Neurons on the Move: Migration and Lamination of Cortical Interneurons

Clare Faux^a Sonja Rakic^c William Andrews^c Joanne M. Britto^{a, b}

^aCentre for Neuroscience, University of Melbourne, and ^bHoward Florey Institute, Florey Neuroscience Institutes, Parkville, Vic., Australia; ^cDepartment of Cell and Developmental Biology, University College London, London, UK

Key Words

Interneuron • Cortical plate • Subtype specification • Migration • Lamination

Abstract

The modulation of cortical activity by GABAergic interneurons is required for normal brain function and is achieved through the immense level of heterogeneity within this neuronal population. Cortical interneurons share a common origin in the ventral telencephalon, yet during the maturation process diverse subtypes are generated that form the characteristic laminar arrangement observed in the adult brain. The long distance tangential and short-range radial migration into the cortical plate is regulated by a combination of intrinsic and extrinsic signalling mechanisms, and a great deal of progress has been made to understand these developmental events. In this review, we will summarize current findings regarding the molecular control of subtype specification and provide a detailed account of the migratory cues influencing interneuron migration and lamination. Furthermore, a dysfunctional GABAergic system is associated with a number of neurological and psychiatric conditions, and some of these may have a developmental aetiology with alterations in interneuron generation and migration. We will discuss the notion of additional sources of interneuron pro-

genitors found in human and non-human primates and illustrate how the disruption of early developmental events can instigate a loss in GABAergic function.

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Introduction

The neocortex is the part of the brain involved in high-level cognitive functions, and its expansion is regarded as a major evolutionary modification that led to the emergence of intelligence [1, 2]. These processes are achieved through the cellular balance between neuronal excitation and inhibition within cortical circuits. The pyramidal neurons act primarily through the axonal release of the neurotransmitter glutamate to excite cortical and non-cortical targets. In contrast, the majority of inhibitory neurons (interneurons) project locally to arborize in the same or multiple cortical columns [3, 4], and a small number can extend long-range projections into remote cortical areas [5]. This highly diverse neuronal population modulates the output of excitatory pyramidal activity through the actions of the inhibitory neurotransmitter, γ -aminobutyric acid (GABA). Throughout embryonic and postnatal stages, GABA signalling is also required for cell migration, axonal and dendritic remodelling and

synapse formation [6]; thus, interneurons are key modulators of cortical development and plasticity, in addition to playing a crucial role in shaping the spatiotemporal pattern of neuronal activity.

The last few years have seen an explosion in publications surrounding interneuron development. The diversity of subtypes based on morphological, molecular and electrophysiological differences accentuates the highly specialized role these neurons play in cortical circuits. More recently, we have started to recognize the implications of a dysfunctional GABAergic system in neurodevelopmental disorders, and our efforts go towards addressing the underlying causes of such disturbances in cortical function. As mentioned, the functional heterogeneity of interneurons is key in modulating cortical circuit activity, and a number of recent reviews have discussed how this diversity is associated with cortical function [7–9]. In this review, we will focus on how interneurons are reliant on intrinsic and extrinsic cues during embryogenesis to establish subtype specification and discuss the impact of these cues on migration and lamination. Furthermore, we will discuss the latest findings of interneuron generation during human cortical development, as knowledge in these mechanisms has long-term implications in defining the aetiology of many neurological and psychiatric conditions.

Cortical Interneuron Origin

Cortical Interneuron Origin in Rodents

The concept that pyramidal neurons and interneurons arise from distinct progenitors and display different migratory routes was illustrated by a number of key studies performed in rodents. Initially the use of recombinant retroviral labelling identified clones of cells composed solely of either pyramidal or non-pyramidal cells [10, 11] suggesting the existence of separate progenitor pools for these two cell types. Similar studies drew attention to the appearance of tangentially migrating neurons throughout the intermediate zone (IZ), demonstrating the widespread and unorthodox dispersion of these cells within the cortex [12–15]. Although it was not clear at the time that these tangentially migrating neurons originated in the ventral telencephalon, a subsequent series of elegant experiments placing Dil crystals in the ventral telencephalon demonstrated the migration of the cells into the neocortex, a phenomenon that was blocked by an incision made between the dorsal (pallium) and ventral (subpallium) telencephalon [16–19]. It therefore appears that the

majority of interneurons are derived from an extracortical source, the ganglionic eminences (GEs) of the ventral telencephalon. There is however evidence to suggest that the dorsal telencephalon can provide a local source in the rodent cortex [11, 20], and this may also be the case in human and non-human primates. These aspects of interneuron origin will be discussed in more detail below.

In the mouse, the GEs in the ventral telencephalon appear around embryonic (E) day 11 and can be structurally divided into 3 separate areas, lateral (LGE), medial (MGE) and caudal (CGE), depending on the rostrocaudal and mediolateral position (fig. 1). Utilizing Dil labelling of individual GEs, and in vivo transplantation studies, it was confirmed that almost all cortical interneurons are produced within the MGE and CGE [16, 17, 21–24]. The genetic link for GE involvement in the genesis of interneurons was found by analyzing knockouts of the homeobox-containing transcription factors expressed in this region, namely, *Dlx1*, *Dlx2* and *Nkx2.1*. *Dlx1* and *Dlx2* are highly expressed in the GE and the double knockout showed a 70% reduction in the number of cortical interneurons [19]. In comparison, *Nkx2.1* is expressed solely in the MGE, and the knockout exhibits only a 50% decrease in interneuron numbers [25, 26]. More recently, the contribution of interneurons from the CGE has been examined by genetic fate mapping studies indicating that approximately 30% of cortical interneurons are produced within this area [27, 28].

The involvement of the LGE in generating cortical interneurons has been more controversial. Numerous in vitro and in vivo studies have shown that LGE-derived cells fail to migrate to the dorsal cortex [16, 21, 23, 29]; however, others have shown the presence of bromodeoxyuridine-labelled LGE cells in the cortex after heterotopic transplantation [30, 31], and tangentially migrating cells were present in the rat cortex following ablation of the MGE [32]. One caveat for these experiments is that the migratory route of MGE- and CGE-derived interneurons is through the LGE. Nonetheless, we cannot completely rule out the LGE as a potential source of cortical neurons. In addition to the GE, a small percentage of cortical interneurons are derived from the embryonic pre-optic area [33]. Genetic lineage tracing using the transcription factor *Nkx5.1* and in utero labelling to specifically label the pre-optic area has shown that GABAergic cells from this region also migrate to the cortex and hippocampus.

The studies mentioned above indicate that the majority of interneurons are derived from the MGE and CGE and undergo their final mitosis in these regions prior to migration. However, proliferating interneuron progeni-

Fig. 1. Schematic representation of migratory routes utilized by interneurons generated in the GEs. **a** Cortical interneurons born in the MGE and CGE in the ventral telencephalon follow tangential migratory paths into the developing cortex. Once within the cortical wall, cells disperse before entering the cortical plate and reside in a final position. The LGE-derived neurons migrate rostrally and ventrally into the olfactory bulb (OB) and striatum, respectively. **b** Coronal section (indicated in **a**) illustrating the major routes of tangential migration through the embryonic telencephalon. Interneurons migrate from the MGE (M) and traverse the LGE (L) whilst avoiding the striatum (Str). Upon entry into the cortical wall, cells migrate in 3 major streams, through the marginal zone at early stages, followed by a second route in the intermediate zone and at later stages through the subplate. **c** Intracortical migration represented as multidirectional migration within the marginal zone (indicated in **b**), the inward and outward radial migration from the tangential paths into the cortical plate and the ventricle-directed migration towards the ventricular zone.

tors have been observed in the postnatal subventricular zone (SVZ) [11, 20, 30] and the IZ [20] of the cortex. Wu et al. [20] determined that these cells originated in the GE, and maintained the ability to proliferate after reaching the cortex to produce GABAergic daughter cells. A separate study has identified a pool of proliferating GABAergic precursor cells in the postnatal dorsal white matter [34], and although the authors infer the origin of these cells is the LGE/CGE, this is yet to be determined. The requirement for these proliferating GABAergic intermediate progenitors in the cortex remains unknown; however, they may provide a source of inhibitory cells during the late stages of cortical maturation.

