LIM/homeodomain genes encode transcription factors that are characterized by the association of two N-terminal LIM domains with a C-terminal homeodomain. The LIM motif encodes metal-binding cysteine and histidine-rich domains (Michelsen *et al.* 1994; Pérez-Alvarano *et al.* 1994, 1996; Konrat *et al.* 1997), and was first identified in the protein product of three genes: the nematode lin-11 (Freyd *et al.*, 1990); mec-3 (Way and Chalfie, 1988); and the rat Islet-1 (Karlsson *et al.*, 1990) genes. It has been suggested that the LIM domain functions as a protein-protein interaction motif (Schmeichel and Beckerle 1994; Arber and Caroni 1996), which regulates the binding specificity of the homeodomain to the DNA (Dawid *et al.*, 1998). Several members of this family have been implicated in regulating specific aspects of patterning, neuronal identity, differentiation, and axon pathfinding in diverse tissues in both invertebrate and vertebrate organisms (Hobert and Westphal 2000).

LIM/homeodomain proteins can be subdivided into six classes, based on the sequence conservation of their homeodomain (Hobert and Westphal 2000). Lhx6 and Lhx8 (also termed L3 or Lhx7) (Grigoriou *et al.*, 1998) belong to the most divergent class of LIM/homeodomain encoding genes (Hobert and Westphal 2000), which also includes the Drosophila arrowhead (Curtis *et al.*, 1995) and the C.elegans lim-4 (Sagasti *et al.*, 1999). Lhx6 and Lhx8 were first identified in a genetic screen performed to discover novel members of the LIM homeodomain family of transcription factors involved in the development of the nervous system (Grigoriou *et al.*, 1998). During development, both genes are expressed in a highly overlapping pattern in the first branchial arch and the forebrain (Grigoriou *et al.*, 1998).

Lhx6 and Lhx8 mRNAs are first detected in the oral ectomesenchyme of the maxillary and mandibular processes of the first branchial arch and the palatal shelves, at embryonic day (E)9.5. Their expression is progressively restricted to the mesenchyme of individual teeth, and is finally downregulated by postnatal day (P) 2 (Grigoriou *et al.* 1998; Zhao *et al.* 1999; Denaxa *et al.* 2009). Genetic loss of function studies using embryos deficient for both Lhx6 and Lhx7 highlighted their role in tooth development and patterning, as well as for normal cranial skeleton and palatal formation (Denaxa *et al.*, 2009).

In the forebrain, expression of Lhx6 and Lhx8 is first detected around E11.5 in the MGE (Grigoriou *et al.*, 1998). However, their expression is progressively restricted into distinct neuronal populations. In the adult mouse brain, Lhx6 is expressed in interneurons of the striatum and the cortex (see next section), whereas Lhx8 expression is maintained in cholinergic (ChAT) projection neurons of the basal forebrain, and ChAT[+] interneurons of the striatum (Asbreuk *et al.* 2002; Zhao *et al.* 2003; Fragkouli *et al.* 2005). Analysis of several different Lhx8-deficient mouse lines revealed a requirement for LHX8 for the specification of these two neuronal types (Zhao *et al.* 2003; Mori *et al.* 2004, Fragkouli *et al.* 2005). Moreover, a number of studies established that LHX8 forms a hexamer with ISLET1, another LIM-homeodomain transcription factor, and together they determine the cholinergic neuronal fate in the vertebrate basal telencephalon (Fragkouli *et al.* 2009, Lopes *et al.* 2012; Cho *et al.* 2014).

Finally, Lhx6 and Lhx8 are also expressed in certain domains of the developing hypothalamus and distinct hypothalamic nuclei in the adult brain (Grigoriou *et al.* 1998; Blackshaw *et al.* 2010; Kim *et al.* 2021). LHX6 in particular has been shown to be implicated in an amygdalar-hypothalamic pathway controlling reproductive behaviours (Choi *et al.*, 2005), and more recently in promoting sleep by controlling the function of a specific subpopulation of GABA-expressing neurons of the ventral zona incerta, in the hypothalamus (Liu *et al.*, 2017).

