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REVIEW

Mechanisms regulating GABAergic neuron development

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Abstract Neurons using gamma-aminobutyric acid (GABA) as their neurotransmitter are the main inhibitory neurons in the mature central nervous system (CNS) and show great variation in their form and function. GABAergic neurons are produced in all of the main domains of the CNS, where they develop from discrete regions of the neuroepithelium. Here, we review the gene expression and regulatory mechanisms controlling the main steps of GABAergic neuron development: early patterning of the proliferative neuroepithelium, production of postmitotic neural precursors, establishment of their identity and migration. By comparing the molecular regulation of these events across CNS, we broadly identify three regions utilizing distinct molecular toolkits for GABAergic fate determination: telencephalon–anterior diencephalon (DLX2 type), posterior diencephalon–midbrain (GATA2 type) and hindbrain–spinal cord (PTF1A and TAL1 types). Similarities and differences in the molecular regulatory mechanisms reveal the core determinants of a GABAergic neuron as well as provide insights into generation of the vast diversity of these neurons.

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Abbreviations

AP	Anterior-posterior
bHLH	Basic helix-loop-helix
cb	Cerebellum
CGE	Caudal ganglionic eminence
CNS	Central nervous system
CoP	Commissural pretectum (mixed GABAergic and glutamatergic)
dI4, dI6, dILa	Subpopulations of GABAergic neurons in dorsal spinal cord
DV	Dorso-ventral
GABA	Gamma-aminobutyric acid
hb	Hindbrain
HD	Homeodomain
hyp	Hypothalamus
JcP	Juxtacommissural pretectum (GABAergic)
LGE	Lateral ganglionic eminence
mb	Midbrain
m1–m5	Progenitor domains producing GABAergic neurons in midbrain
MGE	Medial ganglionic eminence
MHB	Midbrain–hindbrain boundary
MZ	Mantle zone
OB	Olfactory bulb
p1	Prosomere 1, pretectum
p2	Prosomere 2, thalamus
p3	Prosomere 3, prethalamus
PcP	Precommissural pretectum (glutamatergic)
POA	Preoptic area
pTHr	Rostral thalamus (GABAergic)
pTHc	Caudal thalamus (glutamatergic)
sc	Spinal cord

SNpr	Substantia nigra pars reticulata
SVS	Subcortical visual shell nuclei
SVZ	Subventricular zone
tel	Telencephalon
TF	Transcription factor
V0–V2	Subpopulations of GABAergic neurons in ventral spinal cord
VTA	Ventral tegmental area
VZ	Ventricular zone
ZF	Zinc finger
ZLI	Zona limitans intrathalamica

Introduction: steps of neuronal fate specification during development

Neuronal fate specification during development is a multistep process through a gradual restriction in cellular competence, culminating in the establishment and maintenance of a defined phenotype (Fig. 1). The earliest step restricting cellular competence during development is patterning of the proliferative neuroepithelial cells: exposure of multipotent progenitor cells to regional patterning molecules secreted by adjacent tissues and local organizers in the developing neural tube [1, 2]. Patterning cues trigger an array of downstream signaling events that are thought to manifest in a combinatorial expression of multitude of downstream homeodomain (HD) transcription factors (TFs), giving cells unique identities depending on their exact spatio-temporal position in the neural tube. Patterning genes establish and maintain domain borders in the CNS, often by mutual cross-repression. Loss of patterning gene function is accompanied with a loss of domain-specific identity, which is often compensated by a respective expansion of adjacent domains.

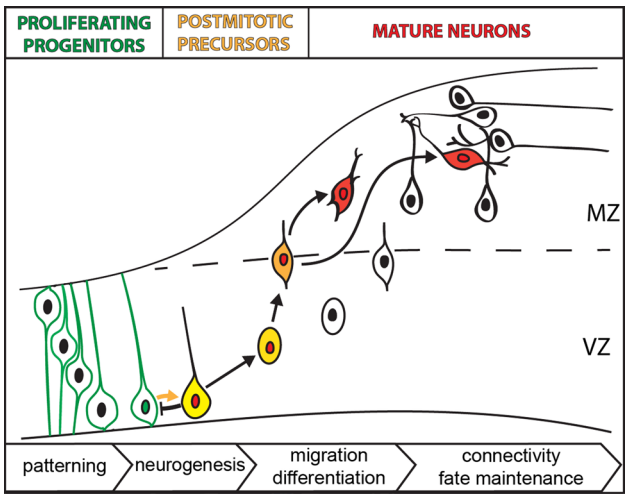

Fig. 1 Steps of neuronal development. Proliferative, multipotent progenitors reside in the ventricular zone (VZ) where they get a regional identity (patterning) by intercellular signals. Progenitors undergo neurogenic divisions, generating both proliferative progenitor cells (*green*) and newly born postmitotic precursors (*yellow*, *red* nucleus). The lateral inhibition process prevents differentiation of adjacent progenitors. Postmitotic precursors (*orange*) move out of VZ to mantle zone (MZ) while undergoing terminal differentiation process (*red*). Once out of the VZ, the precursors may tangentially migrate to their final positions and they establish contacts with their targets. In contrast to this simplified scheme presented here, additional progenitor populations exist in some brain regions such as the forebrain

At the time of neurogenesis—exit of postmitotic precursor cells from the ventricular zone (VZ) neuroepithelium—basic helix-loop-helix (bHLH) genes are central to the timing (and nature) of the execution of differentiation programme in competent progenitors [3] (Fig. 2). bHLH gene activity follows the HD TF expression borders and progenitor cells fated for the same cell type typically express the same bHLH TFs. Such neuronal cell type-specific bHLH factors fall into so-called proneural gene families, showing molecular and functional similarity to *Drosophila* proneural genes [4]. Antagonism between different bHLH factors is evident in some regions of the developing CNS, but the mechanistic basis of cross-repression between proneural genes has not been demonstrated. The borders of proneural gene expression domains may also be maintained either by patterning genes or by dedicated bHLH or HD TFs that can be widely coexpressed with a particular proneural gene and repress the alternative proneural factors. Recent research shows that HD proteins can act in synergy with proneural proteins in neuronal progenitors to promote a commitment to a particular fate [5, 6]. Fate priming effect could be manifested for example via cross-talk with Notch pathway, chromatin remodeling factors or shifting of proneural gene activity towards cell cycle exit-promoting targets [7, 8]. Direct protein–protein interactions between proneural and HD TF have been shown to facilitate DNA binding and mediate activation of specific target genes [5, 6]. Such interactions provide a direct link between a HD code, proneural genes, and neuronal fate specification in the neural tube.

Exposure to an appropriate set of patterning cues and proneural activity, however, does not impose an imperative differentiation regime on neuronal progenitors. Several observations point towards a crucial function of postmitotic selector genes in the control of the identity of neuronal precursors as they move into the mantle zone (MZ). First, although the proliferative neural progenitors already contain specific TF codes, production of definitive neuronal components, including subtype-specific gene products, is activated only at the cell cycle exit. Second, there exist bi- or multipotent progenitor domains that give rise to different types of neurons in parallel or sequentially. Third, inactivation or ectopic expression of certain TFs in newly born neurons can trigger commitment to an alternative fate. For

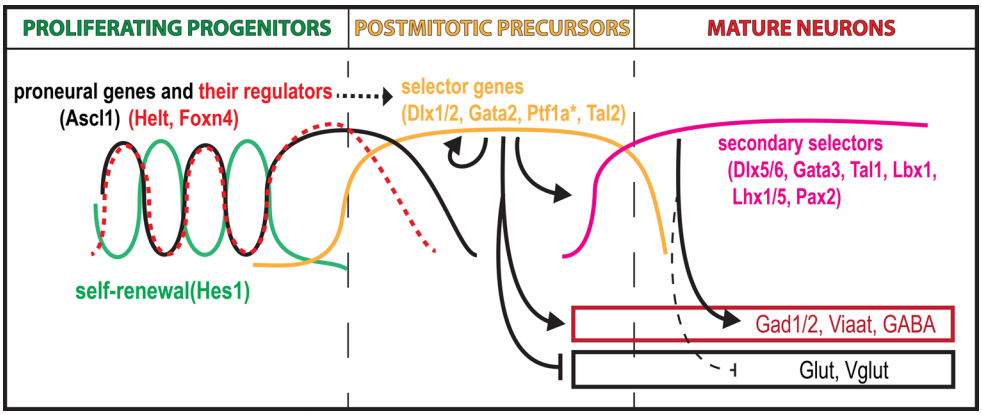

Fig. 2 Gene regulatory mechanisms underlying GABAergic fate specification. The *graphs* represent the expression level of key TFs during the course of GABAergic neuron development. In the proliferative progenitor cells, the expression levels of proneural genes and their regulators oscillate with the phase of the cycle opposite to the self-renewal promoting genes (such as *Hes1*). Cell cycle exit occurs at the high expression phase of proneural genes. At cell cycle exit, proneural gene expression is briefly stabilized and self-renewal genes silenced. At the same time, the expression of primary fate selectors is induced. Primary fate selectors positively autoregulate their own expression and induce subtype-specific genes as well as downstream TFs (secondary selector genes) in the neuronal precursors. As neurons mature, primary fate selector gene expression often ceases while the regulation of subtype-specific genes may be carried out by the secondary selector genes. The *asterisk* indicates that, unlike the dorsal spinal cord where *Ptf1a* induction is observed at cell cycle exit, *Ptf1a* is expressed already at the progenitor stage in the cerebellar ventricular zone