Interneuron Origin in Human and Non-Human Primates

The ability to conduct in vitro and in vivo manipulations, as well as access to transgenic and fate mapping technologies, has made rodents a pertinent model to advance our understanding of cortical development. Nonetheless, if we compare across species, there is an obvious evolutionary increase in the number of both pyramidal neurons and interneurons found in the cortex of higher primates. This is evident by the increase in proportion of

GABAergic neurons from 15% in rodents to 25% in the monkey and reaching 34–44% in certain supragranular layers in the macaque and human [35]. In addition, the existence of interneurons displaying widely varying morphologies in primates indicates that not only are more interneurons required, but newer forms have also been generated. The double bouquet cell originally described in the human cortex by Ramon y Cajal in 1899 and later rediscovered in primates [36] is an archetypal example of this variation. Thus, the question can be raised of whether developmental mechanisms have evolved an additional source of progenitors to proportionately balance the increase in excitatory neurons in a more complex brain.

A hint that this may indeed be the case for human and non-human primates was discovered by Letinic et al. [37] in 2002. This study identified cells in the ventricular zone (VZ) and SVZ of the dorsal telencephalon at mid-gestation, which co-expressed GABA with the GE-associated transcription factors Mash1 (ASCL) and Dlx1/2. In rodents, these transcription factors are associated with interneuron generation [38, 39], and although Mash1 is expressed by progenitors in the GE, it is normally undetectable in postmitotic migratory interneurons. The proliferative capacity of these novel GABA/Mash1-posi-

tive cells was tested using retroviral labelling in organotypic cultures and a clonal analysis revealed expression of GABA and *Dlx2* in the migrating cells and *Mash1* expression in both the dividing progenitors and migrating cells [37]. This study highlighted for the first time a local cortical origin of GABAergic interneurons capable of generating the majority of interneurons; however, these results are not without controversy. It is possible that the *Mash1*-positive progenitors are a form of migrating intermediate progenitor/amplifier cell originating in the GE. In addition, it has recently been shown that radial glial cells in the human cortex can directly produce either *Tbr2*-positive or *ASCL*-positive cells thereby generating both excitatory and inhibitory lineages, respectively [40]. Interestingly, in this latter study the authors could not distinguish the distinct precursors for inhibitory neurons as all *ASCL*-positive cells co-expressed *Sox2* (a neural stem cell/progenitor cell marker) and/or *Tbr2*. In rodents, *Mash1* has also been associated with the generation of oligodendrocytes [41] and the relevance of this in human development is not yet known.

A study in the monkey cortex has revealed a temporal perspective on interneuron generation and migration. Not only was it confirmed that GABAergic cells were generated in the VZ/SVZ of the dorsal telencephalon (*Mash1*-positive) and GE (*Mash1*-negative), these results suggested also that the site of origin dictated the birthdate of interneurons, as well as their laminar positioning [42]. To summarize, the GE-derived interneurons arise during early gestation and are located in the marginal zone (MZ) and subplate (SP), whereas at later stages of gestation cortically derived interneurons are generated. The lack of time lapse analysis precludes any definitive confirmation of the migratory routes adopted from the two sites of origin; nonetheless, these data illustrate an evolutionary conservation of *Mash1*-positive progenitors in the dorsal telencephalon. Subsequent studies, driven largely by Zecevic and colleagues, have broadened our understanding of interneuron biology during human cortical development [43–46]. By analysing the expression profiles of GE-associated transcription factors (*Nkx2.1*, *Dlx1*, *Dlx2*, *Lhx6* and *Mash1*) combined with an interneuron subtype marker (calcium-binding protein, calretinin) and a proliferation marker (*Ki67*), the authors have corroborated the presence of a progenitor population within the VZ/SVZ.

Ultimately, it would be ideal to identify the subtype fate of interneurons generated in the dorsal telencephalon; however, limitations of studying human tissue prevent this. Abnormalities in cortical interneuron develop-

ment have been linked to a number of human disorders (outlined in the section ‘Neurodevelopmental disorders and interneuron development’) and a recent study investigating fetal or infant cases of holoprosencephaly with severe ventral forebrain hypoplasia [47] may shed light on interneuron progenitor fates. In these cortices, a substantial reduction was observed in interneurons positive for the markers nitric oxide synthase 1, neuropeptide Y and somatostatin (SST); in contrast, calretinin-positive cells were still present. Interestingly, the interneuron subtypes that showed the greatest reduction are derived from the ventrally located GE, and the presence of the calretinin-positive interneurons is indicative of an additional progenitor population outside the ventral telencephalon. The significance of these subtypes, and connection to the site of origin, will become apparent in the following section, where we discuss in detail the generation of interneuron diversity.

Interneuron Diversity

The first section of this review outlined the regions within the telencephalon that generate interneurons, but the next phase of interneuron development is fate determination and cortical positioning. Interneurons are a heterogeneous population and the task of classifying them into subpopulations is a daunting one. Over the past few years various attempts have been made and more recently a consortium of scientists specializing in anatomy, physiology and development convened to create a unifying nomenclature of GABAergic interneurons in the cortex, the Petilla terminology (Petilla Interneuron Nomenclature Group) [48]. We will briefly describe the main approaches used for interneuron classification below; however, a detailed description of interneuron subtypes is beyond the scope of this review and has recently been provided elsewhere [8, 9, 48–50].

Subtype classifications are generally based on 3 major criteria: (1) the molecular profile, (2) morphology and (3) electrophysiology of the interneuron. The first of these rely on the expression of molecular markers and is probably the simplest and most commonly used. These include: the calcium-binding proteins parvalbumin (PV), calbindin (CB) and calretinin (CR); certain neuropeptides, such as SST, vaso-active intestinal peptide (VIP), neuropeptide Y, cholecystokinin and corticotropin-releasing factor [51–53]; potassium channels such as *Kv3.1* and *Kv3.2* [54, 55]; the secreted glycoprotein reelin [27]; nitric oxide synthase [53], and the serotonin receptor

5-hydroxytryptamine 3A (5HT3aR) [56, 57]. Based on their expression patterns, recent studies have shown that PV, SST and 5HT3aR are exclusively expressed by 3 distinct subpopulations and when combined account for the majority of GABAergic cells [50, 56, 58]. Further subdivisions of interneurons arise from the combinatorial expression of the molecular markers listed above [27, 53, 58]. The second major criterion, cell morphology, accounts for differences in soma size and shape, dendritic and axonal arborizations and location of postsynaptic connections. Finally, electrophysiology depicts the firing properties that characterize interneuron activity within the cortical circuitry [7, 8]. It is now widely believed that each of the above criteria should be used when identifying or describing specific interneuron subtypes. Interestingly, it was noted at the end of the Petilla meeting that these segregations are primarily for the benefit of investigators trying to categorize a diverse system governed by its role in neuromodulation. Regardless, these classifications have recognized the large diversity of interneurons that exists across various regions of the cortex [8, 27, 51, 58–63].