Induction and regulation of Lhx6 expression in the MGE

During embryogenesis, Lhx6 expression begins around E11.5 in the subventricular (SVZ) and mantle zone (MZ) of the MGE, while it is largely excluded from any other adjacent basal forebrain structures (Grigoriou *et al.*, 1998). Lhx6 expression is directly activated by Nkx2.1 (Du *et al.* 2008; Sandeberg *et al.* 2016), a homeobox transcription factor that plays a fundamental role in the specification of the MGE neuroepithelium (Sussel *et al.*, 1999). Nkx2.1 mutants show severe patterning defects in the basal forebrain and a dramatic loss of Lhx6, as well as Lhx8 and Shh expression, the latter being a known ventralising morphogen (Sussel *et al.*, 1999). Interestingly, at later developmental stages, the network dynamics among these four genes change. Flandin et al., proposed a model in which LHX6 together with LHX8 promote the activation of the Shh gene in the same cells. SHH secretion from Lhx6/Lhx8-positive cells feeds forward onto the overlying ventricular zone (VZ) of the MGE, further promoting its identity, via the upregulation of Nkx2.1 and Nkx6.2 transcription factors (Flandin *et al.*, 2011).

More recently, the CTCF (CCCTC-binding factor) genome organizing protein has been shown to regulate the expression of Lhx6 in the MGE. CTCF is not important for Lhx6 induction, since early Lhx6 expression is unaffected in Ctcf cKO embryos, but has a critical role in maintaining its optimal expression levels in immature GABAergic cells of the MGE. Several of these cells are known to co-express LHX8 (Fragkouli *et al.* 2009; Lopes *et al.* 2012). In Ctcf mutants, Lhx6 downregulation is complemented by an up-regulation of Lhx8 expression in the MGE, which most probably results in the change of fate of Lhx6^{+} GABAergic cells destined for the cortex, to Lhx8^{+} GABAergic projection neurons that remain in the basal forebrain (Elbert *et al.*, 2019). Several CTCF binding sites have been identified in both Lhx6 and Lhx8 loci (Elbert *et al.*, 2019). Thus, CTCF might regulate the choice between these two cell fates by gating a cross inhibitory regulation between Lhx6 and Lhx7.

The zinc-finger transcription factor Sp9 has been also been identified as a regulator of Lhx6 expression in the MGE. Chromatin immunoprecipitation sequencing (ChIP-Seq) experiments have identified several Sp9 peaks in the promoter and enhancer regions of Lhx6, while binding of Sp9 in one of these regulatory sequences activates transcription in an *in vitro* cell system (Liu *et al.*, 2019). However, the complex phenotype of Sp9 cKO mice suggests that the modest decrease of Lhx6 expression that is observed in the MGE of the mutant mice might be partially responsible for the multiple defects of Sp9^{-} MGE-derived cortical interneurons.

