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Decision Making During Interneuron Migration in the Developing Cerebral Cortex

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Abstract

Appropriate interneuron migration and distribution is essential for the construction of functional neuronal circuitry and the maintenance of excitatory/inhibitory balance in the brain. GABAergic interneurons originating from ventral telencephalon choreograph a complex pattern of migration to reach their target destinations within the developing brain. This review examines the cellular and molecular underpinnings of the major decision-making steps involved in this process of oriental navigation of cortical interneurons.

Keywords

Interneurons; migration; laminar organization; neural circuitry; cerebral cortex

Introduction

The functions of the central nervous system (CNS) requires balanced and coordinated activities between the excitatory, glutamatergic projection neurons and inhibitory GABAergic (gamma-aminobutyric-acid) interneurons. In contrast to the projection neurons that are generated in the dorsal telencephalon (pallium) and migrate radially over a relatively shorter distance into the developing cortical plate, interneurons originate from distinct regions of the subpallium and migrate tangentially in multiple streams, across areal boundaries of the developing telencephalon, to reach their intended destinations in the neocortex, striatum, hippocampus, and olfactory bulb (OB)[1]. During this process, interneurons precisely integrate their cell-intrinsic characteristics with input from local environmental cues to facilitate decisions that are necessary for appropriate patterns of migration (Text Box 1). This review provides a summary of the major decision-making

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steps involved in interneuron migration and the cellular and molecular mechanisms underlying each of these steps. In particular, we focus on the determinant steps that enable cortical interneurons to navigate towards and incorporate into defined neural microcircuitry in the cortex and the challenges remaining in our understanding of this process.

Text Box 1

Origins and migratory routes of interneurons in the developing brain

Interneurons are highly heterogeneous and diverse neuronal population that arises from progenitor pools within the lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), caudal ganglionic eminence (CGE), preoptic area (POa), and septal anlage of the subpallium in the developing telencephalon[2–6]. Post-mitotic interneurons from these distinct proliferative domains exit through distinct pathways[7–12], dorsally to the cortex, ventrolaterally to the striatum, caudally to the hippocampus and rostrally to the OB, to reach their final target destinations.

The most extensively studied of these pathways is the GE-derived GABAergic interneurons migrating towards the dorsal cortex. Early tracing studies have demonstrated that different streams of interneurons arising from GE are able to transit across the cortico-subpallial boundary, and course tangentially into the cortex. An early stream of interneurons (~ E11.5 in mouse) from MGE migrate dorsolaterally onto the top of the preplate, where many of them eventually become layer I Cajal-Retzius neurons[2]. Later during corticogenesis (~ E13-E15 in mouse), a second and more prominent stream of interneurons, mainly from MGE, rapidly migrate into the neocortex, through the intermediate zone (IZ)[2]. This latter stream is joined by interneurons from LGE, although much less robustly and via a more restricted route through the cortical proliferative zone[1, 2]. At later stages of corticogenesis, interneurons enter the cortex via multiple streams, largely through lower IZ and subventricular zone (SVZ), as well as through migratory streams in subplate (SP) and marginal zone (MZ). Additionally, CGE has been shown to be another major source of cortical interneurons. 3-D profile of cortical interneuron migration indicates that simultaneous with the MGE derived streams, a wave of interneurons originating from CGE migrate in a lateral and medial direction to enter the caudal-most end of the cerebral cortex[8, 9, 13] (Figure 1).

Subpallially originating interneurons also tangentially migrate toward other destinations within the developing brain: ventrolaterally to the striatum, caudally to the hippocampus and rostrally to the OB. MGE together with the adjacent POa gives rise to striatal interneurons that migrate tangentially into the developing striatum, where they differentiate and integrate into the local striatal neural circuitry[7]. CGE is the largest source of hippocampal interneurons. By E13.5 in mouse, a stream of CGE-derived interneurons rapidly migrate towards the caudal end of telencephalon, where they enter MZ and eventually settle down in the hippocampus[9, 13]. In contrast, LGE give rise to most if not all interneurons that migrate rostrally and populate both the glomerular and granule cell layers of the olfactory bulb[7, 10, 14, 15]. The migration of olfactory interneuron precursors continues throughout postnatal period and adulthood, providing a constant supply of interneurons to the local neural circuits of the olfactory bulb[16, 17]. The

subventricular zone (SVZ), a mitotically active region in the dorsal-medial corner of striatum that is derived from embryonic LGE, gives rise to these postnatal olfactory interneurons[18, 19]. Compared to the embryonic stages of olfactory interneuron migration, during which loosely associated neurons disperse through the extracellular space, new born interneurons in neonates and adults organize into a network of interlinked chains, surrounded by astroglial tubes, to migrate in a restricted and highly oriented route named rostral migration stream (RMS) [16, 17].

Decision-making steps of interneuron migration

The cellular dynamics (Text Boxes 1, 2) underlying the navigation of interneurons from their sites of birth to their final areal and laminar destinations (Text Box 3) can be broadly divided into six decision-making steps and the mechanisms serving each of them are examined below.