The Generation of Interneuron Diversity

To comprehend how such a high level of diversity is created, we need to adopt a developmental perspective and follow the life span of an interneuron from birth to maturation. If we do this, there are 3 key phases when the identity of an interneuron can be influenced: (1) specification at birth, (2) exposure to signals during migration and final positioning in the cortical plate (CP) and (3) synaptic maturation and connectivity that ultimately defines the neuromodulatory function of an interneuron. It becomes evident that these are either an intrinsic property of the interneuron or the influence of extrinsic factors from the cortical surrounds. Nonetheless, there is evidence to suggest that all 3 play a role in determining the fate of an interneuron. We will focus here on the rodent model, as the wealth of data allows us to present a rationale for each phase of development.

The first event would state that interneurons are specified at the time of birth and therefore subtype specification is largely defined within the GE. The obvious molecular candidates would be transcription factors (table 1), and Rubenstein and colleagues have been influential in discovering an array of factors that define the GE as a distinct developmental domain [39, 64–69]. *Dlx1* and *Dlx2* are expressed throughout the SVZ of the GE and confer an interneuron fate upon the newly born cells. Distinct subtypes of interneurons are spatially and/or temporally segregated within the pool of *Dlx*-positive

progenitors, and transplantation studies [23, 70], genetic fate mapping [28, 56, 71] and cell culture analysis [72] have provided a broad map of subtype origin. More specifically, MGE-derived interneurons are mainly PV-positive fast-spiking basket cells and SST-positive intrinsic bursting Martinotti cells, while all CGE-derived cells are positive for 5HT3aR, exhibit a range of firing potentials and morphologies, and are further subdivided by their expression of VIP, CR and neuropeptide Y [7, 8].

A spatial bias also exists within the MGE itself as PV-positive cells arise primarily from the ventral MGE and SST-positive cells from the dorsal MGE [73, 74]. Interestingly, it appears that a gradient of sonic hedgehog activity is driving this spatial bias [69, 75–77]. If these findings suggest parity with the generation of interneuron diversity in the spinal cord [78], then domain-creating transcription factors would need to be present in the MGE. Indeed, central to interneuron specification is an array of transcription factors (*Nkx2.1*, *Nkx 6.2*, *Lhx6*, *CoupTFI*, *Cux 1, 2*, *Sox6* and *Dlx5/6*) [29, 65, 79–87]; however, expression patterns do not create clearly defined boundaries that are subtype specific. More recently, attempts were made to delineate progenitor domains by the combinatorial expression of transcription factors [39, 68]; once again, the borders are not sharply defined, and multiple subtypes could be produced within the progenitor regions.

We have described specification occurring in a spatial manner; however, increasing evidence suggests that a temporal regulation also exists [27, 60, 86]. Interneuron genesis in mice takes place between E9 and E16, and the peak production from the MGE occurs around E12–E13. In contrast, the initiation and peak production of interneurons from the CGE is around E12 and E15–E16, respectively [27, 60]. This temporal pattern is reflected by the subtypes that are generated, for example, most SST-positive Martinotti cells are predominantly born at E9, SST- and CR-double-positive cells at E12 and most VIP-positive cells at E15 [60, 86]. In comparison, although PV-positive cells are produced throughout the entire genesis period, PV-positive chandelier cells are produced at E15 [74] implying specific temporal delineation in subtype generation. This developmental scenario is analogous to the generation of pyramidal neurons, where the temporal expression of transcription factors (*Brn1/2*, *Svet1*, *Cux1*, *Cux2*) controls the sequential production of deep versus superficial cortical neurons [88]. Furthermore, as described above, the temporal profile of interneuron subtype generation may exist in humans, albeit from different cortical sources.

Table 1. Genes involved in interneuron development

Role in interneuron development	Transcription factors	Ligand-receptor signalling
Proliferation	β -Catenin (Wnt-mediated) [230]	Cyclin D ₂ [231]
Differentiation	Cux1/Cux2 [82] Dlx1, 2, 5, 6 [39, 64, 65, 80, 85] Lhx6, 8 [69, 162] Mash1 [37–39]	GDNF/GFR α_1 [126] Ryk [232] Shh [69, 75, 77]
<i>Subtype specification</i> MGE derived	Lhx6 [69, 162] Nkx2.1 [72, 79, 162] Nkx6.2 [86] Sox6 [84]	BMP/BMPRI [89] BDNF/TrkB [31, 90, 91] Kir2.1 [96]
CGE derived	Coup-TFI [81]	
<i>Migration</i> Tangential	Arx [157, 158, 218] Coup-TFII [29] Dcx [106, 107, 218] Dlx1, Dlx2 [19, 160, 161] Lhx6 [87, 156, 159]	BDNF/TrkB [31, 125] CXCL12/CXCR4, 7 [144, 145, 183–186, 188] GDNF/GFR α_1 [126] HGF/SF [115] Netrin 1 [189] NRG1/ErbB4 [99, 146, 149] p35 [108]
Guidance through ventral telencephalon		Eph/ephrin [141, 142] Robo [136, 137, 140] Sema [129, 130, 140]
Regional distribution		GDNF/GFR α_1 [128]
Switch to radial	Sox6 [83, 84]	Connexin 43 [182] Netrin 1 [189]
Lamination and termination	Sox6 [83] Fezf2 [204]	BDNF/TrkB [125] CXCL12/CXCR4/CXCR7 [144, 184, 186, 187] KCC2 [207] Kir2.1 [96] p35 [108] Reelin [180, 200, 202, 203]

Overall, there is clear evidence to suggest that both the progenitor location and time of birth are two highly influential factors in determining the fate of an interneuron. Interestingly, many characteristics used to define an interneuron are not evident until late postnatal ages and even adulthood. Synaptic maturation of interneurons is a protracted process strongly regulated by experience-driven neural activity (this can span up to the first two decades in humans). This leaves abundant time for interneuron identity to be modified during migration into the CP and integration into functional circuits, leading us to the second and third phases of interneuron specification where extrinsic factors can influence interneuron iden-

tity (table 1). It has been shown that certain dorsalizing signals, such as BMP4, can increase the number of PV-positive cells, with a concomitant decrease in SST-positive cell number [89]. Brain-derived neurotrophic factor (BDNF) signalling also differentially alters interneuron subpopulations both in vitro and in vivo [31, 90, 91]. In addition, cell morphology is modified by environmental signals, such as BDNF, the soluble form of neural cell adhesion molecule and even GABA, which all regulate axonal and dendritic branching as well as synaptogenesis [92–95]. Altered neuronal excitability may also play a role in interneuron specification, as demonstrated recently in an elegant study by De Marco Garcia et al. [96]. This

study found that altering the electrical activity of CGE-derived interneurons, by overexpressing the potassium channel Kir2.1, caused a pronounced change in the morphology of CR- and reelin-positive cells. In contrast, VIP-positive neurons were unaffected. Interestingly, the alteration in cell morphology only arose when neuronal activity was modified after postnatal day 5, a time well beyond genesis in the GE.

The extrinsic activation of intracellular signalling pathways is crucial in modulating neuronal excitability, and it is hardly surprising that molecular changes arise during synaptogenesis. For this reason many believed that interneurons were 'naïve' until these later stages of development and this may not be far from the truth. Taken together, the studies described above indicate that interneurons within the CP are not necessarily naïve, but are restricted in fate by transcription factor expression at birth and are further refined following exposure to the cortical environment and integration into microcortical networks. It is therefore becoming increasingly apparent that the combination of all 3 phases in interneuron development contributes to generating interneuron heterogeneity in the adult cortex.