example, GABAergic to glutamatergic fate switch has been observed in striatal precursors upon misexpression of the zinc finger (ZF) TF FEZF2 [9], which normally determines specific subtype identities in cortical glutamatergic neurons and diencephalic identity [10, 11]. Similar examples of TFs driving GABAergic differentiation have also been identified (see below). Thus, the definitive fate specification can occur at the time of or shortly after the neurogenic cell cycle exit. In this step, selector and terminal differentiation genes activate so-called differentiation cassettes—sets of genes allowing the neuron to exhibit its fate-specific function [12] (Fig. 2). Loss or gain of a selector gene function can lead to activation of an alternative differentiation cassette, regardless of the cells' patterning history. Therefore, this scenario will not affect numbers of postmitotic neural precursors, but alters their cellular subtype composition, function, and connectivity.

The neuronal fate also requires active maintenance [13]. Transcriptional regulatory mechanisms controlling neuronal differentiation often retain activity also in the mature neurons. Recent studies have demonstrated cases of continuous requirement of developmental regulators for the expression of neuron-type-specific genes postnatally [14, 15].

The TFs defining specific progenitor domains, the proneural genes expressed in these domains, and the domain-specific neuronal progeny have been depicted for nearly all brain regions: telencephalon [16, 17], diencephalon [18–20], midbrain [21, 22], rhombomere 1 [23–25], other rhombomeres [26, 27], and spinal cord [28, 29]. In this review, we aim to unite this understanding to provide an overview of both shared and unique mechanisms of GABAergic neurogenesis in the different domains of the developing mammalian CNS (Fig. 3a).

Patterning of the neuroepithelial GABAergic progenitor populations

Early brain patterning

The early neural tube compartmentalizes into five large domains along anterior–posterior (AP) axis: secondary prosencephalon, diencephalon, mesencephalon or midbrain, rhombencephalon or hindbrain, and spinal cord. Molecular fingerprints underlying AP patterning of the CNS are established by extracellular signals, such as Wnts, fibroblast growth factors, and their inhibitors, from the organizer tissues both outside and within the neural tube [1, 30, 31]. Early brain domains are further divided into subdomains called neuromeres. A considerable body of fate-mapping studies have now been integrated into a neuromeric model, linking molecular AP coordinates of progenitor cells in a neural tube with their neuronal derivatives in the adult/mature CNS [32–34].

Throughout neuromeres, an array of dorso-ventral (DV) domains can be distinguished. These domains are also established by spatio-temporally graded extracellular signals, such as ventral Sonic hedgehog (SHH) and dorsal bone morphogenetic protein, whose activity is translated

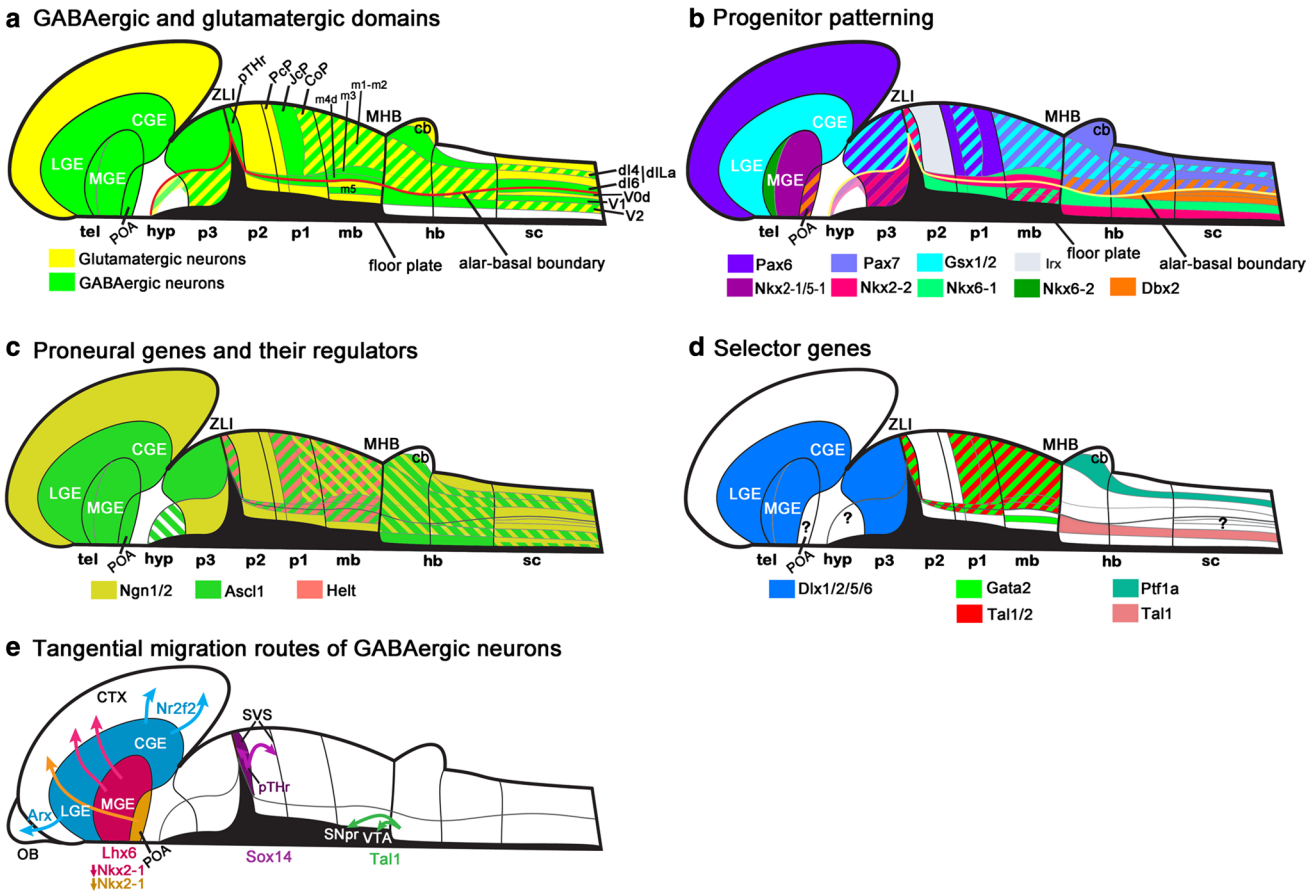

Fig. 3 GABAergic and glutamatergic domains and their gene-expression in the developing CNS. **a** Domains producing GABAergic and glutamatergic neurons. **b** Expression of TFs responsible for patterning of the proliferating progenitors. **c** Expression of proneural genes and their regulators, which control several aspects of neurogenesis. **d** Requirements for selector genes in the differentiation of the postmitotic GABAergic precursors. Note that the domain of selector gene expression can be larger than the domain of its function. For example, *Gata2* is expressed in the ventral hindbrain, but not required for GABAergic fate selection there. Some of the GABAergic domains have not been associated with a selector gene function to date (labeled with *question marks*). **e** Known tangential migration routes and the TFs controlling the migratory behavior in GABAergic cells

into a well-described HD TF code defining distinct progenitor populations [2, 35, 36]. The DV patterning is best understood in the spinal cord, but the same mechanisms appear to operate in the other parts of the CNS.