Text Box 2

Cellular dynamics of migrating interneurons

Unlike the stereotypical migratory behavior of many neurons that extend a single leading process in the direction of migration, interneurons search for guidance signals by vigorously and continuously extending multiple, diverging branches from the leading process to better sense and align with the source of the orienting gradients[20, 21]. The branch that best aligns with the net gradient of the guidance cues then is stabilized, while other branches retract, and the nucleus moves in the direction of the stabilized leading process. Further, interneurons can also alter migratory direction by reversing their polarity, i. e., by converting the trailing process directly into a leading process while the previous leading process retracts like a trailing process[22].

Once the migratory direction is decided, interneurons advance forward by performing a repeated cycle of two-phase nucleokinesis[23]. First, as the leading process is stabilized, organelles including the centrioles and Golgi apparatus within the perinuclear cytoplasm form a presomal swelling and extend into the leading process. In the second phase, the nucleus translocates toward the presomal swelling as the trailing process retracts toward the new position of the cell soma. This two-phase nucleokinesis results in the characteristic saltatory mode of interneuron migration, alternating between a resting phase, when the leading process is actively extending and exploring, and a moving phase, when the cell soma translocates in a new direction[23, 24]. Two sets of cellular forces facilitate the nuclear movement in migrating interneurons: the microtubule-dependent pulling force and the actomyosin-dependent pushing force. The pulling force is generated by the microtubule “perinuclear cage”, which envelops the nucleus and is tethered to the centrosome to couple the nuclear movement with the direction set by the leading process[23]. In contrast, non-muscle myosin II that accumulates at the rear end of the cell body provides the contractile pushing force for the forward movement of nucleus[23]. This pattern of coordinated leading process/nucleokinesis dynamics is repeated to facilitate directional movement of interneurons.

Text Box 3

Laminar and areal allocation of cortical interneurons

Once in the dorsal cortex, interneurons employ multiple modes of migration as they move to specific areal and laminar locations within the emerging CP[22, 25–28]. The local migration within the dorsal cerebral wall is crucial in determining the final positioning of cortical interneurons. For example, interneurons migrating in MZ stream undergo multidirectional local migration, actively contacting radial glial endfeet, before turning inwards and moving radially towards the CP[8, 25–28]. Interneurons in SP or IZ/SVZ streams also switch their mode of migration from tangential to radial, and extensively contact the radial glial processes as they migrate up towards the CP[8, 26–28]. Moreover, a subpopulation of interneurons within IZ exhibit “ventricle-oriented migration”, during which they migrate radially into VZ, and pause at the bottom of VZ, extending multiple processes to scan the ventricular surface, possibly to obtain positional information or modulate progenitor proliferation, prior to migrating up radially towards the CP[22, 26].

Interneurons follow a lateral to medial gradient to colonize the neocortex, with younger neurons arriving at the lateral cortical domains earlier than the medial regions[29] (Figure I. A). After arriving at the appropriate cortical area, interneurons settle into specific laminar positions prior to forming functional synaptic contacts with appropriate projection neuronal partners. Birthdate analysis of specific interneuron subtypes suggests that interneurons follow heterogeneous developmental rules for laminar positioning[8, 30–34]. MGE and POa derived somatostatin$^+$(SST$^+$), parvalbumin$^+$(PV$^+$), and calbindin$^+$(CB$^+$) subtypes show a time-dependent, inside-out pattern of positioning that is similar to projection neurons. In contrast, CGE-derived calretinin$^+$ interneurons show an outside-in placement pattern[8, 29]. Further, vasoactive intestinal polypeptide$^+$ (VIP$^+$) and neuropeptide Y$^+$ (NPY$^+$) interneurons do not show a strict inside-out layering pattern, but preferentially localize to superficial layers or scatter widely within the cortex, respectively[29, 34](Figure I. A, B). The final cortical distribution of interneurons therefore depends on the temporal and spatial origin of interneurons, subtype specification, as well as on interactions with radial glial scaffold and projection neurons.