Tangential and Radial Migratory Routes

Neuronal migration constitutes a fundamental process during cortical development, and through a sequence of highly orchestrated events the characteristic laminated structure of the adult cortex is formed. The ability of neurons to navigate the cellular milieu while integrating multiple guidance cues is a marvel in itself, and great efforts are made to comprehend the molecular basis of this process. The cellular events during corticogenesis provide an elegant model for investigating such processes as the two neuronal populations have adopted distinct migratory behaviours to eventually reside in a common terminus. Pyramidal neurons generated locally in the neuro-epithelium migrate radially from progenitors in the VZ/SVZ towards the CP, whilst interneurons generated in a subcortical progenitor zone embark on tangential migration (parallel to the ventricular surface) before entering the CP. Regardless of subtype or site of origin, all interneurons must migrate vast distances to reach a final destination.

There are 3 major routes of migration observed for interneurons during corticogenesis; the first is along well-defined tangential paths from the GE towards the corticostriatal junction and into the cortical wall, the

second encompasses multidirectional migration within these migratory paths and the third involves a shift towards a radial trajectory so as to enter the CP (fig. 1). These last 2 routes will be referred to as 'intracortical' migration, indicating the phase of interneuron movement into the laminated CP generated by pyramidal neurons. Although we focus this review on cortical interneurons, these migratory streams are also utilized by hippocampal interneurons, which traverse the cortex before entering the hippocampal primordium in a stage-dependent manner [17, 19, 23, 97]. Various guidance molecules, substrates and intrinsic programming signals are required to direct the migrating interneurons to their correct laminar position, and these will be discussed in the following sections. First, however, we will describe the dynamic cellular mechanisms of interneuron movement, as this is instrumental for guidance-directed migration.

The Branching Dynamics of Migrating Interneurons

Unlike pyramidal cells, which are associated with radial glial fibres and migrate primarily in a straight trajectory, migrating interneurons navigate without any obvious physical support and change direction frequently. To do so, and similar to growing axons, interneurons use their leading process (neurite) as a compass, having a growth-cone-like structure at the distal end. Whilst axons manoeuvre the growth cone towards or away from chemotactic cues, interneurons continuously produce multiple branches from the leading neurite, subsequently selecting a single branch oriented in the direction of the attractive cue [98, 99] (fig. 2). This migratory behaviour is disparate to the chain migration of olfactory interneurons in the rostral migratory stream [100], but turns out to be required for directional guidance. The individual searching behaviour of cortical interneurons is evidenced by vigorous and dynamic neurite branching, and intermittent leaps made by the nucleus to advance the cell (nucleokinesis). This saltatory nuclear translocation appears uncorrelated to the dynamic branching of neurites at the leading edge of the cell [98, 101]. A recent study examining the relationship between nucleus movement and the temporal extension and retraction of neurites has highlighted independence between these two cellular mechanisms, that is, once the choice of a leading neurite is made, the nucleus moves despite the degree of branching in the neuritic harbour [102]. This is not to say that neuritic branching is decoupled from nucleokinesis, as signalling unequivocally occurs from the growth cone to the cell, but rather these cellular dynamics represent a very effi-

cient manner for searching and moving through an unknown environment.

The process of nucleokinesis occurs in two phases. First, cytoplasmic organelles (i.e. the Golgi/centrosome) move forward and separate from the nucleus. This is followed by the splitting of the centrosome and nuclear translocation towards the organelles. Interestingly, close observation of this nuclear movement revealed that when an interneuron is migrating in a relatively constant direction, the nucleus tends to alternate between left and right leading neurite branches [99]. Nuclear movement occurs through actomyosin-dependent pushing forces from the rear of the cell and microtubule-associated pulling forces ahead of the nucleus [98, 103, 104]. One of the key steps in interneuron migration is the stabilization of the microtubules in the leading neurite. Disruption in microtubule dynamics, for example through the deletion of microtubule-associated proteins, such as lissencephaly 1 (Lis1) [105] and doublecortin (Dcx) [106, 107], or upstream regulators like p35/Cdk5 [108, 109], leads to abnormal neurite branching and causes the misguided migration of the cells.

Tangential Interneuron Migration

Tracing, fate-mapping and loss of function analyses have shown 3 major migratory paths that interneurons follow from their origins in the ventral telencephalon to the cortex [110–112]. Specifically, an early cohort (E12 in the mouse) first reaches the cortex and migrates at the level of the preplate. A second and more prominent cohort migrates predominantly through the IZ. At the later stages of corticogenesis (E14–E15) and after the formation of the CP, 3 distinct tangential migratory streams are evident in the developing cortex, located in the MZ, SP and lower IZ/SVZ (fig. 1) [17, 30, 112]. Thus, intricate molecular mechanisms including an array of motogenic factors, chemotactic guidance cues, transcription factors and neurotransmitters are employed by interneurons throughout tangential migration (table 1) [113, 114] and we will discuss each in turn.

Motogenic Cues

A number of soluble factors have been proposed to play a role in cortical interneuron migration by acting as ‘promovement’ or motogenic factors. For instance, hepatocyte growth factor/scatter factor enhances the migration of cells away from the ventral telencephalon, and loss in its activity causes undirected migration of interneurons within the GE leading to a reduction in the number of interneurons in the cortex [115]. Members of the neu-

rotrophin family have also been proposed as motogenic factors in the migration of interneurons. Neurotrophins are widely expressed in the developing cortex [116–119] and interneurons express the tyrosine kinase receptors TrkB and TrkC, the cognate receptors for neurotrophins [120, 121]. Both BDNF and neurotrophin 4 stimulate interneuron migration, and analysis of the TrkB-null cortex revealed a significant reduction in the number of CB-positive interneurons [31]. Recently, the calcium-dependent activator protein for secretion 2 has been shown to promote BDNF secretion, and analysis of null mice for this protein revealed a decreased number of GABAergic neurons and their synapses in the hippocampus [122], thus confirming a role for BDNF in interneuron migration. However, the role of BDNF in cortical interneuron development is not without debate. Other studies have suggested that disruption of BDNF signalling leads to downregulation of CB and other neuropeptides expressed in interneurons [91, 123, 124]. This would cast some doubt as to whether the reduction of interneuron numbers in the absence of TrkB reflects an actual defect in migration or simply a reduction of cell markers. Additionally, changes to the endogenous levels of BDNF may impair cortical development, and the effects on interneuron positioning may be a secondary phenotype. This is indeed the case when analysing the nestin-BDNF transgenic mice, where exogenous levels of BDNF not only led to an inappropriate segregation of Cajal-Retzius cells and interneurons in the MZ, but altered cortical organization and impaired final radial migration of interneurons [125].

The neurotrophin glial cell line-derived neurotrophic factor is highly expressed in interneuron migratory pathways in the cortex [126]. Members of the glial derived neurotrophic factor ligand family signal by binding to glycosylphosphatidylinositol-anchored receptors, GFR α_{1-4} , in collaboration with the RET receptor tyrosine kinase [127]. Interneurons in GFR α_1 -null mutants were found misrouted in the MGE and significantly reduced in the cortex. A follow-up study, using the homozygous GFR α_1 -null rescued by expression of *Gfra1* gene from the *Ret* locus, revealed regionalized loss of PV-positive interneurons [128]. This presents a scenario where guidance molecules may guide certain subtypes of interneurons to discrete regions of the cortex.

