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REVIEW ARTICLE
Cellular and molecular mechanisms controlling the migration of neocortical interneurons

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Abstract

The discovery, approximately 15 years ago, that cortical GABAergic interneurons originate outside the pallium has revolutionized our understanding of the development of the cerebral cortex. It is now clear that glutamatergic pyramidal cells and GABAergic interneurons follow largely distinct development programs, a notion that has challenged our views on how these neurons assemble to form precise neural circuits. In this review, I summarize our current knowledge of the mechanisms that control the migration of neocortical interneurons, a process that can be subdivided into three consecutive phases: migration to the cortex, intracortical dispersion, and layering.

Introduction

As in many other regions in the brain, functioning of the cerebral cortex requires the coordinated activity of excitatory (glutamatergic) and inhibitory (GABAergic) neurons. In contrast to other regions, however, the two main classes of cortical neuron are generated in distant progenitor pools. Pyramidal cells – as most cortical glutamatergic neurons are normally called – are born from progenitor cells located in the pallium (i.e. the cortical anlage), whereas interneurons are generated remotely in several progenitor pools of the subpallium, the same region that gives rise to the basal ganglia and parts of the amygdala and septum. Consequently, pyramidal cells and GABAergic interneurons follow largely distinct migratory programs to converge in the mature cerebral cortex. Whereas pyramidal cells migrate radially to adopt their corresponding laminar position in the nascent cortex, interneurons perform a complex choreography to reach their final position. First, they reach the pallium via a long tangential migration from the subpallium; second, they spread out tangentially to occupy the entire cerebral cortex; and third, they integrate into specific layers of the cortex. As different classes of interneurons originate from distinct progenitor pools in the subpallium and adopt their final position following specific rules, each of these steps is likely to be differentially regulated for the various classes of cortical interneuron, adding even more complexity to this already convoluted process.

Our knowledge of the mechanisms controlling the migration of cortical neurons is largely based on neocortical interneurons, which will be the focus of this review. In the following sections, I will review our current understanding of the cellular and molecular mechanisms regulating the three consecutive phases through which neocortical interneurons adopt their final position in the cortex. Before that, I will briefly summarize the studies that led to the identification of the remote origin of cortical interneurons.

Origins of cortical interneurons

The coexistence of two different modes of cell migration in the developing cortex, radial and tangential migration, was first shown by lineage tracing experiments in the late 1980s (Price & Thurlow, 1988; Walsh & Cepko, 1988; Austin & Cepko, 1990). This idea gave support to early histological studies describing the existence of tangentially orientated cells in the developing cortex (Stensaas, 1967; Morest, 1970; Shoukimas & Hinds, 1978), and was further substantiated by pioneering time-lapse experiments in slices (O'Rourke *et al.*, 1992) and clonal analyses of X-inactivation mosaics (Tan & Breen, 1993; Tan *et al.*, 1995). At that time, however, the pallial–subpallial boundary was conceived as a rather impermeable boundary separating the nascent cortex from the basal ganglia (Fishell *et al.*, 1993; Krushel *et al.*, 1993), even though the finding of cortical cells expressing Dlx2 – a characteristic transcription factor of subpallial progenitors – had led to the suggestion that these cells reach the cortex by migration (Porteus *et al.*, 1994). This hypothesis was experimentally proved by tracing experiments in whole embryo cultures at mid-gestation that revealed the existence of a stream of cells migrating from the developing subpallium towards the cortex (De Carlos *et al.*, 1996). Subsequent slice culture and mouse genetic experiments demonstrated that most of the cells that reach the cortex from the subpallium correspond to GABAergic interneurons (Anderson *et al.*, 1997; Tamamaki *et al.*, 1997).

The precise origin of cortical interneurons within the subpallium has only been elucidated in recent years, and there are important gaps exist in our knowledge of this process. There are several recent reviews that comprehensively describe the origins of cortical interneurons (Gelman & Marín, 2010; Anastasiades & Butt, 2011; Fishell & Rudy, 2011), so only a brief summary of our current understanding is provided here. The embryonic subpallium has five

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major proliferative regions: the lateral ganglionic eminence (LGE), the medial ganglionic eminence (MGE), the caudal ganglionic eminence (CGE), the preoptic area (POA), and the septum anlage. The pioneer tracing studies that discovered the tangential migration from the subpallium to the pallium suggested that the LGE was the origin of cortical interneurons (De Carlos *et al.*, 1996; Anderson *et al.*, 1997; Tamamaki *et al.*, 1997). However, it soon became obvious that the methods used to label migrating cells in these studies could also accidentally mark neurons of a different origin that migrate through the LGE on their way to the cortex. Analysis of mouse embryos lacking the transcription factor Nkx2-1, which is specifically expressed in the MGE and POA, as well as slice tracing and *in utero* transplantation studies comparing the properties of LGE-derived and MGE-derived neurons, revealed that the MGE is one of the main sources of cortical interneurons (Sussel *et al.*, 1999; Lavdas *et al.*, 1999; Wichterle *et al.*, 1999). Similar experiments were subsequently used to identify the CGE as another important source of cortical interneurons (Nery *et al.*, 2002; López-Bendito *et al.*, 2004; Butt *et al.*, 2005). More recently, genetic lineage tracing experiments have refined this picture by confirming that most cortical interneurons originate from the MGE and CGE (Fogarty *et al.*, 2007; Xu *et al.*, 2008; Miyoshi *et al.*, 2010; Rubin *et al.*, 2010), and adding the POA as the source of a small fraction of cortical interneurons (Gelman *et al.*, 2009, 2011).