GABAergic progenitor domains in the telencephalon

In the rodent telencephalon, the alar subdivision of the secondary prosencephalon, a sharp boundary (pallial–subpallial boundary) separates mutually exclusive domains of GABAergic and glutamatergic neurogenesis [37]. GABAergic neurons are generated from the subpallial neuroepithelium that comprises morphologically and molecularly distinct domains, the lateral, medial, and caudal ganglionic eminences (LGE, MGE, CGE) and the preoptic area (POA) [38] (Fig. 3a). Furthermore, at least 18 molecularly distinct subdomains have been identified in the subpallium [16]. Subpallial positions, and thus the respective HD TF-expression profiles of GABAergic neuron progenitors, have been associated with co-neurotransmitter and calcium-binding protein expression in the respective progeny, their target position in cortical layers, striatum, or hippocampus, and electrophysiological properties [31, 39–41].

While the TF code downstream of SHH is useful for determining the spatial identity of the domains of interest, there is little evidence supporting their direct involvement in the GABAergic fate determination in telencephalon. An exception to this is *Nkx2-1*, which is a patterning gene and seems to be involved in tangentially migrating interneuron subtype specification in the MGE and POA of the subpallium [42]. In *Nkx2-1* mutant mice, MGE territory transforms into LGE-like neuroepithelium [42] and fails to produce parvalbumin and somatostatin (SST)-positive cortical interneurons [39], as well as SST and neuropeptide Y (NPY)-positive GABAergic neurons of the hippocampus [43]. Recently, POA was shown to contribute SST, PV,

reelin, nitric oxide synthase, NPY, and vasoactive intestinal peptide (VIP)-producing GABAergic interneurons in deep layers of cortex [44, 45]. POA progenitors are characterized by *Dbx1, Nkx5-1*, and *Nkx2-1* coexpression. Genetic fate mapping with *Dbx1-cre* mice showed that migrating POA-derived cells produce NKX2-1 [44], which regulates their tangential migration pattern (see below). In contrast, it has not been demonstrated that NKX2-1 directly regulates genes associated with GABAergic neurotransmission.

Other TFs are also expressed in telencephalic GABAergic progenitors and are more clearly associated with fate-restriction functions (Fig. 3b). This seems to be achieved via suppression of factors promoting alternative fates. HD TFs *Gsx1/2* are expressed in all subpallial domains, POA and prosomere 3 (p3, prethalamus) of the diencephalon [16, 46, 47]. GSX2 is involved in defining the pallial–subpallial boundary by inhibiting expression of pallial TFs and specifying the LGE identity [48]. In the *Gsx2* mutant, a dual identity switch is observed in the LGE territory. The dorsal LGE acquires a pallium-like phenotype, accompanied by the ventral shift of the pallial–subpallial boundary [49]. As a result, expression of GABAergic markers (*Ascl1, Dlx1/2*, and *Gad1*) is lost and pallial glutamatergic markers (*Pax6*, *Ngn2* and *Tbr2*) upregulated in the dorsal LGE [17, 48, 50]. In contrast, ventral LGE of *Gsx1/2* mutants acquires properties similar to the MGE, upregulating *Lhx6* and *Nkx2-1* expression [17]. Overexpression of either *Gsx1* or *Gsx2* in dorsal telencephalon induces ectopic expression of GABAergic fate determinants (*Ascl1*, *Dlx1/2*) at the expense of glutamatergic fate (*Pax6*, *Tbr1* expression). Interestingly, GSX1 and GSX2 had an opposite impact on neurogenesis, while GSX1 promoted differentiation and GSX2 overexpression suppressed neurogenesis [51, 52]. Thus, GSX1/2 may control both GABAergic progenitor identity and contribute to timing of neurogenesis. In conclusion, it seems that NKX2-1 generally specifies tangentially migrating cortical interneuron progenitor identities in the MGE, CGE, and POA, while NKX2-1-negative cells in LGE remain flexible in their migration patterns. In the LGE (and likely CGE) GSX1/2 promotes commitment to GABAergic fate by suppressing pallial glutamatergic development but also regulates development of regionally specified subpopulations of GABAergic neurons.

In rodents, as discussed above, the regions producing glutamatergic and GABAergic neurons are largely segregated to dorsal (pallial) and ventral (subpallial) regions. In contrast, in primates, the pallial region also produces GABAergic neurons [53, 54]. These neurons appear to have characteristics, such as localization and co-neurotransmitter expression, which are distinct from the GABAergic neurons migrating from the ventral subpallial domains. In humans, up to two-thirds of the cortical GABAergic neurons were estimated to be derived from the dorsal neuroepithelium. In other regions of the brain, such as the midbrain, hindbrain, and spinal cord, the dorsal neuroepithelium gives rise to mixed populations of GABAergic and glutamatergic neurons. Therefore, by the production of GABAergic neurons in the dorsal telencephalon, primate species may realize an existing binary competence in the pallium. Furthermore, restriction to glutamatergic fate does not appear absolute in the rodent pallium either, as dorsal pallial progenitors also generate a specific subset of GABAergic interneurons migrating to the olfactory bulb (OB) [55, 56].

GABAergic progenitor domains in the diencephalon and midbrain

The developing diencephalon is divided into three main domains, prosomeres p3 (prethalamus), p2 (thalamus), and p1 (pretectum), which are further subdivided into smaller units. In the alar region, p1 gives rise to three (precommissural, juxtacommissural, and commissural pretectum; PcP, JcP, and CoP) and p2 to two (rostral and caudal thalamus; pTHr and pTHc) subdomains differing in their gene expression and neural derivatives [18, 57]. The patterning of the developing diencephalon is refined by Zona limitans intrathalamica (ZLI), a signaling center between p3 and p2, which secretes SHH, as well as other signaling molecules. Several diencephalic regions give rise to GABAergic neurons (Fig. 3a). The neuroepithelium of p3 molecularly resembles the GABAergic domains of anterior forebrain expressing *Gsx*, *Dlx*, and *Arx* genes. In addition, FEZF1 and FEZF2 are required for the patterning of p3 by counteracting thalamic (p2) identity, and for proper formation of the organizer ZLI between p3 and p2 [58]. In the alar p2 and p1, GABAergic neurons are derived from the pTHr, JcP, and CoP regions. These express SHH regulated HD TFs, such as *Nkx2-2*, as well as *Pax6* and *Pax7*, which define regional identities (Fig. 3b) [59]. *Gsx1* is expressed in the pTHr, but not required for development of this domain. In addition, throughout the basal p1 and p2, a small parabasal region gives rise to GABAergic neurons ([60], Allen Developing Mouse Brain Atlas, http://developingmouse.brain-map.org).

Several molecularly distinct GABAergic progenitor domains have been identified at different DV levels of the midbrain, as defined by expression of HD TFs, such as *Nkx6-1* and *Nkx2-2* [21, 22, 24]. The most dorsal regions of the midbrain and the CoP of the diencephalic p1 give rise to intermingled populations of GABAergic and glutamatergic neurons.

GABAergic progenitor domains in the hindbrain and spinal cord

In the hindbrain and spinal cord there are many subgroups of GABAergic progenitors expressing different TFs

responsible for their patterning (Fig. 3b). DV patterning divides the spinal cord into 11 progenitor populations (dorsal dP1–dP6 and ventral vP0–vP2, vMN and vP3), which produce distinct types of neurons. In addition to the spatial patterning, the progenitors may change over time as the timing of postmitotic differentiation from the progenitor domain also affects the phenotype of the neurons [61]. However, in the GABAergic neuron lineages, the mechanisms of this temporal patterning are not known.

In the ventral spinal cord, vP0, vP1, and vP2 give rise to molecularly distinct groups of GABAergic neurons. vP2 domain appears multipotent, generating GABAergic V2b (characterized by the expression of *Gata2, Gata3*, and *Tal1*), related V2c (*Sox1*-expressing) and glutamatergic V2a (*Chx10*-expressing) neurons [62–65]. Forkhead TF *Foxn4* is coexpressed with *Ascl1* in vP2 [66]. FOXN4 is required for GABAergic V2b and V2c, but not glutamatergic V2a neurogenesis from vP2 progenitors [66]. Overexpression of *Foxn4* results in ectopic GABAergic neurogenesis, but only in the presence of ASCL1 [66, 67]. vP0 and vP1 progenitor domains lie within the *Dbx2, Ngn1/2*-expressing territory [68]. Borders of dP6, vP0, and vP1 domains are defined by cross-repressive interactions between HD TFs NKX6-1/DBX2 and NKX6-2/DBX1 [69]. vP0 and vP1 give rise to a variety of cell types [70–72], but the mechanisms underlying this heterogeneity are poorly understood. Interestingly, the GABAergic nature of vP1 and vP0-derived interneurons is transient—they switch from GABAergic to glycinergic neurotransmission postnatally. vP0 progenitors are bipotent, giving rise to both GABAergic V0d and glutamatergic, $EVX1^+$, V0v commissural interneurons [68, 72]. *Dbx1* is expressed in the progenitors of both $EVX1^+$ and $EVX1^-$ progeny [68], and its function is required for the vP0 domain identity in both mouse [72, 73] and zebrafish [74]. Inhibitory commissural neurotransmission is affected in *Dbx1* mutant mice [72]. However, the specific function of DBX1 in the determination of the GABAergic V0v fate is impossible to assess directly without specific markers for this population. vP1 progenitors are patterned by DBX2 and NKX6-2, and they are fated to $EN1^+$ GABAergic interneurons [69, 75]. In *Nkx6-2* mutant spinal cord, ventral expansion of *Dbx1* is observed in the VZ concomitant with loss of $EN1^+$ and ectopic $EVX1^+$ cells in MZ [69].