Chemotactic Molecules

Once generated in the MGE, postmitotic interneurons journey towards the cortex by first traversing the developing LGE (striatum primordium) en route to the corti-

costriatal junction. Guidance cues play a key role in directing interneuron migration in this area. Most will be familiar with chemo-attractive and chemorepulsive cues required for axon guidance; interestingly, these same families of proteins are involved in the guidance-directed migration of interneurons. To avoid entering the striatum, migrating interneurons express neuropilins (Nrp1 and Nrp2) and plexin coreceptors that respond to the chemorepulsive ligands semaphorin (Sema) 3A and 3F emanating from the striatal mantle [129]. In addition, the proteoglycan chondroitin-4-sulphate is expressed in the striatal mantle [130], which, in conjunction with the semaphorins, creates an exclusion zone for migrating interneurons to channel into adjacent paths and thus define the formation of migratory routes into the cortex. The Sema proteins are also active in the neocortex and act to direct interneuron migration in the tangential streams, preventing them from entering the CP [131].

The chemorepulsive ligand Slit1 is strongly expressed throughout the VZ and SVZ of the GE as well as the preoptic area [132–135] and the corresponding receptor roundabout (Robo) is expressed by interneurons. The complementary expression patterns of Slit-Robo suggest Slit proteins might repel interneurons from the GE to the cerebral cortex [136–139]. Surprisingly, no defects in the tangential migration or differences in the number or distribution of interneurons (GABA-, Lhx6- or Dlx2-positive) were detected in the cortices of Slit1/Slit2 double mutant [111]. Nonetheless, the analysis of two different Robo1-deficient transgenic models have shown a significant influx of CB-positive cells within the developing striatum, as well as an increased number of interneurons within the developing and adult cortex [136, 137]. This suggests that Robo1-null effects could be Slit independent, and this has been confirmed with the recent discovery that Robo1 modulates semaphorin-neuropilin/plexin signalling to steer interneurons around the striatum and into the cortex [140].

Keeping with the classic collection of guidance cues, the membrane-bound ephrin and Eph receptor tyrosine kinases (Eph) also play a role in interneuron migration. Experimental *in vitro* and *in vivo* evidence has revealed the involvement of ephrins in directing migration and enhancing the motility of neurons [141, 142]. Ephrin A5 and its receptor EphA4 are complementarily expressed in the VZ and SVZ of the GE, respectively, and CB-positive cells isolated from the MGE express the EphA4 receptor [141]. *In vitro* stripe assays have demonstrated that both ephrin A5 and ephrin A3 are potent chemorepellents for MGE-derived neurons. Downregulation of the EphA4 re-

ceptor, using siRNA, reduced the repulsive effect of ephrin A3 implicating EphA4 in mediating in part the repulsive effects of ephrin A3 [142]. Together, these results suggest that Eph/ephrin signalling acts as a repulsive cue that restricts cortical interneuron migration from inappropriate regions and are contributing factors in defining the migratory route of cortical interneurons.

Even though inhibitory cues are necessary to guide migration, interneurons are also directed towards the cortex in response to attractive cues. One such candidate is the chemokine CXCL12 (stromal cell-derived factor, SDF1) which signals through the receptors CXCR4 and CXCR7. During early corticogenesis (up to E14.5), CXCL12 expression is high in the MZ and SVZ, whereas at later stages, expression remains high in the MZ but is dramatically reduced in the SVZ [143]. The receptors CXCR4 and CXCR7 are expressed on tangentially migrating interneurons [144]. It has been shown that CXCL12 attracts interneurons from the MGE, guiding them to the tangential migratory streams and maintaining them here until the appropriate radial migratory cue is received (see radial migration below) [145].

A second candidate, the neuregulin 1 (NRG1) family of proteins, is essential for interneurons to leave the MGE, travel through the LGE permissive corridor, circumvent the corticostriatal notch and enter into the cortical wall [146]. There are several lines of evidence to suggest a role for NRG1 signalling during interneuron migration. Flames et al. [146] found that different isoforms of NRG1 play distinct roles along the migratory path. The membrane-bound isoform of NRG1 (type III) is found highly expressed by so-called corridor cells present in the SVZ but not the VZ of the LGE. Together with the inhibitory action of semaphorins emanating from the striatum, a permissive corridor is created along the SVZ for interneurons to traverse the LGE. To cross the corticostriatal notch, interneurons require the secreted isoforms of NRG1 (types I and II), which are expressed in the neocortex and act as a long-range chemo-attractant for migrating interneurons. The immediate action of interneurons exposed to an exogenous source of secreted NRG1 is to alter the direction of migration by the extension of a new leading neurite in the direction of the source (fig. 2) [99]. In the long term, when cortical NRG1 expression is reduced, there is a concomitant accumulation of ErbB4-positive interneurons at the corticostriatal junction [147] and the complete loss of NRG1 in the forebrain leaves interneurons incapable of leaving the MGE [146].

The expression of ErbB4 (NRG1 receptor) in cortical interneurons [148, 149] is conserved across a number of

species including rodents, macaques and humans [150], and NRG1 has reproducibly emerged as being a candidate susceptibility gene for schizophrenia [151–155]. A dysfunctional GABAergic system is an underlying element in schizophrenia, and the link between NRG1 and early interneuron migration suggests a developmental aetiology. The importance of this will be discussed when we review neurodevelopmental disorders associated with interneuron migration.

Transcription Factors

The idea that transcription factors are involved in migration is quite removed from the classic role of enhancing or repressing genes for cell fate determination; however, this can be achieved through the regulation of guidance cue receptors. For example, loss of function studies for *Lhx6* lim-homeobox transcription factor [87, 156] and *Arx* homeodomain transcription factor [157, 158] in mouse brain slices have shown impeded tangential migration of interneurons into the cortex. Recently *Lhx6* has been shown to mediate its effects through promoting expression of receptors involved in interneuron migration (*ErbB4*, *CXCR4* and *CXCR7*), and through promoting the expression of transcription factors either known (*Arx*) or implicated (*bMaf*, *Cux2* and *NPAS1*) in controlling interneuron development [159].

The homeobox genes *Dlx1/2* are essential not only for the migration of interneuron precursors but also for their maturation in the cortex [19, 160]. Recent evidence suggests that *Dlx1* and *Dlx2* regulation of interneuron migration depends on its ability to restrain neurite outgrowth. These effects appear to be mediated by *Dlx1/2* repression of several genes involved in regulating cytoskeletal dynamics including *PAK3* and *MAP2* [160]. *PAK3* expression is low in migrating interneurons and upregulated upon arrival at the cortex when it is required for neurite outgrowth. The repressive action of *Dlx1/2* on *PAK3* in MGE-derived interneurons is critical in promoting tangential migration, and this was elegantly demonstrated by reducing the aberrant *PAK3* and *MAP2* expression in the *Dlx1/2* double mutant to substantially rescue the tangential migration defects [160]. In a parallel study, Le et al. [161] found that *Dlx1/2* mediated the repression of the receptor *Nrp2* and therefore may facilitate migration through regulating the response to class 3 semaphorins.

The homeodomain factor *Nkx2.1* is specifically expressed in MGE interneuron progenitors and required for the specification of cortical interneuron subtypes [79, 162]. The expression of *Nkx2.1*, however, is downregu-

lated in interneurons entering the migratory route in the cortex [163], and this downregulation is in fact an active step taken by cortical interneurons to coordinate their programmes of differentiation and migration [163]. *Nkx2.1* was also shown to repress *Nrp* levels. The ectopic expression of *Nkx2.1* in migrating MGE-derived cells rendered them insensitive to *Sema3A/Sema3F* chemorepulsion, likely due to a reduction in the expression of *Nrp1* and *Nrp2* [163]. Collectively, the above examples exemplify the dynamic temporal expression of transcription factors and how this function is required not only for interneuron differentiation, but also for the coordination of interneuron migration.