The available data indicate that neocortical interneurons are produced in the MGE, CGE and POA in an estimated ratio of 6 : 3 : 1 (Fig. 1). The MGE is the source of two main classes of cortical interneuron, fast-spiking parvalbumin (PV)-containing basket and chandelier cells, and somatostatin (SST)-containing interneurons, many of which typically show intrinsic burst-spiking or adapting non-fast-spiking electrophysiological profiles, and have long axons that extend into layer I (Martinotti cells). The CGE produces two large groups of interneurons: rapidly adapting interneurons with bipolar or double-bouquet morphologies, which frequently express calretinin and/or vasointestinal peptide; and rapidly adapting interneurons with multipolar morphologies, which express neuropeptide Y (NPY) and/or reelin, but not SST. Finally, the POA primarily produces multipolar and rapidly adapting NPY-containing interneurons and a smaller proportion of PV-containing and SST-containing interneurons.

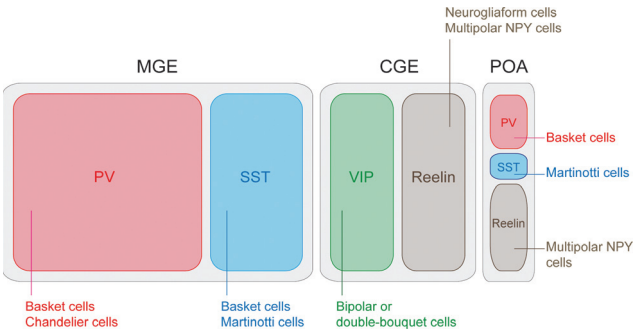

FIG. 1. Major groups of cortical interneurons and their developmental origins. (i) Fast-spiking PV-containing interneurons. These include two main classes of interneuron: basket ells and chandelier cells. Most of these interneurons are generated in the MGE, although a small percentage of PV-containing basket cells are derived from the POA. (ii) SST-containing interneurons. These show intrinsic-burst spiking or adapting non-fast-spiking electrophysiological profiles. Many of these neurons have the morphology of Martinotti cells, but other are more similar to basket cells and have near fast-spiking properties. Most SST-containing interneurons are generated in the MGE, except for a small proportion of Martinotti cells that are produced in the POA. (iii) Rapidly adapting interneurons with bipolar or double-bouquet morphologies. These cells very frequently express vasointestinal peptide (VIP), and many of them also contain calretinin (CR). These interneurons are derived from the CGE. (iv) A very heterogeneous group of interneurons, including rapidly adapting interneurons with multipolar morphologies and neurogliaform cells. Most of these cells express reelin but not SST, and many also express NPY or nitric oxide synthase. These cells are derived from the CGE and the POA.

Tangential migration to the pallium

Newborn interneurons have an enormous ability to migrate throughout the developing telencephalon, a feature that is common to all interneurons, independent of their origin. Indeed, migrating MGE-derived, CGE-derived and POA-derived interneurons are indistinguishable, as they all have a morphology that is common to many tangentially migrating GABAergic neurons in the developing brain (Marín *et al.*, 2006). One of the most prominent features of these cells is that their leading process branches continuously during the migratory cycle (Martini *et al.*, 2009; Yanagida *et al.*, 2012). These branches are generated and modified in response to cues present in the extracellular environment, and seem to serve as the main mechanism that determines the direction of the migrating cell (Martini *et al.*, 2009; Lysko *et al.*, 2011). Interestingly, recent work has shown that this process is, at least in part, mediated by a primary cilium that interneurons assemble in the membrane of the leading process (Baudoin *et al.*, 2012). Thus, the different classes of interneuron use similar cellular mechanisms to translocate to the cortex, but they specifically respond to particular guidance factors based on the complement of receptors that they express, a process that is controlled by region-specific transcriptional programs (Nóbrega-Pereira & Marín, 2009).

MGE-derived interneurons

The initial movement of interneurons away from the progenitor zones of the MGE is probably mediated by chemorepulsive cues present in this region (Fig. 2). For example, Slit1 and Efna5 are

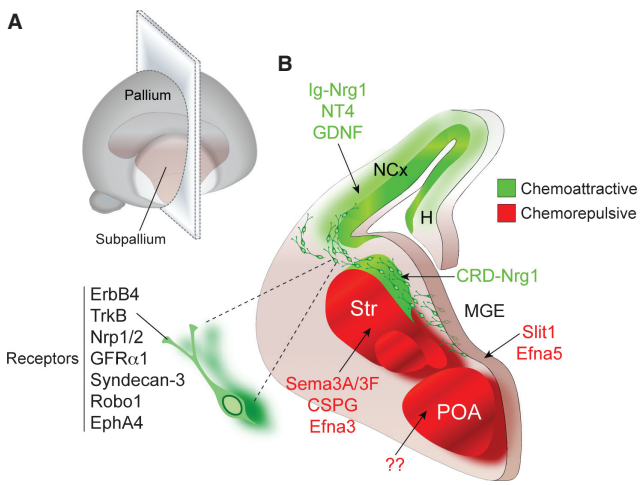

FIG. 2. Molecular mechanisms controlling the migration of MGE-derived interneurons to the cortex. (A) Schematic representation of an embryonic day 13.5 telencephalic hemisphere, depicting the location of the pallium and subpallium. (B) Schematic representation of a transversal hemi-section through the telencephalon, in which the migration of MGE-derived interneurons is illustrated. Interneurons respond to chemorepulsive (red) and chemoattractive (green) factors, many of which have been identified, in the basal ganglia and cortex. Migrating interneurons express a complex set of receptors to detect these molecules. CSPG, chondroitin sulfate proteoglycans; H, hippocampus; NCx, neocortex; Str, striatum.

expressed in the ventricular zone of the MGE (Marillat *et al.*, 2001; Zimmer *et al.*, 2008), and experimental evidence suggests that these factors repel MGE-derived interneurons (Zhu *et al.*, 1999; Zimmer *et al.*, 2008). Recent work suggests that Slits also regulate neurogenesis in the MGE (Borrell *et al.*, 2012), and so it is conceivable that the early steps in the migration of interneurons might also depend on the contribution of these factors to their initial polarization.