In the dorsal spinal cord ($PAX7^+$), dP4 and dP6 domains generate *Lbx1, Pax2* expressing GABAergic neurons of spinal cord dorsal horn [76]. However, dP6 expresses *Dbx* genes similar to vP0 and vP1, and therefore its patterning resembles the more ventral domains. Early dP4 progenitors express *Gsx1/2* and *Ascl1* and generate dI4 interneurons. In dI4 cells GSX1/2 specify GABAergic competence by the repression of *Ngn2* in the progenitors, demonstrated by ectopic *Ngn1/2* expression in the dorsal spinal cord in *Gsx1/2* mutant mice, as well as the loss of *Ngn1/2* transcripts after overexpression of *Gsx2* [77]. In a later wave of neurogenesis, GABAergic dILa interneurons and glutamatergic excitatory dILb neurons are generated from a common progenitor pool in the dorsal spinal cord [78].

In the hindbrain, the progenitor domains appear similar to the spinal cord. Ventrally, GABAergic neurons are derived from *Nkx6-1*-expressing progenitors [24]. Some of these contribute to GABAergic neurons found in the dopaminergic nuclei of the midbrain [24, 60]. Although PTF1A marks dorsal proliferative GABAergic progenitor populations and is required for GABAergic neuron groups in the hindbrain [79], it is unclear whether it operates as a regional patterning gene. As PTF1A functions as a regulator of differentiation in the dorsal spinal cord, we discuss its function in this context below.

Comparison of the molecular identity of neuroepithelial domains giving rise to GABAergic neurons

In the early neuroepithelium, competence of GABAergic neurogenesis is centralized around the alar–basal boundary region and alar plate (Fig. 3a). The progenitor domains are patterned by multiple TFs, often belonging to the HD family and regulated by extracellular signals (Fig. 3b). Although some of these TFs, such as GSX1, are shared by several GABAergic domains from the telencephalon to spinal cord, none of them is present in all of the GABAergic progenitor domains or appears specific for the GABAergic phenotype (Fig. 3b).

While domains close to alar–basal boundary produce GABAergic neurons either exclusively or in spatially coherent groups, dorsal domains seem predisposed to bimodal competence and typically generate intermixed populations of GABA- and glutamatergic cells. Simultaneous generation of multiple cell types correlates with the overlapping expression of the proneural genes *Ascl1* and *Ngn1/2* in these regions (see below) (Fig. 3c). However, the production of distinct cell types in such populations is not necessarily temporally synchronized.

Neurogenesis: execution of competence

Neurogenesis and proneural genes

Molecular mechanisms driving neurogenesis are manifold, involving extrinsic signals, cell biological properties of the progenitors, and cell-intrinsic gene regulatory networks [4, 80]. Proneural factors are key transcriptional regulators of neurogenesis and comprise conserved bHLH TFs, such as ASCL1 and NGN1/2. Although first implicated in the neurogenic cell cycle exit and generic neuronal identity, these TFs also appear to directly control other aspects of neuronal

development, including progenitor proliferation, precursor fate selection and migration [3, 81]. In general, expression of the proneural genes shows a cyclic pattern in the neural progenitors, is briefly stabilized at the neurogenic cell cycle exit and down-regulated in the differentiating/maturing neurons [82] (Fig. 2). Traditionally, proneural TFs are thought to cell autonomously drive the cell cycle exit and expression of neuron-specific genes and, at the same time, through direct activation of the NOTCH ligand *Delta*, non-cell-autonomously stimulate NOTCH signaling and maintain stem/progenitor cell properties in the adjacent progenitor cells. The cell cycle exit function of proneural genes has been suggested to involve transcriptional regulation of cell cycle inhibitors as well as antagonism of SOXB1 transcription factors, which support the proliferative neural stem cell identity [83, 84]. However, the cell cycle regulatory function of the proneural genes appears more complex. For example, a recent study suggested that the direct transcriptional targets of ASCL1 include genes both inhibiting and promoting cell cycle progression [81]. The effect of the proneural TF gene on cell cycle may depend on different transcriptional cofactors, mode of expression (cyclic vs. stabilized expression) or post-translational modifications.

In addition to affecting the cell cycle, proneural genes regulate the identity of the differentiating neuron both directly, by activating neuron-specific genes, and indirectly by activating downstream TF cascades (see below). The expression of distinct proneural genes correlates with the type of neurons produced. For example, *Ascl1* is associated with GABAergic and *Ngn1/2* glutamatergic neurogenesis [3]. Although likely indirectly, ASCL1 and NGN1/2 have been shown to cross-repress each other in some brain regions, which can contribute to their distinct expression patterns.

Proneural gene function in the telencephalon

In contrast to the diversity of TFs that define and pattern the GABAergic neuron progenitor domains, almost all of the developing GABAergic neurons share the expression of the proneural gene *Ascl1* (Fig. 3c). However, although the GABAergic progenitor domains commonly express *Ascl1*, its role revealed by loss-of-function studies appears to be region-specific. In the ventral telencephalon, especially in MGE, ASCL1 is required in the VZ progenitors to generate sufficient subventricular zone (SVZ) basal progenitors and GABAergic neuron precursors [85]. In turn, increased *Ascl1* expression in the dorsal telencephalon can drive ectopic GABAergic neurogenesis [86]. Thus, in addition to the regulation of cell cycle exit, ASCL1 promotes development of GABAergic identity, both directly [81] and through activation of TF genes such as *Dlx* important for GABAergic identity (see below). Antagonistic interactions between proneural genes were also demonstrated in the dorsal telencephalon, where the loss of Ngn1/2 leads to upregulation of *Ascl1* and production of GABAergic neurons [87].

Proneural gene function in the diencephalon and midbrain

The complex roles of proneural factors are demonstrated in the diencephalon and midbrain, where ASCL1 has subdomain-specific functions. In the diencephalon, it promotes cell cycle exit in the p3 domain, inhibits cell cycle exit in the rostral p2 domain (pTHr) and suppresses *Ngn2* expression and glutamatergic neurogenesis in the p1 domain [19]. In the dorsal midbrain, ASCL1 is required for GABAergic neurogenesis. In contrast, without ASCL1 GABAergic neurogenesis is only delayed in the ventral midbrain, where Ascl1 controls cell cycle exit in a subdomain-specific fashion [88].

In the midbrain, the proneural gene function appears to be regulated by a bHLH-Orange domain TF HELT. *Helt* is expressed in a mosaic (likely cyclic) pattern in pretectal (p1), thalamic (pTHr) and midbrain proliferative GABAergic progenitors [19, 21, 89, 90]. *Helt* mutant mice display a defect in the production of midbrain GABAergic neurons, especially in superior and inferior colliculi, dorsal periaqueductal gray and midbrain reticular formation [90]. Despite these deficiencies, *Helt* mutant mice display no gross anatomical defects. Instead, except for the ventro-lateral embryonic midbrain (m5 domain), prospective GABAergic progenitors re-specify into glutamatergic phenotype expressing *Pou4f1* and *Vglut2* [22, 90]. As *Ngn1/2* are ectopically expressed in the *Helt*-deficient VZ, while *Helt* overexpression results in the loss of *Ngn1/2* expression, a model emerges where HELT directs the selection of GABAergic over glutamatergic fate via repression of *Ngn1/2*, which in turn promote glutamatergic neurogenesis [22]. On the other hand, increase in the numbers of $LHX1^+$, and $GAD1^+$ cells were observed upon *Helt* overexpression in the presence of ASCL1 [22, 91]. Also in cultured cells, cotransfection of *Helt* and *Ascl1* potentiated GABAergic differentiation [91]. These results indicate that HELT may also act as a priming factor promoting GABAergic neurogenesis upon *Ascl1* expression.