Nkx2.1 is only briefly expressed in the MGE lineage, and although it is required for the induction of Lhx6, its function is dispensable for the maintenance of Lhx6 expression (Sandeberg *et al.*, 2016). On the other hand, Lhx6 expression is maintained in tangentially migrating interneurons (Lavdas *et al.* 1999; Liodis *et al.* 2007, Zhao *et al.* 2008), as well as in differentiated interneurons of the postnatal and adult brain. LHX6 is exclusively expressed in nearly
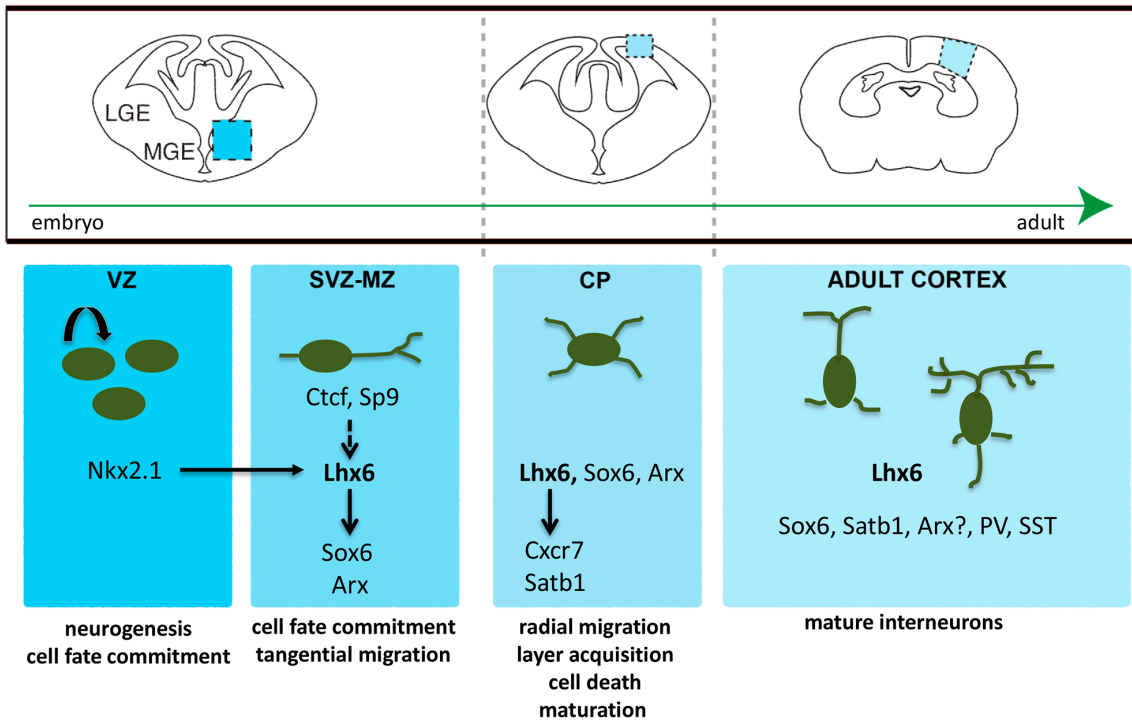
100% of MGE-derived PV-and SST-expressing interneurons within the adult cortex and hippocampus (Fogarty *et al*. 2007; Liodis *et al.* 2007; Zhao *et al.* 2008) (Fig. 1).

The role of Lhx6 in cortical interneuron development

Following description of the unique expression pattern of Lhx6 in the embryonic and adult telencephalon, several groups have begun to investigate its role in cortical interneuron development. The first loss of function data for Lhx6 resulted from small interfering RNA (siRNA) studies. Focal electroporation of an Lhx6 siRNA in the MGE of mouse embryonic brain slices inhibited the migration of GABAergic interneurons into the cortex (Alifragis *et al*., 2004).

Generation and analysis of the first Lhx6 mutant animals confirmed the above *in vitro* results, and further revealed that LHX6 controls not only the tangential but also the radial migration of immature interneurons into the cortex, as well as their differentiation into PV- and SST-expressing interneurons. More precisely, Lhx6$^{-/-}$ animals presented a delay in the front of migration during embryonic stages, but examination of their cortices at P15 revealed a similar number of GABA-expressing interneurons compared with controls, although their distribution into the various cortical layers was affected. In addition, Lhx6-null mutant mice displayed a severe reduction in both SST$^+$ and PV$^+$ interneuron numbers within the cortex (Liodis *et al*., 2007).

Zhao et al., using a different Lhx6 loss of function allele (Lhx6$^{PLAP/PLAP}$), confirmed the above results and further identified additional molecular defects in Lhx6$^{PLAP/PLAP}$ interneurons, including a reduction in the Cxcr4 and Arx expression levels (Zhao *et al*., 2008; see also subsequent sections).