Newborn interneurons seem to respond to several motogenic cues that promote the tangential migration of these cells (Fig. 2). For example, the migration of MGE-derived interneurons is strongly stimulated by brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT4) (Polleux *et al.*, 2002). Similarly, glial-derived neurotrophic factor (GDNF) and hepatocyte growth factor both stimulate the migration of interneurons *in vitro* (Powell *et al.*, 2001; Pozas & Ibañez, 2005). However, the direct involvement of these molecules in the regulation of the migration of MGE-derived interneurons *in vivo* is less clear. For instance, genetic experiments have revealed that TrkB, the tyrosine kinase receptor for BDNF and NT4, is dispensable for the tangential migration of interneurons to the cortex (Carmona *et al.*, 2006; Sánchez-Huertas & Rico, 2011). In addition, MGE-derived interneurons only seem to express MET *in vitro*, and conditional deletion of the *MET* gene from interneurons has no effect on the final distribution of these cells (Eagleson *et al.*, 2011). The function of GDNF in the migration of cortical interneurons seems to be mediated by its GFRα1 receptor, and the heparan sulfate proteoglycan syndecan-3, independently of the RET tyrosine kinase, and genetic evidence supports a role for these molecules *in vivo* (Canty *et al.*, 2009; Bespalov *et al.*, 2011). Nevertheless, the complex distribution abnormalities observed in GFRα1 receptor mutants suggest that GDNF may play a role in the organization of MGE-derived cortical interneurons that extends beyond the direct regulation of their migration (Canty *et al.*, 2009).

In vitro experiments have shown that, in addition to neurotrophic factors, both GABA and glutamate enhance the initial migration of MGE-derived interneurons (Cuzon *et al.*, 2006; Manent *et al.*, 2006; Bortone & Polleux, 2009; Inada *et al.*, 2011). This function is mediated through the tonic activation of $GABA_A$ and AMPA receptors, respectively, which are expressed in interneurons soon after these cells start their migration (Soria *et al.*, 1999; Métin *et al.*, 2000; Cuzon *et al.*, 2006; Cuzon & Yeh, 2011). The mechanism through which GABA and glutamate promote the migration of interneurons remains unclear, but it seems to depend on the ability of these neurotransmitters to depolarize the plasma membrane of embryonic interneurons, thereby increasing their intracellular calcium levels (Soria *et al.*, 1999; Métin *et al.*, 2000; Bortone & Polleux, 2009). Thus, ambient GABA and glutamate contribute to regulate the motility of cortical interneurons by setting the appropriate calcium 'tone' in migrating neurons.

During their transit through the subpallium, cortical interneurons actively avoid entering the POA and the striatum, two structures that develop in close proximity to the MGE (Fig. 2). The molecular nature of the chemorepulsive activity present in the POA has not been identified. It was initially proposed that Slits could mediate the effect of this region on the migration of MGE-derived interneurons (Zhu *et al.*, 1999), but both experimental manipulations and genetic analyses indicate that these factors do not contribute to the chemorepulsive activity found in the POA (Marín *et al.*, 2003). In contrast, several lines of evidence suggest that the striatum is hostile to the migration of cortical interneurons, because projection neurons in this region express class III semaphorins such as Sema3A and Sema3F (Marín *et al.*, 2001). This function is mediated by neuropilin receptors, which are expressed by interneurons migrating to the cortex but are absent from those targeting the striatum (Marín *et al.*, 2001; Nóbrega-Pereira *et al.*, 2008; Gant *et al.*, 2009). Recent studies suggest that Robo1 receptors may also help cortical interneurons to sense striatal semaphorins (Hernández-Miranda *et al.*, 2011). In addition, it has been shown that chondroitin 4-sulfate-carrying proteoglycans expressed in the striatum restrict the diffusion of Sema3A away from this region (Zimmer *et al.*, 2010), which may allow interneurons to migrate towards the cortex, traversing territories that are inmmediately adjacent to the developing striatum (Marín *et al.*, 2001; Nóbrega-Pereira *et al.*, 2008). Additional molecules have been suggested to mediate the chemorepulsive activity of the striatum. For example, *in vitro* experiments indicate that interactions between ephrinA molecules and their EphA receptors may also contribute to the routing of cortical interneurons away from the striatum (Rudolph *et al.*, 2010), but further genetic evidence seems to be necessary to clarify the function of Eph/ephrin signaling in this process.

MGE-derived interneurons follow a gradient of increasing permissivity towards the cortex, most likely created by the diffusion of long-range chemoattractive cues from the pallium (Marín *et al.*, 2003; Wichterle *et al.*, 2003). To date, the only chemoattractive factor identified that regulates the migration of MGE-derived interneurons to the cortex is neuregulin-1 (Nrg1), a protein that contains an epidermal growth factor-like domain that signals through receptor tyrosine kinases of the Erbb family (Fig. 2). Two different isoforms of Nrg1 are expressed in the developing telencephalon: CRD-Nrg1, a membrane-bound protein that is expressed in the route followed by MGE-derived interneurons towards the cortex; and Ig-Nrg1, a diffusible protein that is produced in the pallium (Flames *et al.*, 2004). Experimental evidence suggests that these different isoforms of Nrg1 act as short-range and long-range attractants, respectively, for migrating interneurons, and that this function is mediated by Erbb4, the neuregulin receptor expressed by MGE-derived interneurons (Yau *et al.*, 2003; Flames *et al.*, 2004). Consistently, genetic studies have revealed that perturbation of ErbB4 function decreases the number of MGE-derived interneurons that reach the cortex (Flames *et al.*, 2004; Fisahn *et al.*, 2009).