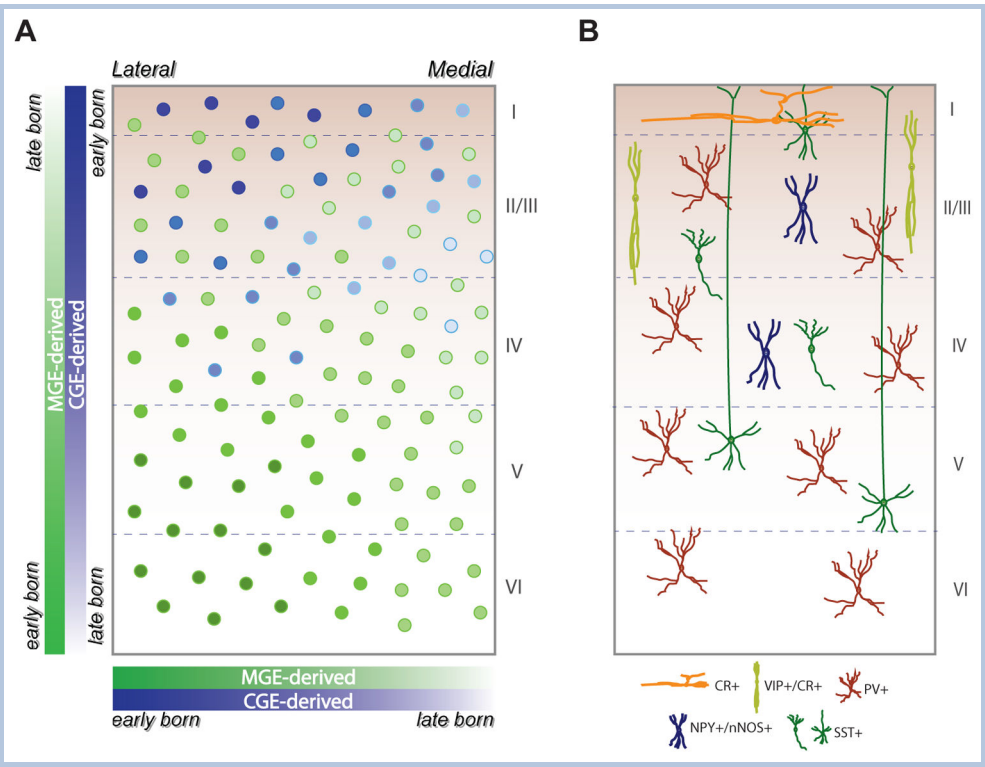

Figure I. The developmental distribution of interneuron subtypes

(A) Schematic of a coronal section through the mouse neonatal cerebral cortex showing the areal and laminar positioning of MGE- and CGE-derived GABAergic interneurons. Both MGE- and CGE-derived interneurons reach their final areal positions in a lateral to medial gradient (i.e., arriving first in laternal regions of cortex). MGE-derived interneurons show an inside-out pattern of distribution, whereas CGE-derived interneurons exhibit an outside-in pattern of distribution. MGE-derived interneurons distribute relatively evenly in the neocortex, whereas CGE-derived interneurons preferentially distribute in superficial layers. (B) Laminar distribution of main subtypes of interneurons. PV^+ interneurons are abundant throughout cortical layers II–VI. SST^+ interneurons mainly localize to layers II–V. CR^+ interneurons preferentially distribute in layer I. VIP^+/CR^+ interneurons preferentially distribute through layer II/III. $NPY^+/nNOS^+$ interneurons mainly localize to layers II–IV. PV, parvalbumin; SST, somatostatin; CR, calretinin; VIP, vasoactive intestinal polypeptide; NPY, neuropeptide Y; nNOS, neuronal nitric oxide synthase. I–VI: cortical layers.

Exit from the proliferative zone and initiation of migration

Newborn interneurons cluster around radial glial fibers or coalesce as migratory stream as they exit from the subpallial proliferative zone (Figure 1)[4, 35]. Newborn interneurons initiate their exit away from the proliferative zone in subpallium by utilizing a combination of chemorepulsive guidance cues and motogenic factors[36, 37]. Chemorepulsive cues play a key role in guiding the path of exit of migrating interneurons away from the VZ of GE. Diffusible guidance proteins Slit1 and Netrin1, known chemorepulsive cues for axonal

growth and guidance, have been shown *in vitro* to repel interneurons from GE region, although, in vivo genetic models failed to provide direct evidence supporting their repulsive influence on interneuron migration[38–40]. Further, a recent study has demonstrated that guidance molecule Ephrin-A5 acts as the repellent force to facilitate the exit of newborn interneurons from GE[41]. Ephrin-A5 is expressed in the VZ of GE, while its signaling receptor EphA4 is strongly expressed in newborn, GE-derived interneurons[41]. *In vitro* assays showed that down-regulated Ephrin-A5 in the VZ of GE led to ectopic invasion of interneurons into VZ[41]. In contrast, exogenously applied Ephrin-A5 recombinant protein restores the avoidance of VZ by migrating interneurons[41].

Once repelled away from the proliferative zone, several motogenic factors have been identified to stimulate the migration of newborn interneurons from GE[24, 42]. Of these, dysfunction of hepatocyte growth factor/scatter factor (HGF/SF) signaling resulted in impaired cell mobility and reduced interneuron migration into the cortex[42]. Other growth factors including brain-derived neurotrophic factor (BDNF), neurotrophin 4 (NT4) and glial cell line-derived neurotrophic factor (GDNF) have also been suggested to be potent motogenic factors for newborn interneurons in GE[24, 43]. Although genetic evidence is still lacking to conclude a direct role for these molecules in the initiation of interneuron migration *in vivo*, several *in vitro* experiments using isolated interneurons and cortical slices have clearly suggested their influence on interneuron motility[42–45]. Together, these observations suggest a combination of chemorepellent and motogenic cues present in the proliferative zones of the GE may impel newborn interneurons to exit GE and initiate their migration.

Selection of migratory route towards dorsal cortex

Once migration is underway, interneurons face the challenge of selecting a specific migratory route into the dorsal or ventral cortex (Figure 1). Interneurons with different temporal and spatial origin in the subpallium follow specific migratory routes, suggesting that distinct origins of interneurons help prespecify their migratory routes. Indeed, the results of isochronic and heterochronic transplantation experiments have shown that interneurons are cell-autonomously committed to their specific migratory fate as early as E11.5 for LGE-derived interneurons and E13.5 for MGE and CGE-derived interneurons[9, 13, 15, 46]. The intrinsic migratory fate of interneurons are specified by the combinatorial expression of several key transcription factors that are expressed within the progenitor domains of the subpallium[22, 47–51]. These transcription factors not only define subpallial patterning and interneuron differentiation, but also provide migratory route instructions for the newborn interneurons[22, 47–53]. One of these transcription factors is Nkx2.1. Its expression is maintained in newborn interneurons migrating into striatum, but is downregulated in interneurons destined for the cortex. This differential Nkx2.1 expression is necessary for interneurons to migrate into cortex and serves as a sorting mechanism for directional migration of cortical and striatal interneurons[52]. In contrast, COUP transcription factor II (COUP-TFII), preferentially expressed in the CGE, is required for the CGE-derived interneuron migration in the caudal direction[54]. Notably, overexpression of COUP-TFII in MGE interneurons is sufficient to change their migratory orientation to caudal direction when transplanted into the CGE environment, thus providing an example of how a single,

locally expressed transcription factor activity is capable of determining the migratory fate of interneurons in its local environment[54].