In addition to the midbrain, HELT also supports GABAergic progenitor identity of the pretectal progenitors in the diencephalic p1 [92, 93]. However, despite a fate switch to an excitatory phenotype, *Ngn1/2* were not upregulated in the p1 of *Helt* mutants [93].

Proneural gene function in the hindbrain and spinal cord

In the hindbrain and spinal cord, *Ascl1* and *Ngn1/2* expression patterns less clearly distinguish between GABAergic and other phenotypes. *Ascl1* expression is linked to

GABAergic neuron production in some ventral (NKX6-1$^+$) and dorsal (GSX1$^+$, PTF1A$^+$) domains. However, the medial (DBX2$^+$) GABAergic populations appear ASCL1 negative. In the developing cerebellum and dorsal spinal cord, ASCL1 is required for development of a subset of late born GABAergic interneurons [94–97]. However, during GABAergic neurogenesis from the cerebellar VZ, also *Ngn1/2* are expressed and may guide differentiation of specific subsets of GABAergic neurons [98, 99]. In particular *Ngn2*, a direct target of PTF1A, has been shown to be important for the cell cycle progression of progenitors of GABAergic Purkinje cells and the maturation of these neurons [99, 100].

Comparison of proneural gene function in brain regions giving rise to GABAergic neurons

In conclusion, a major regulator of GABAergic neurogenesis is the proneural TF ASCL1, which has multiple functions at different stages and regions undergoing production of postmitotic GABAergic precursors. In some domains, the proneural factors ASCL1 and NGN1/2 antagonize each other to control GABAergic vs. glutamatergic neurogenesis. HELT is a regulator of proneural gene activity and the neuronal differentiation balance specifically between ZLI and the midbrain–hindbrain boundary (MHB). In other regions, especially in the hindbrain and spinal cord, both ASCL1 and NGN1/2 may promote generic GABAergic development, but they also regulate differentiation of distinct GABAergic neuron subsets.

Subtype specification in postmitotic neurons

Selector genes and fate determinants

Although the expression of proneural genes can be spatially restricted, proneural activity mostly activates pan-neuronal genes and further regulation of neuronal fate involves additional subtype specification factors. Subtype specification factors are TFs, which act as promoters or inhibitors of a certain cell fate, driving neuronal precursors towards a specific subtype, simultaneously preventing expression of genes characteristic to other cell types. Such bimodal regulators are called selector genes and a few of them have been characterized in the choice between GABAergic vs. glutamatergic neuron phenotype in the mammalian CNS [9, 101–104] (Fig. 2). Terminal selector genes are defined as TFs that are activated at the cell cycle exit and can maintain their own expression by autoregulation during differentiation, retaining activity up to the mature neuron stage. Terminal selector activity leads to both activation of batteries of functionally related genes contributing to particular aspect(s) of neuronal phenotype, and suppression of the determinants for alternative fate(s). The loss of a selector gene does not affect production of postmitotic neuronal precursors or their survival but leads to loss of a specific neuronal identity accompanied by a transformation into an alternative fate.

Currently, a GABAergic over glutamatergic selector function has been unambiguously demonstrated for PTF1A in the dorsal spinal cord, for GATA2/TAL1 complex in the ventral spinal cord, and GATA2 and TAL2 in the midbrain and p1 of diencephalon. GABAergic subtype selector function has been shown for GATA2 in rostral p2 (pTHr) and suggested for DLX TFs in the telencephalon (Fig. 3d).

DLX family TFs and forebrain GABAergic neurons

The expression of *Dlx* family HD TFs is a uniting feature of the GABAergic neurogenesis domains in the anterior forebrain: telencephalon and diencephalon up to the ZLI [105, 106]. *Dlx2* is also expressed in the migratory OB GABAergic neurons in the embryonic and adult brain [107]. *Dlx1/2* expression is activated in the VZ and the loss of *Dlx1/2* affects gene expression in VZ, SVZ and MZ [108, 109]. However, the targets of DLX1/2 include region-specific progenitor markers, but not general determinants of progenitor identity such as Hes1 [108], supporting the link between DLX function and subtype identity. *Dlx1/2* expression in the GEs is regulated by ASCL1 binding on its intergenic enhancers [110]. Conserved DLX/MSX/NKX binding motifs are also found in the *Dlx1/2* enhancer, near the ASCL1 binding site [110]. Thus, ASCL1 may interact with HD TFs to induce *Dlx1/2* expression. *Dlx1/2* enhancers also contain elements through which they positively autoregulate their own expression [111]. During the progression of differentiation, DLX1/2 are gradually replaced with DLX5/6, as DLX2 directly activates *Dlx5/6* transcription [105, 109, 112].

DLX1/2 are required for the generation of postmitotic GABAergic interneurons from the SVZ progenitors [113]. As *Dlx1* is activated at a slightly later stage than *Dlx2*, the dose effect in this function should be considered. *Dlx1/2* double mutant mice lack all telencephalic GABAergic neurons: from striatum, cortex, OB, and hippocampus. Both defects of migration and failure to maintain GABAergic identity appear to contribute to this phenotype [43, 113, 114].

Dlx genes appear to regulate GABAergic neuron phenotype both directly and by activation of a next layer of transcription factors. Ectopic overexpression of *Dlx2* and *Dlx5* in forebrain slice cultures was shown to activate the expression of *Gad1* and *Gad2* [106]. Notably, *Dlx2* overexpression could induce similar GABAergic differentiation in the midbrain slices as well [115]. Differential activity of

Dlx enhancers seems to correlate with a tendency towards particular subtype of progeny, suggesting that the basis for subtype diversification may be established very early, by *cis*-regulatory control over *Dlx* transcription [116]. Indeed, developmental differences in *Dlx* gene expression have been shown to contribute to interneuron subtype segregation and/or maintenance. For example, the SST^+ and NPY^+ subtypes were affected in *Dlx1* mutant cortex and hippocampus, while CALB2 $(CR)^+$ GABAergic neurons were lost in hippocampus but not in the cortex [117]. Some of the DLX targets are involved in differentiation of forebrain GABAergic neuron subtypes. For example, a zinc-finger homeobox TF ZFHX1B was found to be directly regulated by DLX2 and to drive cortical GABAergic interneuron differentiation as well as to suppress striatal GABAergic neuron differentiation [118].

Microarray studies have listed a multitude of additional subtype-specific and migration-related genes and as targets of DLX1/2, including *Calb1*, *Sst*, *Arx*, and *Lmo3/4* [119]. Enriched Gene Ontology categories within de-regulated genes in *Arx* mutant clearly point to a function in axon guidance and neuronal migration [119]. Cross-comparisons of microarray data from *Dlx1/2* and *Arx* mutants with wild-type samples, as well as DLX5/6-positive and -negative cells revealed that despite a major overlap between the targets of these TFs, there are also significant sets of genes independently regulated either by the DLX family members or ARX. Although an extensive list of putative target genes is now available, the understanding whether a certain TF regulates the transcription of the listed targets directly or indirectly is still mostly lacking. For example, direct binding of ARX was demonstrated only in the enhancers of three ARX-dependent genes [119].

In addition to the telencephalon, DLX TFs regulate GABAergic differentiation also in the p3 region of the anterior diencephalon. Interestingly, DLX2 appears to regulate GABAergic subtype identity in this region [93] (see also discussion below).

GATA2 and the posterior diencephalon and midbrain

Gata2 and *Tal2* expression is a hallmark of all GABAergic precursors in the area spanning from ZLI to MHB [19, 21] (Fig. 3d). In the midbrain, *Gata2* is activated after *Ascl1* and *Helt* in GABAergic precursors soon after their cell cycle exit [21]. Midbrain GABAergic neuron precursors also express *Tal2* in a pattern similar to *Gata2* [120, 121]. However, *Gata2* and *Tal2* are activated independent of each other [121]. Both genes are required for GABAergic neuron development at a postmitotic stage. Mutants of *Gata2* show a transformation of all midbrain GABAergic precursors into glutamatergic fates, while it does not affect patterning or proneural gene function in the VZ progenitors [21]. Terminal selector function of GATA2 is strongly suggested by this fate transformation phenotype together with the induction of GABAergic neuron differentiation in ectopic locations by *Gata2* overexpression [21]. Similar GABAergic-to-glutamatergic fate transformation was also observed in the midbrain of *Tal2* mutants, although the most ventral midbrain is less sensitive to *Tal2* inactivation and the two mutants show subregion-specific differences [121]. GATA and TAL factors have been suggested to operate as components of a common transcription factor complex [122]. Similar phenotypes of *Gata2* and *Tal2* mutants could reflect a partnership in binary terminal selector complex, where either one missing protein would render the complex inactive.