CGE-derived and POA-derived interneurons

As compared with MGE-derived interneurons, relatively little is known about the tangential migration of CGE-derived and POA-derived interneurons. However, the routes followed by CGE-derived and POA-derived interneurons to reach the cortex are largely distinct from those used by MGE-derived interneurons, suggesting that interneurons born in the CGE and POA respond, at least in part, to a different set of guidance cues. In particular, most CGE-derived interneurons colonize the cortex through its caudal pole (Yozu *et al.*, 2005), whereas POA interneurons reach the cortex via a route that courses superficially to the striatum (Marín *et al.*, 2001; Gelman *et al.*, 2009; Zimmer *et al.*, 2011). The idea that interneurons born in different regions of the subpallium are intrinsically different in their ability to respond to guidance cues is based on several lines of evidence. First, transplantation experiments have shown that CGE-derived interneurons consistently migrate caudally to reach the cortex, even when transplanted into the MGE (Yozu *et al.*, 2005). Second, the expression of COUP-TFII, a transcription factor that determines CGE cell fates, is sufficient to drive MGE cells to migrate caudally when transplanted into the CGE (Kanatani *et al.*, 2008). Third, interneurons that reach the cortex through routes that course superficially (putatively POA-derived) or deep (putatively MGE-derived) to the striatum seem to express different guidance receptors (Zimmer *et al.*, 2011). Altogether, these data demonstrate

that the tangential migration of interneurons is regulated in a region of origin-specific manner.

Our knowledge of the factors that regulate the migration of CGE-derived and POA-derived interneurons is very limited. *In vitro* experiments suggest that stimulation of the CB1 cannabinoid receptor promotes the migration of cholecystokinin-expressing interneurons (Berghuis *et al.*, 2005), a population of interneurons that is derived from the CGE (Morozov *et al.*, 2009). In addition, many CGE-derived and POA-derived interneurons express serotonin receptors, and this neurotransmitter seems to restrict the migration of CGE-derived interneurons cells *in vitro* (Vitalis *et al.*, 2007; Riccio *et al.*, 2009). Similarly, activation of α2-adrenergic receptors in CGE-derived interneurons also constrains their migration (Riccio *et al.*, 2012). Additional *in vivo* experiments are required to clarify the role of these molecules in the migration of cortical interneurons. Also, it seems evident that the molecular nature of the main factors controlling the tangential migration of CGE-derived and POA-derived interneurons remains to be elucidated.

Intracortical dispersion

Travel across the pallial–subpallial boundary marks the termination of a phase in the migratory program of cortical interneurons, in a manner that is perhaps analogous to the midline crossing by commissural axons. Indeed, the subpallium becomes refractory to cortical interneurons once these cells have reached the pallium (Marín *et al.*, 2003), and the direction followed by interneurons within the cortex seems to be generally less organized than in the early phases of their migration. For instance, although interneurons colonize the cortex following a general lateral-to-medial gradient (Marín *et al.*, 2003; Tanaka *et al.*, 2003; Cuevas *et al.*, 2005), individual cells seem to be able to move in multiple directions (Ang *et al.*, 2003; Tanaka *et al.*, 2003, 2006). Thus, from a conceptual viewpoint, this second phase in the migration of cortical interneurons primarily involves the homogeneous dispersion of interneurons throughout the entire cerebral cortex.

Organization of migratory streams

Interneurons do not disperse throughout the cortex in an indiscriminate way, but rather use a very specific set of routes or migratory streams (Fig. 3) (Marín & Rubenstein, 2001). Most interneurons migrate through one of two large migratory streams, a superficial route that courses through the marginal zone (MZ), and a deep route that largely overlaps with the subventricular zone (SVZ) (Lavdas *et al.*, 1999; Wichterle *et al.*, 2001). A smaller fraction of interneurons migrate through the subplate (SP). Remarkably, interneurons stay away from the cortical plate (CP) during this phase, whereas pyramidal cells begin forming cortical layers in this location. This observation suggests that the dispersion of cortical interneurons throughout the cortex requires the active avoidance of the CP, their final place of residence.

The mechanisms that control the preferential migration of interneurons through these migratory streams are beginning to be elucidated. Interneurons do not seem to be actively excluded from the CP because of the existence of chemorepulsive activity in this region (López-Bendito *et al.*, 2008). Instead, interneurons seem to migrate preferentially through the MZ, SP and SVZ because cells in these regions or immediately adjacent to these regions express molecules that facilitate the migration of interneurons through these routes. So far, only one molecule, the chemokine Cxcl12, has been shown to mediate this process. Cxcl12 (also known as Sdf1) is strongly expressed by the leptomeninges and by intermediate progenitor cells transiently populating the SVZ (Tham *et al.*, 2001; Stumm *et al.*, 2003; Daniel *et al.*, 2005; Tiveron *et al.*, 2006), and is expressed, to a minor extent, by cells in the SP (Stumm *et al.*, 2007). Cxcl12 is a potent long-range chemoattractant for MGE-derived interneurons (Li *et al.*, 2008; López-Bendito *et al.*, 2008), but its limited diffusion properties *in vivo* (owing to its strong affinity for heparan sulfates) would explain the relative confinement of interneurons to the migratory streams found in the cortex. Consistent with this idea, mouse mutants with altered expression of *Cxcl12* in the meninges or in the SVZ show defects in the intracortical migration of interneurons that are specific to the affected migratory route (Tiveron *et al.*, 2006; Sessa *et al.*, 2010; Zarbalis *et al.*, 2012).