It is likely that transcription factors specify the intrinsic migratory fate of interneurons by modulating the expression of signaling receptors and cytoskeletal components that impart them with competence to respond selectively to route specific environmental cues. For example, the MGE-derived cortical interneurons avoid ventral POa and lateral striatum as they migrate toward dorsal cortex[39, 55]. Chemorepulsive cues play an essential role in establishing this pattern. EphrinB3 expressed in POa and its derivatives acts as a repulsive cue by binding to EphA4 receptor expressed by MGE-derived cortical interneurons[56]. This repellent activity prevents MGE interneurons from migrating in a ventral direction and is possibly responsible for their dorsal orientation toward the cortex[56]. Also, the repellent activity mediated by class 3 semaphorins (Sema3A and Sema3F) present in the developing striatum is largely responsible for the sorting between MGE-derived cortical interneurons and striatal interneurons. The expression of Neuropilin 1 (Nrp) and Nrp2 receptors by MGE-derived interneurons destined to cortex, but not by striatal interneurons, ensures cortical interneurons are competent to respond to the repulsive actions of Sema3A and Sema3F, and thus enabling them to migrate around the developing striatum and enter the neocortex[57]. Importantly, Nkx2.1 has been shown to directly repress *Nrp* levels[57]. Thus, the downregulation of Nkx2.1 expression in MGE-derived interneurons renders them sensitive to Sema3A/Sema3F repellent cue, and facilitates their choice of specific migratory route. The downregulation of Nkx2.1 in cortical interneurons requires transcription factor Sip1. Sip1 also contributes to the sorting of cortical vs. striatal interneurons by repressing Netrin1 receptor Unc5b expression in cortical interneurons to facilitate their entry into the neocortex[58, 59].

In addition to repulsive cues, GE-derived interneurons also utilize gradients of permissive and attractant cues to migrate towards cortex[39]. Two isoforms of Neuregulin-1 (Nrg1), a membrane-bound isoform, CRD-Nrg1, and a diffusible isoform, Ig-Nrg1, have been shown to act as short-range permissive and long-range chemoattractant cue, respectively, for cortical interneurons[60, 61]. CRD-Nrg1 is expressed throughout the LGE from the VZ to the developing striatal mantal zone, providing a permissive corridor from the MGE to the pallial-subpallial boundary[60]. In contrast, Ig-Nrg1 is released in the neocortex, providing a diffusible cue that attracts cortical interneurons towards the neocortex as they exit the CRD-Nrg1^{+} permissive corridor[60]. The function of Nrg1 requires activity of ErbB4 receptors[60, 61]. Consistently, perturbation of ErbB4 signaling decreases the number of interneurons entering the neocortex[60, 61].

Further, recent evidence suggests that neurotransmitters including ambient GABA, glycine, glutamate and dopamine promote interneuron migration and their entry into the neocortex[62–74]. Glycine functions through GlyRs to regulate interneuron migration velocity and nucleokinesis by controlling actomyosin contractility[74]. Acute loss of GlyR function impairs interneuron corticostriatal boundary crossing and entry into the neocortex[74]. In contrast, migrating interneurons appear to activate their response to ambient GABA signal or glutamate once they reach the neocortex. This switch-on response is accomplished by altering the expression profile of distinct $GABA_A$ receptor subunits (increased expression of

the α1-, α2-, γ5-, γ2-, and γ3-subunits) and activation of AMPA receptors, respectively, as interneurons navigate from subpallium to the neocortex[62, 68, 69, 71, 72]. Moreover, a balance in distinct dopamine receptor activities differentially modulates interneuron migration from GE to cortex: D1 receptor activation promotes, whereas D2 receptor activation decreases interneuron migration[67]. Taken together, interneurons integrate their transcription factor and signaling receptor expression profile with extrinsic environmental cues (e.g., chemorepulsive cues, chemoattractive cues, and neurotransmitters) to facilitate the selection of a migratory route from the GE to the cortex.

Choices of migratory streams within the neocortex

Interneurons form specific migratory streams through MZ, SP and IZ/SVZ as they traverse the neocortex[22, 26] (Figure 1). This migratory pattern raises the question of whether interneurons randomly distribute in these streams or actively choose one of these three streams. If the latter is true, what are the factors that determine the choice of the migratory stream and does the selective path of migration plays a role in the eventual emergence of the interneuron subtype identity?