In addition to the GABAergic neurotransmission-related genes, GATA2 and TAL2 are required for the activation of downstream TF genes, including *Tal1, Gata3, Six3*, and *Sox14* [19, 21, 121]. These may regulate the maintenance of the GABAergic phenotype or specific aspects of GABAergic neuron development (see below). For example, SOX14 regulates migration of GABAergic neuron precursors during development of distinct diencephalic nuclei [93].

Curiously, mature midbrain contains an exceptional population of GABAergic neurons: development of GABAergic neurons associated with the dopaminergic nuclei [substantia nigra pars reticulata (SNpr), and GABAergic component of ventral tegmental area (VTA)] is independent of GATA2 function. The reason for this is that these GABAergic neurons have their developmental origin in the ventral hindbrain, where GABAergic fate is independent of GATA2, but dependent on TAL1 function [24, 60], (see below).

The selector function of GATA2 appears to be context dependent. In the diencephalic p1, GATA2 acts as a selector for GABAergic over glutamatergic fate as in midbrain: *Gata2* mutant GABAergic precursors acquire a glutamatergic phenotype. In pTHr however, the loss of GATA2 imposes a GABAergic subtype respecification: mutant precursors switch to a p3-like differentiation programme, activating *Dlx1/2* and *Arx* expression [19]. On the contrary, inactivation of *Dlx2* results in ectopic upregulation of GATA2 targets *Tal1* and *Sox14* characteristic to the pTHr-like program in the p3 [93]. Thus, DLX2 and GATA2 may act as opposing switches regulating distinct subtypes of GABAergic neurons on the anterior and posterior side of the ZLI, respectively.

TAL1 and PTF1A in the hindbrain and spinal cord

TAL1: ventral hindbrain and spinal cord

In the ventral spinal cord, the V2b population of GABAergic neurons is derived from the most dorsal

Nkx6-1-expressing progenitors and is also characterized by *Gata2* and *Tal1* expression [62, 64, 103]. The early V2 postmitotic precursors are multipotent, giving rise to both GABAergic V2b and glutamatergic V2a neurons, and initially ubiquitously express *Gata2* [62, 64]. However, at cell cycle exit, V2 precursors are segregated into two distinct groups by FOXN4-induced NOTCH1–DELTA4 signaling, which initiates the expression of V2b fate determinant *Tal1* [67, 101]. The segregation of V2a/b identities is further refined by the LIM-HD transcriptional cofactor LMO4 that bridges GATA2 and TAL1 into a transcriptional complex. This GATA2–TAL1–LMO4 complex binds DNA consensus of specific topology, found for example in intergenic enhancers of *Gata2/3* or *Gad1* genes [123]. GATA2 as well as TAL1 have been shown to be sufficient for the commitment to V2b phenotype, at the expense of V2a fate [62, 64, 103]. At the same time, the loss of TAL1 results in specific deficiency of V2b neurons [103], while in the *Gata2* mutant, the whole V2 precursor population fails to develop [64].

Similar to the ventral spinal cord, the NKX6-1$^+$ progenitors in the ventral hindbrain also produce a population of GABAergic precursors in a TAL1-dependent fashion [60]. However, in contrast to the spinal cord, these GABAergic precursors are not affected by the loss of GATA2 alone. Correlating with the distinct requirements for GATA2, the gene regulatory mechanisms driving *Gata2* expression are also different in the GABAergic precursors in the ventral hindbrain and spinal cord compared to the precursors in the midbrain and diencephalon [64].

PTF1A: dorsal hindbrain and spinal cord

Cell lineage tracing has demonstrated that the expression of bHLH TF *Ptf1a* is restricted to the GABAergic lineage in the cerebellum. Both PAX2$^+$ (c2v) and CORL$^+$ (c2d) GABAergic populations express *Ptf1a* at the progenitor stage [124]. In accordance with this expression pattern, PTF1A function is central for the GABAergic neurogenesis in the dorsal r1 as *Ptf1a* mutant mice lack all GABAergic neurons of the cerebellum and cerebellar nuclei [125]. Ectopic PTF1A can induce the differentiation of GABAergic neuron-like cells in dorsal telencephalon, confirming the master regulator properties of this gene [125]. In the absence of PTF1A, the presumptive GABAergic precursors adopt a glutamatergic granule cell phenotype [126]. Although these findings are consistent with a selector function, it is also possible that PTF1A regulates regional patterning rather than neuronal differentiation and activation of neuron-type-specific gene expression in the dorsal hindbrain. Genetic fate mapping and loss-of-function studies have shown that similar to cerebellum, *Ptf1a* expression is restricted to the GABA- and glycinergic precursors in the cochlear nuclei and this expression is essential for their development [79]. In contrast to its function in GABAergic neurogenesis in the anterior and medial hindbrain, PTF1A is required for the development of both inhibitory neurons and excitatory glutamatergic climbing fiber neurons in the caudal hindbrain (rhombomeres 6–8; [127]). Thus, in the hindbrain, PTF1A has properties of both a patterning factor and a fate selector.

In contrast to the hindbrain, where it is expressed in the proliferative progenitors, *Ptf1a* is mostly activated after the cell cycle exit in the postmitotic neural precursors of the dorsal spinal cord. PTF1A marks the early born dI4 as well as the late-born dILa GABAergic neuron precursors and instructs their differentiation by allowing the expression of *Lhx1/5* and *Lbx1*, while repressing *Tlx3* that acts as a selector gene for the glutamatergic fate [102, 104, 128]. In the absence of PTF1A, spinal cord dorsal horn sensory interneurons fail to activate the GABAergic differentiation markers *Pax2, Lhx1/5, and Gad1*, and instead are trans-specified into a glutamatergic phenotype (TLX3$^+$, VGLUT2$^+$) [102]. Similarly, LBX1 is both sufficient and necessary for the GABAergic neuron differentiation in dorsal spinal cord [104]. In addition to dI4, *Lbx1* is also expressed in dI6 progeny, in a PTF1A-independent manner [76]. The fate switch phenotypes demonstrate dual properties of both PTF1A and LBX1: supporting the GABAergic and suppressing glutamatergic differentiation cassettes. However, while PTF1A is required in all GABAergic neuron subtypes (characterized by *Sst, Npy, Pnoc, Penk*, and/or *galanin* coexpression), LBX1 loss-of-function does not affect SST$^+$ or PENK$^+$ subtypes [129].

In summary, bHLH TF PTF1A controls GABAergic as opposed to glutamatergic fate selection in both mammalian cerebellum and dorsal spinal cord. The targets activated by PTF1A include *Lhx1/5*, *Lbx1*, *Pax2*, and *Gad1*, while glutamatergic determinants are suppressed. Recent ChIP-seq study showed PTF1A binding to enhancers associated with both cell proliferation and cell-fate specification genes [130], supporting the observation that PTF1A can control various aspects during neurogenesis. Indeed, a mechanism where PTF1A outcompetes NOTCH intracellular domain for RBPJ protein binding, causing a switch from *Hes* expression towards differentiation genes, explains how PTF1A could promote neurogenesis and interact with NOTCH signaling [100, 131].

GABAergic fate in the neural retina

The vertebrate retina is a derivative of anterior neural plate. Retinal field identity is specified by CHX10, RX, and MITF TFs [132]. Retina consists of six cell types, among which amacrine and horizontal cells are inhibitory interneurons (GABA- and glycinergic). Precursors of both amacrine

and horizontal cells express *Neurod4*, *Foxn4*, and *Ptf1a*. FOXN4 lies upstream of *Ptf1a* and also controls the expression of *Neurod1*, which is required for the cell migration. *Ptf1a* a does not control *Foxn4* or *Neurod1* expression or cell migration, but selects GABAergic over glutamatergic cell fate [133, 134]. The downstream targets of PTF1A in retina include *Barhl2*, *Prox1*, and *Gad1* [135, 136].

Considering the efforts in tracking the evolutionary origins and mechanisms of diversification in retinal cell types [137, 138], it is interesting to note that the GABAergic fate specification mechanisms utilized in amacrine and horizontal cell lineages are more similar to the hindbrain and spinal cord compared to the telencephalic or diencephalic regions.