The function of Cxcl12 is mediated in cortical interneurons by two G-protein-coupled receptors, Cxcr4 and Cxcr7. Both receptors are necessary for proper sensing of Cxcl12, because *Cxcr4* and *Cxcr7* mutant mice show similar defects in the tangential migration of cortical interneurons (Fig. 3). In the absence of Cxcr4 or Cxcr7, many interneurons fail to confine their migration to the MZ and SVZ, as observed in normal embryos, and instead invade the CP prematurely (Tiveron *et al.*, 2006; Li *et al.*, 2008; López-Bendito *et al.*, 2008; Sánchez-Alcaniz *et al.*, 2011; Wang *et al.*, 2011). Although it has been suggested that Cxcr4 and Cxcr7 elicited different signaling pathways in response to Cxcl12 (Wang *et al.*, 2011), Cxcr7 seems to primarily regulate the levels of Cxcr4 present in the plasma membrane of migrating cells (Sánchez-Alcaniz *et al.*, 2011). In the absence of Cxcr7, Cxcr4 is rapidly degraded in migrating interneurons, owing to accumulation of Cxcl12. This sophisticated fine-tuning mechanism dynamically adapts chemokine responsiveness in migrating neurons, thereby preventing their desensitization as they migrate through these routes for a protracted period of time (Sánchez-Alcaniz *et al.*, 2011).

It is worth noting that, despite the prominent defects observed in the intracortical dispersion of interneurons in the absence of Cxcl12 signaling, interneurons reach the cortex of *Cxcr4* or *Cxcr7* mutants in normal numbers (Tiveron *et al.*, 2006; Li *et al.*, 2008; López-Bendito *et al.*, 2008; Sánchez-Alcaniz *et al.*, 2011; Wang *et al.*, 2011). This observation reinforces the idea that the mechanisms driving the migration of interneurons from the subpallium to the cortex and those controlling their intracortical migration are different.

Selection of migratory streams

The confinement of interneurons to specific migratory streams in the cortex seems to generally rely on chemokine signaling, but it is unclear whether specific interneurons show a preference for a particular route of migration. Several lines of evidence suggest that the interneurons are not distributed randomly across these streams. For example, a recent study found significant differences in the gene expression profiles of interneurons migrating through the MZ and those migrating through the SVZ (Antypa *et al.*, 2011). This idea is further supported by the observation that interneurons lacking integrin α3 receptors fail to migrate throughout the MZ in the absence of netrin1, whereas migration through the SVZ seems to take place normally (Stanco *et al.*, 2009). Moreover, blocking of $GABA_B$ receptors *in vitro* alters the proportions of interneurons migrating through the MZ and SVZ (López-Bendito *et al.*, 2003). Thus, the specific guidance requisites that support the migration of interneurons through each of these routes are partly divergent, and so it is likely that the interneurons that travel through each of these routes express a different complement of guidance receptors. Interestingly, the region of origin (e.g. MGE vs. CGE) does not seem to influence the choice of migratory stream by cortical interneurons (Miyoshi & Fishell, 2011). This suggests that specific classes of interneuron – and

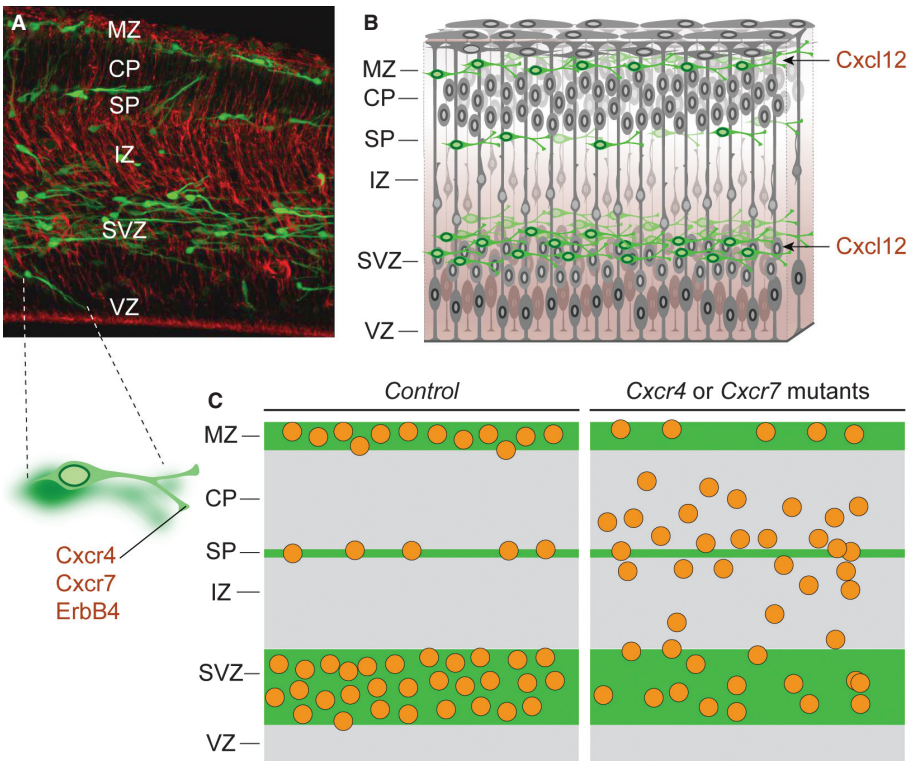

FIG. 3. Migratory streams and intracortical dispersion of interneurons. (A and B) A coronal section through the embryonic pallium, in which migrating interneurons are labeled in green and radial glia cells are labeled in red. The schema illustrates the spatial relationship between migrating interneurons and other elements of the developing cortex. Interneurons migrate preferentially through the MZ and the SVZ, which contain high levels of the chemoattractant Cxcl12. Some interneurons also migrate through the SP. Most MGE-derived interneurons express ErbB4, Cxcr4 and Cxcr7 receptors. (C) Schematic diagrams showing the distribution of migrating interneurons in normal embryos and in mouse mutants lacking the Cxcl12 receptors Cxcr4 or Cxcr7. The concentration of interneurons in the CP of these mutants suggests that the developing CP contains a permissive/chemoattractive factor that interneurons only seem to sense when they lose responsiveness to Cxcl12. IZ, intermediate zone; VZ, ventricular zone.