Cell intrinsic determinants are thought to play an essential role in migratory stream choices of interneurons. For example, transplantation experiments with retinoblastoma (Rb) mutant interneurons showed a dramatic failure of mutant neurons to migrate along the MZ stream in the wild type brain, suggesting a cell-autonomous requirement for Rb protein in interneuronal migration in the MZ stream[75]. Further, pharmacological blockade of the $GABA_B$ receptor resulted in accumulation of interneurons migrating in the SVZ/VZ stream and fewer interneurons in the MZ stream[66]. In contrast, dysfunction of GlyR α2 subunit specifically decreased interneurons migrating in the SVZ stream[74]. In addition, loss of Dopamine D1 receptor signaling significantly decreased the migration of interneurons in IZ and VZ/SVZ streams, whereas loss of D2 Dopamine receptors led to an increase of interneurons migrating in these streams[66, 67]. These results suggest that cell-intrinsic characteristics dictate interneuronal route preferences within the neocortex.

Aside from cell-intrinsic determinants, regionally localized environmental cues also influence the interneuron migration routes within the neocortex. For example, Netrin1 is produced in the cortical MZ and Netrin1's binding to α3β1 integrin is required for the migration of interneurons through the MZ stream in the neocortex[76]. Consistently, in Netrin1/α3β1 integrin double mutants, significantly fewer interneurons migrate through the MZ stream and increased number of interneurons ectopically migrate through the VZ[76]. Further, Cajal-Retzius (CR) cells may provide positional cues for the interneurons migrating in close apposition below them in the MZ stream. It has been shown that either loss of CR cells or abnormal distribution of CR cells disrupt interneuron migration along the cortical MZ[77–79]. Gene expression profile analysis has revealed that a large number of genes including signaling receptors (e.g. Cdh8, Epha3, Robo2) and intracellular signaling modulators (e.g. Cdc42ep3, Plcb1, Rasgdf1b) are differentially expressed between the interneurons that migrate through either the MZ or the IZ stream in the neocortex[80]. Thus, it is likely that distinct intrinsic characteristics of migrating interneurons, either acquired prior to or after their entry into the cortex, in combination with extracellular cues released within

the cerebral wall, dictate the choice of distinct interneuron migratory routes within the cerebral wall.

Determination of local orientation of migration in neocortex

The directional steering of migrating interneurons within or in between streams is achieved by biased choices of leading process branches. This choice correlates tightly with rapid changes in growth cones dynamics. In particular, the stabilized leading branch of a migrating interneuron displays an elaborate growth cone, whereas the growth cones of non-selected branches rapidly collapse prior to branch retraction[20]. Growth cones serve to elongate or retract the branches by receiving various environmental guidance cues and relaying this guidance information to the two main cytoskeletal networks: actin filaments and microtubules[20]. The dynamic interplay between the pushing force exerted via microtubule assembly and the actin-driven pulling force at the leading edge of the growth cone is required for process extension and retraction. Semaphorin signaling in the growth cone provides an illustrative model of how guidance cues coordinate the cytoskeletal rearrangement necessary for local directional migration. Semaphorins function as chemorepellent cues by inducing growth cone collapse via Rho GTPases and associated proteins[81–88]. Semaphorin regulated activation of Rho GTPases Rac1 or RhoA lead to either decreased actin turnover or increased actin contractility, respectively, resulting ultimately in growth cone collapse[81, 82, 84]. Alternatively, semaphorin-mediated signaling could also regulate microtubule dynamics via GSK3β activity, leading to microtubule destabilization and growth cone collapse[86, 88]. As a result, only the branch that is oriented farthest away from source of the repulsive cue gets stabilized and subsequently facilitates the nucleokinesis of the neurons away from the repellent cue. Conversely, the presence of chemoattractants (e.g. Nrg1) influences the initial orientation of the newly extended branches towards the chemoattractant gradients and helps to selectively stabilize the leading process branch that is in closest proximity to the source of the attractant, and thus enables efficient directional change[20].

Although little is known about the molecular mechanisms that directly transfer extracellular guidance cue information to the underlying cytoskeleton in motile interneurons, doublecortin (DCX), a microtubule associated protein known to stabilize mircrotubles, has been shown to play an important role in regulating growth cone dynamics and process stability in migrating interneurons[89–91]. In DCX-deficient interneurons, the leading processes exhibit increased growth cone formation and branching[89–91]. As a result, their ability to make directional changes in response to environmental cues is compromised and DCX-deficient interneurons migrate in a less organized manner from GE into the neocortex[91]. In addition, other cytoskeletal regulators such as microtubule associated protein Lissencephaly 1 (Lis1), Doublecortin-like kinases (DCLKs), their upstream regulators CDK5/p35, and transcription factors such as Dlx1/2, are also known to modulate the oriented extension of the leading process during interneuronal migration[59, 88, 91–97].

Interneuron nucleokinesis, which follows leading process stabilization, also relies on rapid cytoskeletal rearrangements involving both microtubules and actin networks. Nuclear translocation requires centrosome-nucleus coupling by the microtubule perinuclear cage.