More recently, generation of a novel conditional allele of Lhx6 (Lhx6^{fl}) in the mouse, allowed for MGE- specific Lhx6 ablation and simultaneous fate mapping of the MGE lineage. Notably, analysis

of the above mice revealed that the number of MGE-derived interneurons was dramatically reduced in mutant mice compared with controls, suggesting that in addition to its previously described roles, Lhx6 is also required for the survival of MGE-derived interneurons. Indeed, further experiments revealed that Lhx6-deficient MGE-derived interneurons displayed a marked increase in apoptosis, even before the expected developmental cell death program begins (Denaxa *et al*., 2018a). These results, which initially seemed to contradict the original observations showing no significant loss of interneurons in the cortex of either Lhx6 null mutant mice described above (Liodis *et al*. 2007; Zhao *et al*. 2008), prompted the authors to investigate the lineage-identity of GABA-expressing interneurons that are found in Lhx6 mutant cortices. Fate mapping experiments across different developmental stages showed an increased representation of CGE-derived interneurons in the cortex of Lhx6 null mice, which was evident from early postnatal stages and was due to an increase in the fraction of CGE-derived interneurons that survive (Denaxa *et al*., 2018a). It is worth mentioning that this work was the first to present evidence of a non-cell autonomous mechanism controlling the survival of cortical interneurons (for review see Denaxa *et al*. 2018b; Wong and Marin 2019).

Downstream effectors of LHX6 function in cortical interneuron development

With the role of LHX6 in cortical interneuron development well established, several studies have been set up to unravel molecular cascades under LHX6 function (Denaxa *et al*. 2012; Sandberg *et al*. 2016). Here we describe the most prominent LHX6 effectors (Fig. 1).

The first gene described to act genetically downstream of LHX6 was the Sex Determining Region Y (SRY)-Box transcription factor SOX6. Both histological analysis and genome-wide gene expression profiling revealed a dramatic decrease in Sox6 expression levels

TABLE 1

TRANSCRIPTION FACTORS OF THE LHX6 NETWORK AND REPORTED FUNCTION IN CORTICAL INTERNEURON DEVELOPMENT

Transcription Factors	Mouse phenotype relevant to cortical interneuron development	Association with human psychiatric/disorders	References*
ARX	Aberrant migration and differentiation of cortical interneurons	X-linked Mental Retardation with epilepsy and spasticity X-linked Lissencephaly with ambiguous genitalia X-linked Infantile Spasms syndrome Partington syndrome Proud syndrome West Syndrome	Marsh and Golden, 2012
CTCF	Cell fate Migration Laminar Distribution	Mental Retardation-21	Gregor *et al.*, 2013 Janowski *et al.*, 2021
LHX6	Cell fate Migration Laminar Distribution Survival Differentiation	Schizophrenia Turret Syndrome	Volk *et al.*, 2012, Volk *et al.*, 2014, Volk *et al.*, 2016, Bowen *et al.*, 2019 Pagliaroli *et al.*, 2020
NKX2.1	Neuroepithelial patterning Cell fate Migration		
SATB1	Maturation	Autism	Parikshak *et al.*, 2013 J den Hoed *et al.*, 2021
SOX6	Migration Laminar Distribution Differentiation		
SP9	Cell fate Migration		

*Literature providing insight into the association of the described transcription factors with psychiatric/neurological disorders

in the cortex of Lhx6 null compared with control mice (Batista-Brito *et al.* 2009; Denaxa *et al.* 2012). Similarly to Lhx6, Sox6 is expressed only in MGE-derived interneurons, and Sox6-deficient mice exhibit defects in the differentiation and function of PV+ and SST+ cortical interneurons (Azim *et al.* 2009; Batista-Brito *et al.* 2009). Notably, the number of PV-expressing interneurons was more severely affected than that of the SST positive interneuron subset, suggesting that Sox6 might play a more prominent role in the differentiation of PV+ cortical interneurons (Batista-Brito *et al.*, 2009). Nevertheless, overexpression of Sox6 in Lhx6 mutant MGE cells transplanted into the cortex of control mice rescued neither PV or SST expression, while Sox6 overexpression into control MGE cells increased the percentage of SST- vs PV-expressing transplanted cortical interneurons (Vogt *et al.*, 2014).