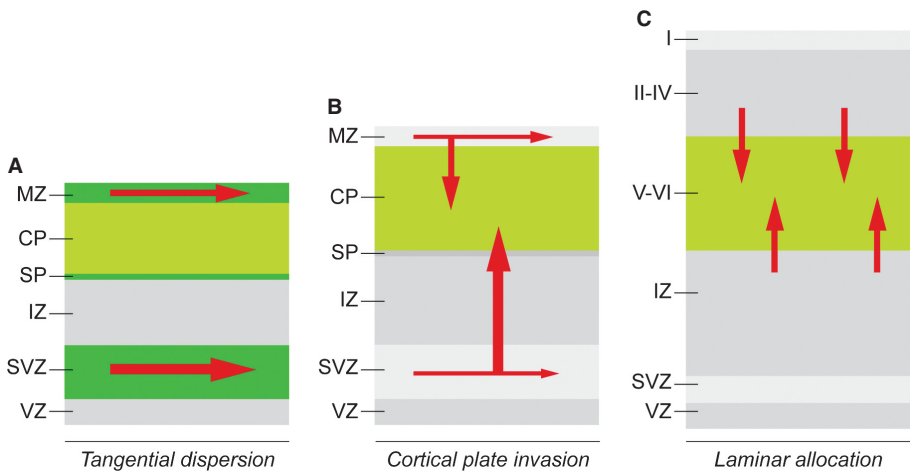

FIG. 4. Three consecutive phases for the integration of cortical interneurons. Schematic representations of the cerebral cortex at three different stages of development are shown. The migration of interneurons within the cortex seems to be largely dictated by permissive or chemoattractive cues (green areas). (A) After arriving at the cortex, interneurons migrate tangentially along stereotyped routes that support their dispersion (dark green). (B) Subsequently, interneurons switch their migration from tangential to radial to invade the CP (light green). Not all interneurons engage in this second phase of their migration at the same time; on the contrary, interneurons reach the CP progressively, depending on their birthdate or lineage (that is, early-born interneurons invade the CP while late-born interneurons are still migrating tangentially to disperse through the cortex). This suggests that the specific loss of responsiveness to Cxcl12 by each cohort of interneurons marks their switch from tangential to radial migration. (C) Finally, interneurons sort out within the CP to localize into specific layers of the cortex, most likely in response to chemoattractive signals expressed by pyramidal cells (light green, only shown for infragranular layers). As in the previous phase, this process is also progressive, and probably depends on the lineage of interneurons.

not just all interneurons born in a particular region in the subpallium – might have a preference to migrate by either one of the two routes, an idea that remains to be experimentally tested.

An alternative, perhaps complementary, view of the existence of different migratory streams in the cortex is that they serve different purposes. It has been shown that interneurons migrating through the

SVZ preferentially colonize the cortex in a lateral-to-medial direction, whereas interneurons in the MZ move in all directions (Ang *et al.*, 2003; Tanaka *et al.*, 2003, 2006; Yokota *et al.*, 2007). According to this idea, interneurons will be allocated to the SVZ or the MZ at different stages of their development, and the movement of interneurons from the SVZ to the MZ will facilitate their dispersion throughout the cortex. This hypothesis is supported by the observation that at least some interneurons are able to migrate from one stream to the other (Nadarajah *et al.*, 2002; Martini *et al.*, 2009; Tanaka *et al.*, 2009). Alternatively, changing lanes might only reflect transient, exploratory movements that migrating interneurons make as they progress through the cortex. In this context, the spreading of interneurons in the MZ has been suggested to depend on a 'random walk' behavior (Tanaka *et al.*, 2009), but it is tempting to speculate that interneurons in the MZ may actually undergo contact repulsion to disperse through the surface of the cortex, as recently shown for Cajal-Retzius cells (Villar-Cerviño *et al.*, 2012).

Tangential-to-radial switch

It is presently unclear what mechanism triggers the tangential-to-radial switch in the migration of cortical interneurons. However, it has been shown that the timing of exit from the migratory streams correlates with the loss of responsiveness to Cxcl12 as an attractant (Li *et al.*, 2008). One possibility is that interneurons have an internal clock that determines their maturation, independently of the environment, which would initiate the transition to radial migration by cells autonomously ending Cxcl12 signaling. This would explain why MGE-derived interneurons invade the CP progressively, with early-born interneurons entering the CP earlier than late-born interneurons (Pla *et al.*, 2006; López-Bendito *et al.*, 2008). The notion that cortical interneurons follow an intrinsically determined developmental program is supported by recent findings on the mechanisms controlling the maturation and death of these cells (Southwell *et al.*, 2010, 2012).

The analysis of *Cxcr4* and *Cxcr7* mutants, in which interneurons accumulate prematurely in the CP (Tiveron *et al.*, 2006; Li *et al.*, 2008; López-Bendito *et al.*, 2008; Tanaka *et al.*, 2010; Sánchez-Alcaniz *et al.*, 2011; Wang *et al.*, 2011), suggests that this lamina of the developing cortex contains a chemoattractive activity for migrating interneurons. These studies have also revealed that this activity is present in the CP from its inception, because, in the absence of Cxcl12 signaling, interneurons concentrate in the CP as soon as they reach the cortex. As interneurons normally tend to avoid the CP during normal embryonic development, the different chemoattractive activities present in the embryonic cortex must be hierarchically organized. In other words, Cxcl12 signaling appears to mask the unknown chemoattractive activity present in the CP until interneurons lose their responsiveness to the chemokine (Fig. 4). This is consistent with the cellular function attributed to Cxcl12, which minimizes the potential of interneurons to sense cues outside the tangential streams by reducing their branching frequency (Lysko *et al.*, 2011). It is worth mentioning that the putative chemoattractive activity present in the CP would only contribute to the recruitment of interneurons within this region; the subsequent sorting of interneurons into different layers occurs at later stages (Pla *et al.*, 2006; Miyoshi & Fishell, 2011), and probably depends on additional factors.