Neurotransmitters

Neurotransmitters are recognized more for a central role in synaptic transmission and the functionality of cortical networks; however, increasing evidence suggests a role in regulating interneuron migration. An assortment of electrophysiological and pharmacological studies have shown that neurotransmitters play a combinatorial role in guiding interneurons across the corticostriatal junction and maintaining the migratory distribution within the cortical wall. To outline the expression profile of neurotransmitters and their corresponding receptors during migration, GABA is present along the main migratory routes and interneurons express GABA_A and GABA_B receptors [164–166]. Dopamine is expressed in the MGE and its corresponding D₁ and D₂ receptors are expressed on interneurons [167, 168] and functional glutamate receptors are present on interneurons migrating in the IZ [169–171]. This story becomes interesting when we examine the phenotypes of the individual receptor knockouts or use of pharmacological blockers throughout the migratory phase.

During corticogenesis, GABA_A receptors bind GABA with higher affinity than mature neurons [172] and the ambient levels of GABA along the migratory route elicit a depolarizing response to modulate migration [164]. Blocking this activity by the treatment of bicuculline or neutralizing GABA antibodies leads to an accumulation of interneurons at the corticostriatal junction; conversely, the addition of GABA enhanced migration into the cortical wall [164]. Several studies have demonstrated the variation in GABA_A receptor subunit expression during development [76, 173] and a recent profiling of single-cells combined with electrophysiological recordings has noted that interneurons migrating in the cortex have a higher affinity, and increased responsiveness to GABA, compared to interneurons in the MGE [166]. This regional

Fig. 2. Interneuron morphology and branching dynamics during migration. Interneurons respond to guidance cues by changing the direction and length of a leading process. Each neuritic process has a growth-cone-like structure at the distal end that is used to scan the environment and determine the direction of movement. Neurites will extend towards chemo-attractants (+), i.e. CXCL12 and neuregulin, and are repelled by chemorepellents (–), i.e. semaphorin and ephrin. Once a leading process is determined, the soma moves to the branch point of the leading neurite, and other cell processes retract. New branches are formed and through a cycle of neurite extension and retraction the interneuron can change the direction of migration.

Fig. 3. Factors affecting interneuron lamination in the rodent cortex. **a** During embryonic development, interneurons are maintained in the tangential migratory streams in the MZ, SP and SVZ by various cues, only transiently entering the CP. Disruption in CXCR4 signalling results in the premature invasion of interneurons into the CP, subsequently disrupting lamination. **b** By the completion of interneuron lamination in the adult, MGE-derived PV- and SST-positive interneurons predominantly occupy deeper cortical layers (layers IV–VI), while CGE-derived 5HT3aR-positive cells primarily occupy more superficial layers (layers II/III). Disruption to reelin signalling (*reeler* mutant) reverses the lamination of these cells. Similarly, a disruption in p35 signalling reverses interneuron lamination with a partial loss in PV- and SST-positive cells. Alterations in GFR α_1 signalling also cause the regionalized loss of a subpopulation of PV-positive cells. In comparison, ablation of *Fzef2* expression causes a shift in PV- and SST-positive interneurons to more superficial layers.

selective response to GABA was accompanied with alterations in GABA isoforms present on individual neurons and highlights the maturation of interneurons during the migration process. In addition, selective antagonists to the GABA_B receptors result in an accumulation of interneurons in the VZ/SVZ and a reduction in the migration through the CP and MZ [165]. It is unclear whether this change in distribution arises initially from misguided routes in the MGE or variation in radial migration within the cortex, time lapse analysis would be beneficial in elucidating this query.

The expression of the dopamine receptors D₁ and D₂ on interneurons and the MGE being a source of dopamine suggests a role for this neurotransmitter in migration [168], and indeed this is the case. Intriguingly, the individual activation of D₁ or D₂ receptors produce opposing effects [167]. Pharmacological blocking of D₁ receptor activity, which induces concomitant activation of the D₂ receptor, decreases the migration of interneurons into the cortex and implies that D₁ receptor activation promotes migration whereas D₂ receptor activation is inhibitory. This was confirmed further by analysis of the individual receptor knockouts. Although there was no change in the total number of interneurons in the CP/MZ, the D₁ receptor knockout showed a significant decrease in the number of interneurons in the IZ/SVZ, whilst the D₂ receptor knockout exhibited an increase in interneurons in this domain [167]. A recent study investigating the downstream molecular mechanisms of D₂ receptor activation in zebrafish [174] has illustrated the conserved nature of this signalling pathway for interneuron development and the importance of maintaining neurotransmitter homeostasis to promote the correct migration and positioning of cortical interneurons.

As described above, a vast array of motogenic and chemotactic cues, transcription factors and neurotransmitters instruct and guide the tangential migration of the interneurons from the ventral telencephalon into the neocortex. Some of these factors also influence the intracortical migration and lamination of the interneurons. We will discuss these processes and the molecules involved below.

Intracortical Migration of Interneurons

Once interneurons arrive in the cortex, different modes of migration are employed. We refer to this as intracortical migration. These migratory behaviours include: (1) the multidirectional migration within tangential routes [175–178], (2) the radial migration for cells moving away from the tangential routes into the CP [99]

and (3) the ventricle-directed migration from the IZ/SVZ towards the VZ [179]. The second migratory mode encompasses both inward radial migration towards the CP from the MZ [31, 175, 176] and outward radial migration towards the CP from the IZ/SVZ [31, 176, 177, 180].

Using flat-mount cortical preparations and real-time microscopy, several groups observed that a substantial proportion of embryonic GABAergic neurons exhibit the multidirectional migration, where the cells move in all directions within the MZ [175, 176] and VZ [177]. Furthermore, Tanaka et al. [178] suggest that GABAergic cells, once reaching the MZ, are liberated from regulation by guidance signals and appear to change direction unpredictably, in a process they term ‘random walk’. The random walk behaviour potentially contributes to the spread of interneurons throughout the cortex; however, we know that the cortex is not uniform and cortical regions vary in interneuron number and subtype content [49]. If this is the case, the distribution of interneurons is not entirely random, but guided to a certain extent by extrinsic or intrinsic signals. Interestingly, Cajal-Retzius cells display multidirectional orientation comparable to the leading neurite angle of interneurons located in close proximity [175]; thus, Cajal-Retzius cells may provide positional cues for migrating interneurons. Furthermore, as Cajal-Retzius cells play a role in early regionalization of the cerebral cortical neuro-epithelium [181], it is tempting to speculate that they can also influence the patterning of the cortical interneurons.

The invasion of the CP by MGE-derived neurons from both the IZ (moving outward) and from the MZ (moving inward) has been shown using in vitro transplantation studies [31] or in vivo with the glutamic acid decarboxylase 67 (GAD67)-green fluorescent protein (GFP) knockin line [176–178]. GAD67 is an interneuron-specific enzyme required for GABA synthesis, and the GAD67-GFP knockin line has been instrumental for real-time imaging of interneuron migration in cortical slices. Tanaka et al. [178] propose that MGE-derived interneurons migrate first to the cortical SVZ, then from the SVZ to the CP, accumulating transiently in the MZ. The existence of this outward migration was confirmed and identified as being characteristic of late-born interneurons (after E15.5) [180]. Finally, there is evidence that cortical interneurons may migrate inwardly towards the VZ, in what has been termed ‘ventricle-directed migration’, perhaps to receive signals that may ultimately assist them in correctly integrating into the cortex [179].