Maintenance of fate: regulators of differentiation batteries

Fate maintenance involves continued expression of neuron-specific terminal differentiation genes (neurotransmitter synthesizing enzymes, receptors, etc.). Genes allocated to a particular function can be coregulated in transcriptional modules, allowing for a small number of TFs to define very complex functionalities [12, 139]. Many TFs regulating early neural differentiation are also expressed in mature neurons [140]. Recently, temporally controlled mutagenesis experiments have revealed late functions of these TFs in the maintenance of the neuronal identity. For example, inactivation of *Nurr1* and *Pet1* results in reduction of cell type-specific gene expression in dopaminergic and serotonergic neurons, respectively [14, 15]. Whether the developmental regulators of GABAergic neurons also control their maintenance is currently unknown. The GABAergic fate determining TFs such as DLX2, GATA2, and PTF1A are down-regulated in maturing neural precursors, but some of these TFs can sequentially switch on their paralogs as differentiation progresses. For example, DLX2 binds a DLX/MSX/NKX motif in *Dlx5/6* enhancer in telencephalon [109, 141], whereas GATA2 and TAL2 activate *Gata3* and *Tal1* expression in the midbrain, perhaps via binding to GATA–Ebox motifs similar to the ones involved in the autoregulation of these genes in spinal interneurons [123]. Thus, while the selector genes *Gata2* and *Tal2* are down-regulated during the final maturation of GABAergic neurons, *Gata3* and *Tal1* expression continues. Therefore, the latter two factors may be involved in the maintenance of the GABAergic neuron-specific gene expression.

Lim HD TFs have been associated with subtype-specific identities [142], and are often activated by selector factors (Fig. 2): *Lhx1/5* are regulated by PTF1A in spinal cord [102] and *Lhx1/5* expression is required for maintenance of GABAergic identity in the spinal cord dorsal horn. LHX1/5 loss-of-function causes late down-regulation of *Pax2*, *Gad1*, and *Viaat* expression [143]. *Lhx1/5* are also expressed in the PTF1A$^+$ lineage in the cerebellum, where their expression precedes the expression of further subtype-divergent genes *Pax2* and *Corl2* [124]. Loss of LHX1/5 function results in late loss of CALB1$^+$ Purkinje cell population (CORL2$^+$), leaving other cerebellar cell populations relatively normal [144]. It is likely that while LHX1/5 control general GABA neurotransmission battery, further diversification of cell types can be achieved by additional TFs. *Lhx1/5* are also expressed in the GABAergic precursors in midbrain [22], pretectum, and rostral thalamus (pTHr) [145]. *Lhx1* expression in midbrain GABAergic, but not glutamatergic populations, requires GATA2 function [21]. However, demonstration of maintenance functions for the selector TFs and their downstream factors would require their inactivation only in the mature GABAergic neurons.

In addition to TFs, microRNAs also regulate neuronal fate, differentiation, and survival [146–148]. Specific microRNA profiles have been linked to differentiated neuron types in mature brain. Comparing microRNA profiles in cortical and cerebellar GABAergic vs. glutamatergic neurons, sets of microRNAs were found enriched in all types of analyzed GABAergic cells. In addition, a number of microRNAs were specifically and differentially expressed in distinct GABAergic neuron subtypes [149]. It will be of great interest to study how microRNAs, likely in collaboration with TFs, establish and maintain subtype-specific gene expression patterns in the GABAergic neurons.

Migration of GABAergic neuron precursors

After the exit from cell cycle and onset of differentiation, neuronal precursors migrate to their final locations in the CNS and form functional synaptic contacts with their targets. In general, neuronal migration occurs radially along radial glial fibers or tangentially along the rostro-caudal or medio-lateral axis [150, 151]. The regulation of neuronal migration involves attractive and repulsive guidance molecules as well as their receptors, cytoskeletal components, cell adhesion, and extracellular matrix molecules [152, 153]. Relatively little is known of the transcriptional regulation of this complex process. In particular, the difficulty in pinpointing a later migratory function for certain transcriptional regulators lies in the fact that they often also affect neuronal fate specification at an earlier phase. In addition, it is hard to determine whether the TFs act cell-autonomously in migrating neurons or in patterning their environment [154]. Here we review the current knowledge on the TFs that regulate especially the tangential migration of GABAergic precursors into different parts of the rodent CNS.

Migration of GABAergic neurons originating from subpallium

Migration of GABAergic cells into the cortex

Cortical GABAergic interneurons comprise a highly heterogenous population that targets both excitatory glutamatergic (pyramidal) neurons as well as other interneurons [155, 156]. Pyramidal neurons are generated locally in the dorsal telencephalon VZ and migrate radially into their final locations in different cortical layers. In contrast, as discussed earlier, the majority of GABAergic interneurons in rodents are born in the subpallium, in the MGE, CGE, and POA (Fig. 3e) [44]. Subpallial GABAergic precursors first migrate along spatially distinct tangential routes into the developing cortex, followed by the final radial distribution into distinct cortical layers. The migrating cells respond to cues in the environment by generating branches in the leading processes [157]. These cues include membrane-bound or diffusible molecules from several families such as semaphorins, neuregulins, neurotrophic factors, chemokines (CXCL12), and neurotransmitters (GABA, dopamine). The set of cues to which each neuron type responds is defined by the set of receptors that the cells express [158–160]. Concerning the migration from the MGE through the deep parts of the septum, a few chemorepulsive factors (SEMA3A and SEMA3F) in the septum and chemoattractive factors (neuregulin 1, NRG1) have been genetically proven [158, 159]. CGE and POA cells take a distinct route to the cortex, suggesting different guidance cues [161–163].

After they cross the pallial–subpallial boundary, GABAergic precursors migrate via a specific set of streams either through the MZ, SVZ, or the subplate [164], staying away from the cortical plate where the pyramidal neurons form the cortical layers [165, 166]. The mechanisms driving intracortical migration are different from the subpallium-to-pallium migration. CXCL12 chemokine signaling mediates this migration by long-range attraction [167–171]. While the MGE-, CGE-, or POA-derived GABAergic interneuron precursors assume different routes during subpallial–pallial migration, the region of origin does not seem to influence their choice of migratory stream in the cortical plate. After the tangential migration into the cortex, interneurons exit from the streams, lose responsiveness to CXCL12 [167], and migrate radially along the radial glia into the cortical plate [163, 168, 172]. Finally, during the first postnatal days in rodents, the interneurons are distributed into specific layers. The organization of interneurons into layers mostly follows inside-out sequence in a manner similar to the pyramidal cells: early born cells occupy deep layers and later-born neurons occupy upper layers [172–174]. It has also been proposed that specific classes of pyramidal cells in different layers may release factors that instruct specific interneurons types to their final destination [172, 175, 176].

The migratory cues and receptors are in turn regulated by region-specific transcription factors [154]. As discussed above, subpallial GABAergic progenitor domains can be distinguished by their differential expression of specific sets of TFs and signaling molecules [38, 163]. Both patterning genes and fate selectors have been linked to the regulation of interneuron migration in the telencephalon, either directly or via downstream TFs. The loss of subpallial interneuron markers DLX1 and DLX2 severely blocks interneuron migration from all subdomains; this is associated with changes in cell shape, survival, and deregulation of cytoskeletal regulators [114]. The reduced expression of cytokine CXCL12 receptor genes *Cxcr4* and *Cxcr7* may contribute to migration defects observed. CXCL12 attracts *Cxcr4* and *Cxcr7*-expressing interneurons to the cortex in tangential streams and *Cxcr7* mutants have defects in leading process morphology during migration [167–169, 177]. Another target of DLX1/2 is the HD TF gene *Arx*, which is expressed in the subpallium and in migrating interneurons. *Arx* mutant mice have smaller cortex, hippocampus, and OB [115, 178, 179] and in humans *ARX* mutations have been implicated in severe cortical migration defects causing lissencephaly [180]. Gene expression profile analyses have identified a number of migration-related genes as ARX targets, including *Cxcr7* [119]. In addition, the DLX-dependent switch from tangential to radial migration may be mediated by ARX [181].

CGE cells express a nuclear receptor TF *Nr2f2* (*Coup-tf2*) that has been shown to promote the tangential migration of the CGE-derived interneurons to the cortex [182]. However, targets for this TF have not been identified yet. MGE- and POA-derived GABAergic precursors first express *Nkx2-1* and its down-regulation in postmitotic cells is necessary for their migration into the cortex [183]. Down-regulation of *Nkx2-1* leads to the expression of neuropilin 2 (*Nrp2*) in cortical interneurons, which are then repelled away from striatum expressing NRP2 ligands *Sema3A/3F*. The cells where the *Nkx2-1* down-regulation does not occur, migrate into the striatum [183]. In addition to NKX2-1, DLX proteins also regulate *Nrp2* expression [184].