From a cellular perspective, interneurons seem to rely on radial glial cells to enter the CP during their tangential-to-radial switch in migration. Time-lapse analyses have revealed that interactions with the basal processes of radial glial cells can potentially influence the migration of interneurons into the CP (Yokota *et al.*, 2007). Moreover, *in vitro* experiments indicate that this interaction might be mediated by connexins (Elias *et al.*, 2010), similarly to the glial-dependent migration of pyramidal cells (Elias *et al.*, 2007; Valiente *et al.*, 2011).

Laminar allocation

The final phase in the migration of cortical interneurons corresponds to their allocation (i.e. their soma) to specific layers of the cortex. This process occurs during the first postnatal days (Hevner *et al.*, 2004; Pla *et al.*, 2006; Miyoshi & Fishell, 2011), and it is likely to be regulated by mechanisms different from those that recruit interneurons within the CP (Fig. 4). It is worth noting that although some classes of interneuron appear to be equally distributed across many layers of the neocortex, most have relatively restricted laminar patterns. For example, chandelier cells reside almost exclusively in neocortical layers II and VI in the mouse (Taniguchi *et al.*, 2012). In the hippocampus, the association of certain classes of interneuron with specific laminar patterns is even more extreme than in the neocortex (Klausberger & Somogyi, 2008). These observations thus suggest that the laminar allocation of interneurons is strictly regulated, probably in a cell class-specific way.

Cell-autonomous and non-cell-autonomous mechanisms

It is well known that MGE-derived interneurons colonize cortical layers following an inside-out sequence of integration similar to that followed by pyramidal cells, with early-born cells populating infragranular layers and late-born cells populating supragranular layers (Miller, 1985; Fairén *et al.*, 1986; Valcanis & Tan, 2003; Pla *et al.*, 2006). This observation led to the suggestion that the laminar allocation of cortical interneurons might be linked to their birthdate, and that interneurons may use similar mechanisms as pyramidal cells to find their appropriate layer (Kriegstein & Noctor, 2004). However, CGE-derived interneurons tend to populate supragranular layers of the cortex irrespective of their birthdate (Miyoshi *et al.*, 2010). This seems to indicate that the time of neurogenesis might not be causally linked to the process of laminar allocation, at least for some classes of interneuron.

An alternative hypothesis that might explain how coetaneous MGE-derived interneurons and pyramidal cells end up in the same layers of the cortex is that interneurons follow specific classes of pyramidal cells to their final destination (Hevner *et al.*, 2004; Pla *et al.*, 2006; Lodato *et al.*, 2011). In other words, molecules produced by pyramidal cells dictate the layering of interneurons. According to this idea, early-born MGE-derived interneurons would follow cues provided by infragranular pyramidal cells (layers V–VI), whereas late-born interneurons would preferentially interact with supragranular pyramidal cells (layers II–IV). Obviously, similar mechanisms may account for the layering of all cortical interneurons, independently of their origin. Two experimental observations are consistent with this hypothesis. First, interneurons and pyramidal cells do not acquire their laminar position simultaneously. On the contrary, interneurons consistently invade the CP well after coetaneous pyramidal cells have begun to differentiate into a particular cortical layer (Pla *et al.*, 2006; Miyoshi & Fishell, 2011). Second, disrupting the normal layering of pyramidal cells modifies the laminar allocation of MGE-derived interneurons (Pla *et al.*, 2006; Ramos *et al.*, 2006; Lodato *et al.*, 2011). For instance, the experimental arrest of pyramidal cells below the corpus callosum is sufficient to

recruit cortical interneurons to this ectopic location (Lodato *et al.*, 2011). Importantly, the identity of the ectopic pyramidal cells determines the specific types of interneuron recruited (Lodato *et al.*, 2011). In summary, interneurons might be programmed to respond to specific cues provided by pyramidal cells, and so the mechanisms controlling this process are more likely to be related to the specification of progenitor cells than to the timing of neurogenesis.

Although cell-autonomous mechanisms seem to be crucial for interneuron layering, it is likely that additional, non-cell-autonomous mechanisms regulate this process. For instance, it has been observed many late-born interneurons modify their layering preference (choosing deep instead of superficial layers) when transplanted heterochronically into younger embryos (Pla *et al.*, 2006). Similarly, the laminar allocation of interneurons is partly dependent on the precise timing of entry into the CP, because interneurons acquire an abnormal laminar distribution when they invade the CP prematurely, as found in *Cxcr4* and *Cxcr7* mutants (Li *et al.*, 2008; López-Bendito *et al.*, 2008; Tanaka *et al.*, 2010; Sánchez-Alcaniz *et al.*, 2011). In addition, pharmacological disruption of the synthesis of serotonin leads to alterations in the laminar organization of CGE-derived interneurons (Vitalis *et al.*, 2007), suggesting that other regions of the brain may influence the layering of interneurons. In this latter case, however, it is not entirely clear whether the effect of serotonin on interneurons might be indirectly mediated by the role that this neurotransmitter plays in the maturation of pyramidal cells.

Stop signals

In seems obvious that interneurons must be instructed to cease their migration once they have reached their appropriate layer within the cortex. Our current view of this process is based on the general idea that calcium transients regulate the motility of migrating cells, and so the termination of migration is promoted by factors that reduce these calcium transients. As summarized above, GABA and glutamate are thought to enhance neuronal migration in the embryo because they both depolarize the membranes of interneurons and stimulate the generation of calcium transients (Cuzon *et al.*, 2006; Manent *et al.*, 2006; Bortone & Polleux, 2009; Inada *et al.*, 2011). Interestingly, GABA becomes hiperpolarizing during early postnatal development, owing to expression of the potassium/chloride exchanger KCC2, which leads to a negative shift in the reversal potential for chloride ions (Ben-Ari, 2002). It has been proposed that this change turns ambient GABA into a stop signal for migrating interneurons, because hyperpolarizing GABA decreases the frequency of intracellular calcium transients (Bortone & Polleux, 2009). Thus, the mechanisms controlling the transition of GABA from depolarizing to hyperpolarizing seem to be directly related to the termination of interneuron migration.