Consistently, in DCX mutant interneurons, the branching defects are coupled with nucleokinesis defects, the latter being characterized by shorter nuclear displacements and abnormal perisomal swelling dynamics[91]. The mechanism of nuclear translocation in interneurons is also heavily dependent upon myosin II-mediated actin contractability at the rear of the cell[23]. Notably, Nonmuscle myosin II inhibition efficiently blocked nuclear translocation in migrating interneurons[23]. Recent studies have also suggested that primary cilium, a microtubule-based sensory organelle, is essential for sensing and integrating networks of signaling pathways necessary for oriented interneuron migration[98, 99]. The membrane of primary cilium is enriched with signaling receptors that enable it to act as a sensor of shallow gradients during oriented interneuronal migration. The proximity and linkage of the primary cilium to the nucleus and centrosomes may facilitate its ability to efficiently convey determinant signals necessary for nucleokinesis. Coordination of branching dynamics and nucleokinesis by signals emanating from different domains of interneurons may thus help set the local migratory direction of interneurons.

Intracortical dispersion of interneurons

Upon traversing the neocortex in different streams, interneurons radially invade the CP once in their appropriate cortical areas[100] (Figure 1). Chemoattractant activity mediated by signals such as chemokine CXCL12 normally confines interneurons within the migratory streams and may regulate their appropriate exit from the streams. CXCL12 is strongly expressed within MZ and SVZ, and at a lower level in SP[78, 100–104]. CXCL12 signaling restricts the migrating cortical interneurons into confined streams by suppressing the leading process branching and thereby maintaining their tangential migratory direction[105, 106]. The expression of both receptors CXCR4 and CXCR7 are required for interneurons to respond to CXCL12[102–104]. In CXCR4 or CXCR7 mutants, interneurons display frequent branching, defects in forming organized migratory streams through MZ and SVZ, and prematurely invade the developing CP[100–103, 105, 107, 108]. Thus, CXCL12 signaling not only confines interneurons into tangential migratory streams, but may also prevent them from invading into the developing CP prematurely.

Within the MZ stream, interneurons exhibit a particular migratory behavior called “random walk”, leading to constant, multidirectional changes[25]. This behavior of interneurons is believed to contribute to the tangential dispersion of interneurons to appropriate cortical areal positions. Layer I Cajal-Retzius cells and interneurons in the MZ stream both show similar multidirectional migration with their leading processes arranged in similar orientations[25, 27, 28]. CR cells occupy the entire surface of the cerebral cortex and arrive through tangential migration at earlier stages of corticogenesis[109]. Repetitive, random cell-cell repulsive interaction mediated by Eph/ephrin signaling appears to be essential for the even dispersion and final distribution of CR cells in the cerebral cortex[109]. This contact repulsion process is also required to establish and stabilize the boundaries between different territories of subgroups of CRs that are born in discrete regions (cortical hem, pallial septum and ventral pallium)[109–111]. Further, contact between interneurons and radial glial endfeet is known to alter the migratory patterns of subtypes of interneurons[26–28]. It is tempting to speculate that similar contact repulsive interactions may exist between individual interneurons within MZ stream, between CR cells and interneurons, or between interneurons

and radial glial endfeet, and may thus contribute to the appropriate dispersion of interneurons within the cerebral cortex.

The final stages of intracortical dispersion of interneurons depend on a tangential to radial switch of the interneuronal migratory mode. To date, the mechanisms coordinating this switch remain largely unclear. A series of isochronic or heterochronic transplant experiments have demonstrated that interneurons of different birthdates remain within the tangential migration streams for similar amount of time (~ 48 hours)[100]. The temporally regulated loss of responsiveness to CXCL12 signaling seems to be critical for this process since the interneurons that radially invade the CP no longer respond to CXCL12 signaling[24, 102, 105]. These observations led to the suggestion that interneurons and the cortical environment might undergo stage-dependent and synchronized maturation to coordinate tangential to radial switch and interneuronal entry into the developing CP.

Further, it is likely that radial glial scaffold is instructive in interneurons' tangential to radial migration transition[24, 26]. The adhesion protein Connexin 43 (CX43) has been shown to be required for the interaction between interneurons and radial glia and deletion of CX43 significantly retards the tangential to radial transition of interneurons[112]. In order to make the tangential to radial directional switch, interneurons rapidly extend new branches that are oriented orthogonally to their tangential migratory direction [20, 24, 26]. Changes in the dynamics of interneuron branching appear to be critical for this transition. For instance, over-activation of PAK3, a member of the p21-activated serine/threonine kinases (PAKs) family, in Dlx1/2 mutant interneurons contributes to decreased branching, excessive leading process extension and the resultant defect in tangential to radial migration transition[97]. Consequently, Dlx1/2 mutant interneurons accumulate in the MZ and IZ in the neocortex[97]. Similarly, inhibition of RhoA/ROCK signaling also leads to leading process elongation, reduced branching, and impaired tangential to radial transition[20]. Recently, Sonic hedgehog signaling mediated by primary cilia was shown to coordinate nucleokinesis and leading process extension dynamics necessary for tangential to radial transition, further highlighting the importance of coordination of these two cellular events for intracortical migration of interneurons[99].