The Aristaless-related homeobox transcription factor (Arx) is another downstream effector of LHX6. Arx expression begins as early as E10.5 in the developing subpallium, and in contrast to Lhx6, its expression is not restricted only in the MGE, but is rather evident in all GE subdomains, as well as the POA (Cobos *et al.*, 2005). As a result, Arx null mice are characterized by abnormal basal ganglia morphogenesis, and exhibit aberrant migration of GABA-expressing cells towards the cerebral cortex (Colombo *et al.*, 2007). Histological and genome-wide gene expression experiments in Lhx6 null compared with control mice were the first to suggest that Lhx6 might be genetically upstream of Arx (Zhao *et al.* 2008; Denaxa *et al.* 2012). Subsequently, chromatin immunoprecipitation experiments clearly showed that LHX6 binds to enhancer elements near the Arx gene locus, while overexpression of ARX in Lhx6-deficient interneuron progenitors transplanted into control cortices rescued the expression of SST and PV, but failed to rescue their laminar distribution (Vogt *et al.*, 2014).

As mentioned above, Lhx6 null mice are characterized by both a delay in their migration towards the cortex and an aberrant laminar distribution of GABA-expressing neurons. More specifically, MGE-derived cortical interneurons in Lhx6 mutants are lost in the middle cortical layers (IV) and are accumulated in superficial and deeper layers (I and V/VI) of the cortex (Liodis *et al.* 2007; Zhao *et al.* 2008; Denaxa *et al.* 2018). Previous studies have shown that these migratory events are mediated by chemokine signalling. CXCL12 (also known as stromal-derived factor 1, SDF-1) is a chemoattractant for cortical interneurons; its prenatal expression in the meninges and the intermediate and sub-ventricular zones (IZ/SVZ) of the developing cortex attracts immature cortical interneurons, expressing the receptors CXCR4 and CXCR7 and promoting their migration along the appropriate routes (Stumm *et al.* 2003; Lopez-Bendito *et al.* 2008; Sanchez-Alcanir *et al.* 2011; Wang *et al.* 2011). CXCR7 expression is greatly reduced in the MGE and migrating MGE-derived cells in Lhx6 mutants (Zhao *et al.*, 2008). In addition, LHX6 directly binds to a Cxcr7 enhancer, and together with its cofactor Ldb1, modulates its activity *in vitro*. Finally, overexpression of CXCR7 partially rescued the laminar distribution of Lhx6-deficient MGE-derived cortical interneuron transplants (Vogt *et al.*, 2014).

The special AT-rich sequence binding protein Satb1 has been found to be downregulated in a genome-wide gene expression profiling study on the dorsal forebrain of E15.5 Lhx6 mutants versus control littermates (Denaxa *et al.*, 2012). Expression analysis in the adult cortex revealed that Satb1 expression is restricted in the MGE-derived lineage of cortical interneurons. In addition, analysis of two independently generated Satb1 mutant lines demonstrated a dramatic decrease in the number of SST- and to a lesser extent of PV-expressing cortical interneurons, in part due to cell death (Close *et al.* 2012; Denaxa *et al.* 2012). Furthermore, SATB1 overexpression in Lhx6 mutant MGE progenitors, which have been cultured on cortical feeder cells from control mice, partially rescued SST expression, while overexpression of a Satb1-specific ShRNA (Small Hairpin RNA) construct into control MGE cells using the same experimental set-up resulted in a dramatic reduction of SST-expressing interneurons. Although these results clearly demonstrated that Satb1 is genetically downstream of Lhx6, there were two pieces of evidence that clearly set Satb1 apart from any of the above-mentioned LHX6 effectors. First of all,

both MGE progenitors, as well as tangentially migrating immature interneurons, lacked SATB1 expression, which initiated only in interneurons that have been already located in the cortical plate (CP), during late embryonic stages (Close *et al.* 2012; Denaxa *et al.* 2012). Secondly, overexpression of LHX6 in MGE precursors failed to up-regulate SATB1 expression. These observations, in combination with the demonstration that neuronal excitability is sufficient to upregulate SATB1 in control but not Lhx6-deficient cultured interneurons, suggested that LHX6 might control later stages of interneuron development by initiating a gene expression profile that allows these cells to respond to emerging environmental cues of the developing brain (Denaxa *et al.*, 2012).