It has been suggested that the switch from tangential to radial migration is dependent on neurite branching

dynamics. While migrating in the tangential migratory streams, interneurons maintain the orientation of the leading neurite parallel to the ventricular surface/pia. Interneurons may linger in the migratory streams for long periods of time [178] before receiving the signal to move into the CP. Once received, the angle of the leading branch changes from small to nearly orthogonal, and the switch from tangential to a radial migratory mode is achieved [99]. From what we know about the guidance-directed migratory behaviour exhibited by interneurons, any cue governing a switch to radial migration needs to be highly regulated both spatially and temporally during corticogenesis.

The molecular cues governing this switch in trajectory are still largely unknown; however, some possible candidates have been identified. The downregulation of connexin 43 expression in interneurons significantly decreased the percentage of radially oriented cells, with a concomitant increase in tangential cell orientation [182]. These studies also verified that the adhesive function of connexin 43, and not formation of hemichannels, was required for interaction with the radial glia. Another regulator, the HMG-box-containing transcription factor Sox6 plays a role as loss of Sox6 in MGE-derived cells causes an accumulation of interneurons in the MZ. This has been interpreted as a defect in the transition from tangential to radial migration [83, 84].

Another approach to control radial migration could be the downregulation of cues required for anchoring interneurons in the MZ during the horizontal dispersion phase. This is observed with the chemokine CXCL12 and its receptors CXCR4 and CXCR7. As described above, CXCL12 expression in the MZ and SVZ [143] is thought to attract cortical interneurons [145]. Loss of CXCL12 signalling increases interneuron branching [183] and dramatically disrupts tangential migration [144, 145, 184–188], resulting in the premature entry of interneurons into the CP and abnormal lamination (fig. 3a). Thus, CXCL12/CXCR signalling may play a dual role, initially attracting interneurons to the neocortex and subsequently maintaining their migration in the tangential streams until the correct radial signal is received.

Other examples of signalling systems required to maintain interneurons in the tangential streams include the interaction between netrin 1 and $\alpha_3\beta_1$ -integrin. An increase in the number of cells switching from tangential to radial migration is observed when this interaction is perturbed [189]. Finally, a possible role for Cajal-Retzius cell and pyramidal neuron involvement is hinted at in the nestin-BDNF transgenic mouse where inappropriate seg-

regation of Cajal-Retzius cells and altered cortical organization impair the final radial migration of interneurons [125]. Considerable progress has been made in recent years regarding radial migration, and future studies will help illuminate other factors involved in this essential process.

Interneuron Lamination

The characteristic 6-layered structure of the mature mammalian cortex is formed largely through the radial migration of the pyramidal neurons. During early cortical development, the first wave of postmitotic pyramidal neurons moves rapidly from the VZ/SVZ to the pial surface, forming a thin mantle layer of cortical primordium called the preplate layer. A second wave of neurons splits the preplate layer into the superficial layer I (MZ) and a deeper SP layer, establishing the CP in between. The CP is then expanded in an 'inside-out' manner, with layer VI forming first, and subsequent waves of neurons migrating past their predecessors to form the more superficial layers (layers V to II) [190–193].

Although cortical interneurons approach the CP from a subcortical source, it is believed that a similar inside-out pattern of lamination occurs, with early-born cells occupying deeper layers and late-born cells populating superficial layers [108, 175, 180, 193–196]. There are, however, exceptions to this rule as it was observed that the early-born cells actually occupy 2 peak locations, a large peak around layer V and a minor peak around layer II/III [197]. Further studies in the rat found that while PV-positive cells did follow the inside-out layering pattern, CR-positive cells followed an outside-in route, with early-born cells located in layer II/III and late-born cells in layers V–VI [198]. It has since become apparent that the final destination of interneurons in the CP is not solely dependent on the time of generation, but is also subject to the site of origin. While cells derived from the MGE follow the location of the pyramidal cells born at the same time [60, 70, 195], CGE-derived cells primarily populate the outer cortical layers regardless of when they are generated [27, 28, 57, 199, 200] (fig. 3b).

Cues Controlling Interneuron Lamination

Cortical lamination in the mouse begins around E11 and is completed by approximately postnatal day 14. Interestingly, although a small number of interneurons have been observed moving in and out of the CP at early stages of corticogenesis [31, 175–177], they do not become

established in their correct layer until late embryonic/early postnatal stages, well after their contemporaneously born pyramidal neuron counterparts [180, 200]. It has been suggested that cues from the cortex, rather than intrinsic genetic programming, controls interneuron lamination [195, 201] (table 1). One well-known molecule thought to play a major role in cortical lamination is the secreted extracellular matrix protein reelin. Loss of reelin signalling reverses the lamination of the cortex to an outside-in pattern, whereby late-born pyramidal neurons are unable to migrate past the early-born cells [180, 191]. Abnormal interneuron layering is also observed with disrupted reelin signalling (fig. 3b) [180, 200, 202, 203]; however, there is some contention to whether this is the direct action of reelin or a secondary effect of disorganized pyramidal neuron layering. Work by Hammond et al. [203] suggests that the laminar position of late-born interneurons (not early-born) is dependent on reelin signalling, whereas Pla et al. [200] found that interneurons were dependent on the location of pyramidal neurons and not reelin signalling. Both studies utilized chimeric models of transplanting wild-type cells into a *Dab1* mutant (intracellular adaptor molecule for reelin signalling), and even though their interpretations differ, one underlying phenomenon remains the same: the influence of pyramidal neurons on directing interneurons into the appropriate laminar position.

This line of reasoning has been explored recently in an elegant study by Lodato et al. [204]. Analysis of the *Fezf2* knockout revealed that the loss of subcerebral pyramidal neurons and replacement by callosal pyramidal neurons causes the abnormal distribution of specific interneuron subtypes (fig. 3b). Furthermore, they showed that different types of glutamatergic pyramidal neurons effectively recruit specific subtypes of interneurons into their immediate vicinity. Thus, it appears that the identity of a pyramidal neuron, as well as its location, can control the laminar fate of an interneuron. The molecular mechanisms used by pyramidal neurons in this attraction remain unknown.

A number of other signalling molecules have been shown to affect interneuron positioning in the cortex. Disruption in the glial derived neurotrophic factor receptor, *GFR α_1* , causes the loss of a subset of PV-positive interneurons in discrete regions of the cortex, predominantly in the visual and frontal cortices [128]. Abnormal interneuron lamination, and partial loss of PV- and SST-positive interneurons, is also observed in *p35* knockout mice [Rakic, Faux and Parnavelas, pers. commun., 108] (fig. 3b). During corticogenesis, *p35* is the primary activa-

tor of *Cdk5*, a serine-threonine kinase, which phosphorylates proteins associated with the cytoskeleton and thereby plays a pivotal role in neuronal migration [205, 206]. Disruptions to the tangential and radial migration of the cells, for example by disrupting the *CXCL12/CXCR4* and *BDNF/TrkB* signalling pathways, can also greatly affect their laminar position [125, 145, 184, 187, 189]. Furthermore, neuronal activity has been shown to affect interneuron layering postnatally. Overexpression of the potassium channel *Kir2.1* alters neuronal excitability by lowering the resting membrane potential of the cell. When induced between postnatal days 0–3 in CGE-derived interneurons, an aberrant increase in CR- and reelin-positive cells is observed in deeper cortical layers and morphological alterations only after postnatal day 5 [96]. Therefore, it is clear that lamination is influenced by multiple mechanisms which we have only just begun to identify.