Termination of migration

Once within the CP, interneurons are directed to their final laminar positions (Figure 1). Several lines of evidence suggest that projection neurons with distinct layer identities selectively affect the distribution of subtypes of interneurons that are destined to populate the same cortical layers. First, majority of MGE-derived interneurons settle down with their coetaneous projection neurons in the same laminar layer, in an inside-out manner (i.e., later born interneurons migrating past earlier born populations to occupy more superficial laminar layer)[30, 33, 113]. A notable exception is the CGE-derived cortical interneurons which tend to populate the superficial layers regardless of their birthdates[114] (Text Box 3). Second, heterochronic transplantations of MGE cells have suggested that both early- and late-born interneuron progenitors are able to switch their laminar fates in their new cortical environment, suggesting that the exposure to cortical environmental cues, can influence interneuronal laminar fate[33]. Interneurons delay their invasion into the CP until their

pyramidal neuronal counterparts have acquired their laminar identities[31, 100, 115]. Consistently, mutants that exhibit premature invasion of interneruons into the CP also show disrupted final laminar and regional distribution of interneurons[100]. Third, interneurons distribute abnormally in the cortex of mutants with projection neuron positioning defects[31, 92, 116–118]. Finally, projection neurons with different layer identities differentially affect the laminar distribution of distinct interneuron subtypes[31, 115, 116, 118]. Clonally related interneurons, similar to projection neuron clones, do not randomly disperse but are frequently arranged into vertical or horizontal clusters in the neocortex[35, 119]. It is possible that coordinated interactions between identity matched, spatially organized clones of inhibitory interneurons and excitatory projection neurons may contribute to the appropriate placement of neurons necessary for a lineage-dependent organization of microcircuits in the neocortex.

In addition to signals from projection neurons, postnatal neuronal activity can also affect interneuron positioning[120]. Once at the final laminar localization, interneurons cease migration by altering their intracellular calcium transients in response to ambient GABA and glutamate signal[64]. KCC2, a potassium/chloride exchanger, is the deciding factor during this process. The upregulation of KCC2 in interneurons as they arrive at their laminar locations triggers a depolarization to hyperpolarizion switch, thereby altering their response to ambient GABA and glutamate from motogenic to stop signal[64]. In CGE-derived interneurons, induced overexpression of the potassium channel Kir2.1 between postnatal days 0–3 alters their excitability and results in an aberrant increase in the localization of CGE-derived Calretinin$^+$ interneurons in deeper layers[120]. Further, participation of cortical interneurons in the emergence of synchronized glutamate-dependent cortical network oscillations during early postnatal stages may also influence the laminar positioning of interneurons[65, 121–123]. Together, these observations suggest that interneurons integrate information about their temporal and spatial origin, subtype identity, and extrinsic signals from projection neurons and CP environment to establish their final laminar fate.

Concluding remarks

Although significant advances have been made in delineating the various molecular mechanisms underlying interneuron migration, many questions about the decision-making aspects of this process remain open. The current approaches to the study interneuron migration use fixed tissue analysis of limited cortical regions, dissociated neurons *in vitro*, or focus on movement of tens of neurons in small areas of often undefined embryonic cortical regions. While these approaches have provided insights into the modalities and molecular control of neuronal migration, they do not help us understand how specific subtypes of interneurons navigate and achieve their laminar and areal positions at the right time in right numbers within the entirety of cerebral cortex. This parceling out of appropriate numbers and types of cortical interneurons to distinct cortical areas is fundamental to the emergence of functional specification and connectivity of cerebral cortex. New methods that can track the behavior of large cohorts of interneurons from the time of birth to the final placement in distinct cortical areas[35, 124] will be necessary to gain comprehensive insights into the impact of interneuron migration in the emergence of neuronal connectome. Combining such approaches with examination of signaling dynamics in developing

interneurons will also facilitate answers to several other related outstanding issues. For example, do interneurons at different decision points along their migration route utilize different signaling networks to mediate their choices? What are the hierarchical relationships between the different signaling networks used to make different choices during the process of migration? STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) analysis of proteins regulating interneuron migration indicates that the strength of interactions between genes in specific signaling pathways predominate over others[94]. But how these distinct signaling networks are recruited seamlessly to facilitate different stages of interneuron migration and epigenetic regulation of these mechanisms remain to be deciphered. Furthermore, how do interneurons sense and coordinate environmental guidance cues with intracellular signal transduction and cytoskeletal rearrangements necessary for oriental cellular movement? Signaling emanating from different cellular compartments (e.g., growth cone, cilium, cell soma etc.) may differentially affect the migratory behavior or decisions of interneurons. On a system wide basis, subtypes of interneurons appear to coordinate their communication with radial glial scaffold and projection neurons to achieve their final area and laminar fate. Elucidation of signaling network dynamics in developing interneurons will help us understand how these patterns of coordination are achieved. Lastly, developmental disruptions of interneurons and the resultant changes in excitatory/inhibitory balance of cortical circuits are thought to be an underlying cause of neurobehavioral disorders[125]. Thus it will be informative to examine (a) if susceptibility genes associated with interneuronal dysfunction in diseases such as schizophrenia, autism, and related neuropsychiatric disorders affect selective steps of interneuron migration? (b) the epigenetic deregulation of these interneuron related developmental pathways in neuropsychiatric disorders, and (c) how such perturbations affect the emergence of excitatory/inhibitory balance of cortical circuits? Answers to these questions will not only lead to a richer understanding of the process of interneuron migration, but will also help illuminate its relevance for normal cortical development and aberrant brain functions in neurodevelopmental disorders.

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Highlights

Process of migration regulates placement and differentiation of interneurons.

Interneuronal placement affects excitatory/inhibitory balance in cortex.

This review evaluates the decision making steps of cortical interneuron migration.