MGE-derived cells also express *Lhx6* once they exit the cell cycle and this expression is maintained in mature inhibitory neurons in the cortex. *Lhx6* expression is lost in *NKX2-1* mutant mice [42, 185, 186]. Deletion of *Lhx6* in mice results in delayed tangential migration and abnormal distribution of MGE-derived interneurons that accumulate in the cortico-striatal boundary [185, 187].

Migration of GABAergic precursors into the olfactory bulb

The subpallium also generates neurons to other regions such as the septum, basal ganglia, and amygdala. In addition, the dorsal part of the LGE produces precursors that migrate rostrally into the OB along the rostral migratory stream (Fig. 3e). This migration also continues in adult rodents [188–190]. A number of guidance molecules and their receptors have been implicated in precursor migration into the OB such as SLIT1, SLIT2, PSA-NCAM, integrins, EPH/ephrin, and Netrin1 [151, 153, 191].

Very little is known of the TFs regulating precursor migration into the OB. As in cortex, DLX1/2 promote GABAergic fate and tangential migration of interneurons into the OB, potentially regulating *ErbB4*, *Robo2*, *Slit1*, and *Prok2* expression [107, 192]. In contrast, interneuron development in the OB is normal in *Nkx2-1* mutants, consistent with the expression of *Nkx2-1* in the MGE [42]. In addition to TFs involved more broadly in GABAergic development, the serum response factor (SRF) has also been implicated in the migration of interneurons into the OB. SRF regulates a variety of immediate early genes as well as genes encoding for cytoskeletal components. In SRF mutants actin cytoskeleton was severely altered [193].

Migration of GABAergic cells in the diencephalon and midbrain

Much less is known of the transcriptional control of tangential migration of GABAergic interneurons into other regions of the CNS. SOX14 that acts downstream of HELT and DLX1/2, is a marker for GABAergic neurons that migrate from the rostral thalamus and pretectum tangentially to form the subcortical visual shell (SVS) nuclei in diencephalon. In *Sox14*-deficient mice, the GABAergic neurons were missing from one part of the SVS, the ventral lateral geniculate nucleus [93].

As mentioned above, GABAergic cells in SNpr and VTA originate in the ventral hindbrain and the SNpr and VTA GABAergic neurons require TAL1 for their development [60]. Recent analyses with *Pitx3* mutant (*Aphakia)* mice suggested that midbrain dopaminergic neurons could guide the migration of SNpr and VTA neurons [194]. This is consistent with the observations that the rhombomere 1-derived, TAL1-dependent, and GATA2-independent midbrain GABAergic neurons are found only in a tight association with the dopaminergic neurons in the ventral midbrain [21, 60]. Interestingly, in the forebrain, dopamine receptors D1 and D2 guide the tangential migration of GABAergic neurons [195]. However, the molecular cues guiding the developing SNpr and VTA GABAergic neurons, as well as their exact migratory patterns, timing, and the transcriptional regulation of this process, remain to be elucidated.

Conclusions and open questions

Diverse mechanisms regulate GABAergic neuron differentiation

No single TF involved in patterning, neurogenesis, or differentiation of GABAergic neurons is shared by all the GABAergic neuron populations (Table 1). On the other hand, most of the TFs important for GABAergic neuron development also have functions in other neuronal lineages or cell types. Based on the molecular mechanisms controlling GABAergic neuron development, CNS can be divided into three main subdomains (Fig. 3

Direct and indirect targets of the precursor patterning and GABAergic fate selector genes

Although TFs driving GABAergic fate selection in the developing mammalian brain have been identified, the mechanistic understanding of the regulatory circuitry is still missing. It is not known how the selector TFs operate with next layer TFs to activate neuron-specific genes, possibly in a relay or feed-forward fashion. It is unclear whether the region-specific targets share enhancer motifs or epigenetic marks and how the patterning, proneural and terminal selector TFs collaborate. If subtype diversity is primed by HD code in progenitors, then we may expect the selector genes to control the GABA/glutamate neurotransmission module alone, but subtype-specific modules such as coneurotransmitters or Ca^{2+}-binding proteins in cooperation with other TFs. This cooperation can manifest by direct physical interactions of selector gene and other TFs (downstream of patterning genes) or alternatively, the regulatory regions of subtype-specific genes may be pre-modulated already in the progenitor stage.

Nature and relative ease of switch between GABAergic and glutamatergic fate

Failure of GABAergic fate specification often leads to adoption of glutamatergic phenotype. The two neurotransmitters are similar in their biochemical synthesis pathways. There are two sources of glutamate in presynaptic terminals. The most prevalent source in functional brain is glutamate recycling, where glutamate is taken up from synaptic clefts by glial cells and presynaptic neurons. In glial cells, glutamate is converted to glutamine and transported to presynaptic neurons where it is converted back to glutamate by glutaminase. Neuronal mitochondria can also produce glutamate as a glucose metabolism intermediate. Presynaptic glutamate is packaged into vesicles by vesicular glutamate transporters (VGLUT, SLC17). Biosynthesis of GABA requires adding one step on top of glutamate biosynthesis

Table 1 Molecular players in key steps of GABAergic neurogenesis

Function				
Brain region	Spatial patterning and progenitor specification HD or bHLH proteins	Proneural genes and their regulators bHLH proteins	Postmitotic subtype selection HD, bHLH, ZF	Maturation, migration, maintenance HLH, HD, ZF
Telencephalon	MGE: NKX2-1 [42] LGE, CGE: GSX1/2 [48, 50, 77] POA: NKX5-1 [45] POA: DBX1 [44] DLX1/2 [106, 108]	ASCL1 [85, 86, 196]	DLX2 [113–115] DLX5/6 [106, 119]	ARX [115, 178, 179] DLX5/6 [119, 192] NR2F2 [182] LHX6 [185]
Diencephalon	NKX2-2 [59, 89] FEZF1/2 [58] GBX2 [197] PAX6 [198]	ASCL1 [91] p1-2: HELT [91, 93]	p3: DLX2 [93] p1-2: GATA2 [19] p1-2: [a]TAL2	p1-2: SOX14 [93] [a]TAL1 [19, 59] [a]GATA3 [199]
Midbrain	NKX2-2 NKX6-1 PAX3/7 [200–202]	ASCL1 [88, 91] HELT [22, 90]	GATA2 [21, 121] TAL2 [121]	PITX2 [203] [a]GATA3 [60, 199] [a]TAL1 [21, 121] [a]LHX1/5 [21, 22]
Ventral R1	NKX6-1 [26, 204]	ASCL1 [91] [a]NGN1/2	TAL1 [60]	TAL1 [60] PITX2 [205]
Dorsal R1 (cerebellum)	EN2 [206–208] PTF1A [125, 209]	ASCL1 [95, 97, 210] NGN1/2 [25, 99]	PTF1A [125, 126]	LHX1/5 [144] NGN1/2 [99] [a]CORL, PAX2 [124, 211]
Dorsal spinal cord	dP4: GSX1/2 [94] dP6: DBX2 [69, 73] PAX2 [128]	ASCL1 [94, 96] NGN1/2 [212]	dI4, dIL, dI6: LBX1 [72, 76, 104] dI4, dIL: PTF1A [102]	LBX1 [72, 76, 104] LHX1/5 [143]
Ventral spinal cord	NKX6-1 [36, 69] V0-1: DBX1/2 [36, 69, 72]	ASCL1 [66] [a]NGN1/2 V2: FOXN4 [66, 67]	V2b: TAL1 [101] GATA2 [64, 103] LMO4 [123] V0d: [a]EVX1- [213]	V2b: TAL1 [63, 103] GATA3 [62, 63] LMO4 [123] V1: EN1 [71]
Mutant phenotype (mouse)	GABAergic progenitors mispatterned or missing	GABAergic neurogenesis delayed and/or diminished	GABAergic precursors respecified to alternative fate	Incomplete differentiation/ impaired functionality

[a] Marked genes are expressed in GABAergic neurons but their role in fate specification or mechanism of action is unclear

pathway, a conversion of glutamate into GABA by glutamic acid decarboxylase (GAD). Thus, the gene batteries for GABA and glutamate biosynthesis naturally largely overlap. In essence, merely switching on *Gad* and inhibiting *Vglut* is enough for a transformation from glutamatergic to GABAergic neurotransmitter identity. However, for changed functionality, neurons would have to package and release GABA from synaptic vesicles. Thus, it would make sense to coregulate *Gad* with vesicular (SLC32) and membrane (SLC6) GABA transporters.

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