The Stop Signal

In comparison to our current, albeit limited, knowledge of the signals involved in lamination, even less is known about the cues that direct an interneuron to stop migration in the correct laminar position and to start arborization. One study, by Bortone and Polleux [207], has suggested that interneurons stop migrating in response to GABA, but only after the interneuron has switched from a depolarizing to a hyperpolarizing state in response to GABA activation. This switch in responsiveness follows the upregulation of the potassium/chloride exchanger *KCC2* [208]. Low levels of *KCC2* expression force the cell into a depolarizing state following GABA stimulation promoting cell migration. An increase in *KCC2* expression reverses the electrochemical potential by extruding chloride ions from the neuron. This results in GABA-stimulated hyperpolarization and causes the cell to stop migrating. The observed upregulation of *KCC2* was non-synchronous, thus making it difficult to determine precisely which interneuron subtypes terminate migration first [207]. It has recently been shown, however, that MGE-derived interneurons upregulate their *KCC2* expression before CGE-derived cells, suggesting that MGE-derived subpopulations stop radial migration before CGE-derived cells [199]. Many questions remain regarding the termination of interneuron migration, such as what regulates *KCC2* expression. Perhaps more intriguing, can various interneuron subtypes respond differently to available intrinsic or extrinsic signals to promote termination and differentiation in defined laminar positions? These and many more questions will drive the in-

terneuron field into the future, as we are only beginning to understand the intricacies of generating the functional balance between pyramidal neurons and interneurons.

Neurodevelopmental Disorders and Interneuron Development

In the adult brain, interneurons play a vital role in modulating neuronal excitability and the generation of temporal synchrony and oscillation among networks of glutamatergic neurons. This role is depicted in an eloquent analogy by Di Cristo [209] ‘to compare interneuron function to the music director of a symphony orchestra, who structures and coordinates the overall musical performance. Without proper direction, the ensemble cannot produce the right melody’. Dysfunction in GABA neurotransmission is believed to be the aetiological basis for a variety of neuropsychiatric disorders such as schizophrenia, autism spectrum disorders, epilepsy and mood disorders [210–214]. This is evidenced by either loss of interneuron numbers, calcium-binding protein characteristics or alterations in synaptic receptors.

In simplistic terms there are 4 possible explanations for a loss in GABA function in a diseased brain. First, loss of a precursor population would significantly reduce the number of interneurons and, depending on the precursor, may reduce these numbers in a subtype-specific manner. Second, perturbations in signalling mechanisms regulating migration, lamination or differentiation will reduce the number and function of integrated interneurons. Third, interneurons may locate in the correct laminar position at birth but become abnormal as maturation proceeds. This reflects the protracted development of GABA circuits occurring over the first two decades of life [215]. Fourth, input of extrinsic fibre systems that continue until the early adult period, such as the dopaminergic afferents, may develop abnormally and delay or prevent interneuron maturation [216]. We will present the following discussion from an embryonic perspective and reflect on abnormal interneuron lamination in relation to signalling pathways we have described previously to be involved with migration.

We have only just begun to appreciate the influence of pyramidal neurons on interneuron development and the link between genes regulating migration of both neurons. The genetic analysis of human brain malformations has identified mutations in 2 genes, *Lis1* (also known as *PAFAH1B1*) and *Dcx*, which result in a pyramidal migratory disturbance known as type 1 lissencephaly, literally

meaning ‘smooth brain’ [217]. This condition is characterized by a 4-layered cortex, with no obvious relationship to the normal 6 layers, in addition to gyral abnormalities that present as a smooth exterior. Historically, mutations in *Lis1* and *Dcx* are associated with abnormal pyramidal neuron migration, but more recently these proteins have been associated with interneuron migration in rodents [106, 107]. The investigation of interneuron defects in several human cases of agyria has revealed a substantial reduction in the number of cortical, but not brain stem and cerebellum interneurons [218]. A significant reduction in the number of CR-positive interneurons is also noted in Miller-Dieker syndrome (*LIS1* mutation) [219]. Human mutations in the transcription factor *Arx*, which is necessary for the *Dlx*-dependent promotion of interneuron migration, are associated with neurological disorders including lissencephaly, mental retardation and epilepsy (X-linked lissencephaly associated with abnormal genitalia, XLAG syndrome). These conditions display aberrant migration and differentiation of interneurons [220], and many of the neurological phenotypes observed in patients can be attributed to interneuron dysfunction.

A deficit in GABA transmission is among the most consistent findings in schizophrenia patients, and these exhibit a degree of interneuron subtype specificity. A number of detailed studies on post-mortem tissue have revealed a decrease in PV-positive interneurons [221, 222] or a global decrease in GAD67 in the dorsal lateral prefrontal cortex [223–225]. It remains unclear if particular subtypes are more vulnerable in a schizophrenic brain, and one line of evidence proposes an increased susceptibility of fast-spiking PV-positive interneurons to the redox dysfunction exhibited in a schizophrenic brain [226]. Moreover, to further characterize changes in the dorsal lateral prefrontal cortex, a recent study has revealed lamina-specific alterations in the GABA_A α_1 - and β_2 -receptor subunits expressed by interneurons [224]. This places emphasis on the impairment of microcircuits rather than global cortical circuits as a causal factor in disease progression.

The identification of susceptible genes by association and gene linkage studies represent a major advance in investigating the aetiology of schizophrenia. One candidate gene, *NRG1* with its receptor *ErbB4*, has reproducibly transpired as being a candidate gene across differing ethnic groups [151–155]. The rodent studies previously described have shown a role for *NRG1* during migration, where type III regulates interneurons locally in the GE, whereas type I and II signal from the cortex and promote

migration. ErbB4 is expressed in interneurons [148, 227] and analysis of the ErbB4 knockout mouse shows a reduction of 50 and 30% of the cortical and hippocampal interneurons, respectively [146, 228]. Interestingly, in the adult hippocampus there was a selective loss of interneurons positive for PV and neuronal nitric oxide synthase, but not SST-positive interneurons which have negligible levels of ErbB4 [229]. From a developmental perspective, all 3 interneurons are generated in the MGE; however, NRG1 is required for the survival of only particular subtypes that are also absent in the human condition.

Concluding Remarks

Our current understanding of the cellular and molecular mechanisms involved in the migration and specification of interneurons is based on decades of research. Together with advances in new technologies, like genetic fate mapping (for the identification of the multiple interneuron subtypes) and high-resolution *in vivo* imaging, there is great promise to enhance our understanding of interneuron development. In particular, researchers are

starting to tackle the intricate issues, such as the influence exerted by pyramidal neurons over different facets of interneuron migration. Questions relating to interneuron lamination, starting with the switch from a tangential to a radial mode of migration, to the subtype-specific positioning of the interneurons with their pyramidal counterparts, are beginning to be addressed. In the years to come, characterization of changes in specific subclasses of interneurons in schizophrenia and other psychiatric disorders will provide important insights into the observed GABAergic dysfunction. Moreover, the evolutionary adaptation of distinct interneuron origins in humans, as well as the existence of additional subtypes, may help to elucidate the potential causes of many neurological conditions. Although simultaneous studies in rodents disclose comparable cues required for human interneuron development, we must bear in mind that the genesis of subtypes specific to higher primates may not be imitated in the rodent model. Thus, like the interneurons themselves, although we have travelled a long way in our journey to decipher the complexities of interneuron development, the path is still long, and there is still much to be learned and ultimately gained.

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