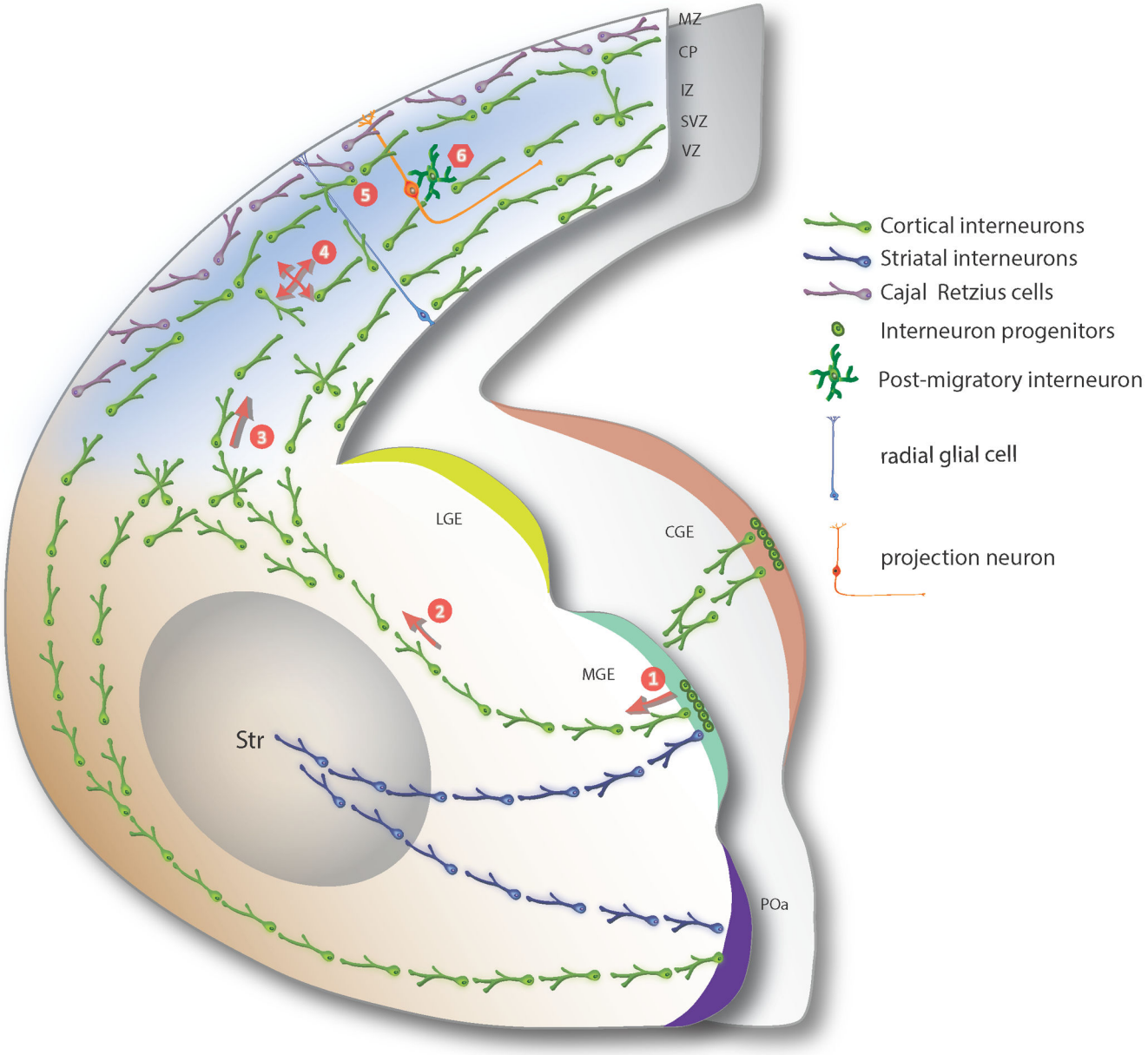

Figure 1. Patterns of interneuron migration in the developing telencephalon

This schema shows rostral and caudal hemi-section through the mouse telencephalon at mid-embryonic (E15) stage. The major decision-making steps (1-6) involved in the migration of cortical interneurons derived from the subpallium are illustrated. Interneurons derived from MGE (green), POa (purple), or CGE (orange) exit the proliferative zones and initiate their migration towards the developing neocortex and striatum. Cortical interneurons traverse around the developing striatum, transit across the cortico-subpallial boundary, and course tangentially into the cortex, whereas striatal interneurons ventrolaterally migrate into the developing striatum. Cortical interneurons transit the neocortex mainly through the MZ, SP, IZ/SVZ migratory streams. Once in the neocortex, tangentially migrating interneurons undergo multi-modal local migration as they reach and settle in specific areal and laminar

locations within the emerging CP, prior to forming functional synaptic contacts with appropriate projection neuron partners. Multiple decision-making steps are involved in this process. These include: (1) exit from the proliferative zone and initiation of migration in the subpallium, (2) selection of migratory route towards the dorsal cortex, (3) choice of migratory streams within the neocortex, (4) local orientation of migration within the cerebral wall, (5) identification of the final areal and laminar location, and (6) termination of migration at the appropriate cortical layer. Arrows indicate net directionality of movement. LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; POa, preoptic area; Str, striatum; MZ, marginal zone; CP, cortical plate; IZ, intermediate zone; SVZ, subventricular zone; VZ, ventricular zone.