Several lines of evidence suggest that KCC2 mediates the change in the function of ambient GABA on migrating interneurons (Bortone & Polleux, 2009). Interneurons begin to express KCC2 a few days after reaching the cortex, and this functions as a trigger for the termination of migration. Consistent with this idea, KCC2 expression correlates with the responsiveness of interneurons to GABA as a stop signal, and premature expression of this channel halts migration (Bortone & Polleux, 2009). It should be noted that the function of KCC2 in this process has only been demonstrated for MGE-derived interneurons. Nevertheless, recent work also suggests that normal excitability is required by most CGE-derived interneurons for them to properly integrate into their final destination (De Marco Garcia *et al.*, 2011). The extent to which activity is directly linked to the termination of migration, as suggested above, or to the ability of CGE-derived interneurons to respond to cues provided by pyramidal cells remains to be experimentally tested.

The mechanisms that regulate the expression of KCC2 remain unknown. One possibility is that interneurons turn on KCC2 expression as part of an intrinsic program of maturation (Inamura *et al.*, 2012). This would allow interneurons to cease migration progressively, depending on their birthdate (Hevner *et al.*, 2004; Pla *et al.*, 2006). In addition to the maturation process that makes interneurons susceptible to sensing GABA as a stop signal, cortical cells may also release other factors that slow down the migration of embryonic cortical interneurons. In this latter case, interneurons would only sense these factors when reaching the CP after losing responsiveness to Cxcl12.

Abnormal interneuron migration in disease

Interneuron dysfunction is increasingly being linked to neuropsychiatric disorders (Marín, 2012; Inan *et al.*, 2013). Although defects in the wiring and fine connectivity of interneurons are more likely to underlie the etiology of some of these conditions, it is also conceivable that migration defects exist in some cases. Studies in mice suggest that many extrinsic factors, such as drugs or stress, disrupt interneuron migration. In addition, mutations in some key genes have been shown to affect the number or final distribution of interneurons.

Prenatal stress in mice impairs the migration and final integration of interneurons in the cerebral cortex without affecting their generation or survival (Stevens *et al.*, 2012). It has been suggested that these defects are mediated by changes in the expression of key genes involved in the migration of interneurons, such as *Erbb4*. In addition, fetal cocaine exposure results in impairment of interneuron migration. The effect of cocaine is thought to be mediated by BDNF, whose expression is decreased in cocaine-treated mice (McCarthy *et al.*, 2011). Alternatively, cocaine has been shown to upregulate dopamine D2 receptors, and their activation reduces interneuron migration (Crandall *et al.*, 2007). In contrast, exposure to relatively low levels of ethanol *in utero* enhances the sensitivity of interneurons to GABA, which, in turn, causes premature tangential migration (Cuzon *et al.*, 2008). Thus, drug abuse and prenatal stress may increase susceptibility to mental disease by impacting on the migration of cortical interneurons.

Genetic defects in humans may also disrupt the distribution of cortical interneurons. For example, interneuron defects have been described in humans carrying mutations in ARX, which causes X-linked lissencephaly with ambiguous genitalia (Bonneau *et al.*, 2002; Marcorelles *et al.*, 2010). In addition, fetuses with Miller–Dieker syndrome have a significant reduction in the number of interneurons present in the cortex (Pancoast *et al.*, 2005; Marcorelles *et al.*, 2010). These defects are probably caused by migration abnormalities, as shown in mouse models carrying the corresponding mutations (Kitamura *et al.*, 2002; Colasante *et al.*, 2008; Gopal *et al.*, 2010). Similarly, a mouse model of DiGeorge syndrome caused by the 22q11.2 deletion showed abnormalities in the distribution of PV-containing cortical interneurons (Meechan *et al.*, 2009). Recent work suggests that these defects might be caused by a reduction in the level of Cxcr4, which would alter the timing of laminar allocation for PV-containing interneurons (Meechan *et al.*, 2012).

A look forwards

The migration of cortical interneurons is one of the best-studied examples of long-range migration in the developing brain, and probably the one with most important biomedical significance. However, there are

important aspects of this fascinating journey that we do not fully understand. For example, we do not know whether interneurons are addressed to a particular region of the cortex or are functionally naïve and able to integrate into any cortical area indiscriminately, a view supported by *in vitro* experiments (Lourenco *et al.*, 2012). Notably, recent work has shown that pontine neurons retain a large degree of topographic organization even after undergoing a long tangential migration (Di Meglio *et al.*, 2013). This would suggest that a similar topographic organization may exist for each of the pools of cortical interneuron progenitors, although this is something that remains to be experimentally tested. A second aspect of the migration of cortical interneurons that is largely unexplored is the process of layer distribution. Although it seems clear that factors released by pyramidal cells probably control this process (Hevner *et al.*, 2004; Pla *et al.*, 2006; Lodato *et al.*, 2011), none of these molecules has yet been identified. Thus, although much progress has been made in understanding the initial migration of interneurons to the cortex and their intracortical dispersion, new developments in this field should contribute to identifying the precise molecular mechanisms that control the allocation of interneurons within the cerebral cortex.

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Abbreviations

BDNF, brain-derived neurotrophic factor; CGE, caudal ganglionic eminence; CP, cortical plate; GDNF, glial-derived neurotrophic factor; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; MZ, marginal zone; NPY, neuropeptide Y; Nrg1, neuregulin-1; NT4, neurotrophin-4; POA, preoptic area; PV, parvalbumin; SP, subplate; SST, somatostatin; SVZ, subventricular zone.

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