LHX6 and neurodevelopmental disorders

Loss of or aberrant cortical interneuron function has been associated with a number of neurodevelopmental disorders (Marin *et al.*, 2012) (Table 1). It is not surprising therefore that Lhx6 null mutant animals display defects in the inhibitory circuits of the cortex and hippocampus. More specifically, *Lhx6* null animals evidence a severe reduction in inhibitory synaptic currents, while hypomorphic Lhx6 mutants, which are characterized by aberrant defects in the number and function of SST- but not PV-positive interneurons, manifest spontaneous seizures from early postnatal stages (Neves *et al.*, 2013).

Similarly to rodents, the major source for cortical interneurons in humans and other primates is the basal telencephalon, which can be subdivided into analogous progenitor domains (Hansen *et al.* 2013; Ma *et al.* 2013). As in rodents, the human MGE is characterized by the expression of NKX2.1 and LHX6 (Hansen *et al.* 2013; Ma *et al.* 2013). In addition, LHX6 is expressed only in SST- and PV positive interneurons, as has been shown by histological analysis of human brain samples, as well as recent genome profiling experiments of human cortical neurons at the single cell level (Krienen *et al.*, 2020). Although *Lhx6* deficient mice develop seizures, LHX6 has not yet been associated with epilepsy in humans. Nevertheless, LHX6 is considered a biomarker for schizophrenia (SCZ), since numerous studies reported a reduction in LHX6 mRNA levels in the PFC of a subset of SCZ subjects (Volk *et al.* 2012, 2014, 2016; Bowen *et al.* 2019). Moreover, recent in silico studies have also identified a positive association between SNPs located in the 3'UTR region of LHX6 and Tourette Syndrome, a neurodevelopmental disorder with a very complex aetiology and pathophysiology (Pagliaroli *et al.*, 2020).

Concluding Remarks

The emergence of novel sequencing methods that allow the profiling of transcriptome and chromatin states from thousands of individual neurons has revolutionized brain development. Several large-scale molecular profiling studies have already revealed a greater molecular diversity of interneurons than previously described (Huang and Paul, 2019). So far, these studies establish that Lhx6 *and* Nkx2.1 are foundational core transcripts for all interneuron identities arising from the MGE (Nowakowski *et al.* 2017; Huang and Paul, 2019). This coincides with work showing that LHX6 and NKX2.1 bind to common regulatory elements (REs) in the MGE that primarily mediate transcriptional activation (Sandberg *et al.*, 2016). Thus, LHX6 together with NKX2.1 pro-

mote a transcriptionally permissive chromatin state and initiate a transcriptional program that controls fundamental molecular and cellular properties, which most probably are common to all MGE-derived interneuron subtypes. Nevertheless, LHX6 might also act together with different transcription factors to promote distinct MGE interneuron fates. For example, it has been suggested that LHX6 together with DLX1 promote the SST fate, whereas the combined function of LHX6 and DLX5/6 promotes the PV identity (Wang *et al.*, 2010). Additionally, interesting findings in hypomorphic Lhx6 mutants, where only SST- but not PV-expressing interneurons are affected (Neves *et al.*, 2013), suggest that differences in the dose requirements for LHX6 expression, therefore the differential binding of LHX6 to yet to be identified transcriptional cofactors, might also be implicated in MGE-derived interneuron cell fate decisions. Finally, Lhx6 expression is maintained in cortical and hippocampal PV- and SST-expressing interneurons during postnatal stages and in adulthood, the functional implications of which remain unknown. Further exploration of the molecular mechanisms underlying LHX6 function in the generation of interneuron types, as well as its potential role in the temporal progression of interneuron maturation, will enhance our understanding of genetic programs controlling cortical interneuron fate and function.

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