Review

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Decision making during interneuron migration in the developing cerebral cortex

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Appropriate interneuron migration and distribution is essential for the construction of functional neuronal circuitry and the maintenance of excitatory/inhibitory balance in the brain. Gamma-aminobutyric acid (GABA)ergic interneurons originating from the 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.

Introduction

The functions of the central nervous system (CNS) require balanced and coordinated activities between the excitatory glutamatergic projection neurons and inhibitory GABAergic interneurons. In contrast to the projection neurons, which 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 (Box 1). This review provides a summary of the major decision-making 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 toward and incorporate into defined neural microcircuitry in the cortex and the challenges remaining in our understanding of this process.

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Decision-making steps of interneuron migration

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

Exit from the proliferative zone and initiation of migration

Newborn interneurons cluster around radial glial fibers or coalesce as a migratory stream as they exit from the subpallial proliferative zone (Figure 1) [2,3]. Newborn interneurons initiate their exit away from the proliferative zone in the subpallium by utilizing a combination of chemorepulsive guidance cues and motogenic factors [4,5]. Chemorepulsive cues play a key role in guiding the path of exit of migrating interneurons away from the ventricular zone (VZ) of ganglionic eminences (GEs). The diffusible guidance proteins Slit1 and Netrin1, known chemorepulsive cues for axonal growth and guidance, have been shown *in vitro* to repel interneurons from GE regions, although *in vivo* genetic models failed to provide direct evidence supporting their repulsive influence on interneuron migration [6–8]. Further, a recent study has demonstrated that the guidance molecule Ephrin-A5 acts as the repellent force to facilitate the exit of newborn interneurons from GEs [9]. Ephrin-A5 is expressed in the VZ of GEs, whereas its signaling receptor EphA4 is strongly expressed in newborn, GE-derived interneurons [9]. *In vitro* assays showed that downregulated Ephrin-A5 in the VZ of GEs led to ectopic invasion of interneurons into the VZ [9]. By contrast, exogenously applied Ephrin-A5 recombinant protein restores the avoidance of the VZ by migrating interneurons [9].

Once repelled away from the proliferative zone, several motogenic factors have been identified to stimulate the migration of newborn interneurons from GEs [10,11]. Of these, dysfunction of hepatocyte growth factor/scatter factor (HGF/SF) signaling resulted in impaired cell mobility and reduced interneuron migration into the cortex [11]. 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 GEs [10,12]. Although genetic evidence remains

Box 1. Origins and migratory routes of interneurons in the developing brain

Interneurons are a highly heterogeneous and diverse neuronal population that arises from progenitor pools within the LGE), MGE, CGE, POa, and septal anlage of the subpallium in the developing telencephalon [2,108–111]. Postmitotic interneurons from these distinct proliferative domains exit through distinct pathways [15,112–116], 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 migration of GE-derived GABAergic interneurons toward the dorsal cortex. Early tracing studies have demonstrated that different streams of interneurons arising from the GE are able to transit across the corticosubpallial boundary and course tangentially into the cortex. An early stream of interneurons (~E11.5 in mouse) from the MGE migrate dorsolaterally onto the top of the preplate, where many eventually become layer I CR neurons [108]. Later during corticogenesis (~E13–E15 in mouse), a second and more prominent stream of interneurons, mainly from the MGE, rapidly migrate into the neocortex, through the IZ [108]. This latter stream is joined by interneurons from the LGE, although much less robustly and via a more restricted route through the cortical proliferative zone [1,108]. At later stages of corticogenesis, interneurons enter the cortex via multiple streams, largely through the lower IZ and SVZ, as well as through migratory streams in the SP and MZ. Additionally, the CGE has been shown to be another major source of cortical interneurons. The 3D profile of cortical interneuron migration indicates that, simultaneously with the MGE-derived streams, a wave of interneurons originating from the CGE migrate in a lateral and medial direction to enter the caudal-most end of the cerebral cortex [15,16,113] (see Figure 1 in main text).

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. The 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 [112]. The CGE is the largest source of hippocampal interneurons. By E13.5 in the mouse, a stream of CGE-derived interneurons rapidly migrates toward the caudal end of the telencephalon, where they enter the MZ and eventually settle down in the hippocampus [15,16]. By contrast, the LGE gives rise to most if not all interneurons that migrate rostrally and populate both the glomerular and the granule cell layers of the olfactory bulb [17,112,114,117]. The migration of olfactory interneuron precursors continues throughout the postnatal period and adulthood, providing a constant supply of interneurons to the local neural circuits of the olfactory bulb [118,119]. The SVZ, a mitotically active region in the dorsal–medial corner of the striatum that is derived from embryonic LGE, gives rise to these postnatal olfactory interneurons [120,121]. Compared with the embryonic stages of olfactory interneuron migration, during which loosely associated neurons disperse through the extracellular space, newborn 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 the rostral migration stream (RMS) [118,119].

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 [11–14]. 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 GEs and initiate their migration.

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 [55,122]. 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; that is, by converting the trailing process directly into a leading process while the previous leading process retracts like a trailing process [19].

Once the migratory direction is decided, interneurons advance forward by performing a repeated cycle of two-phase nucleokinesis [73]. 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 [10,73]. 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 [73]. By 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 the nucleus [73]. This pattern of coordinated leading-process/nucleokinesis dynamics is repeated to facilitate the directional movement of interneurons.

Selection of migratory route toward dorsal cortex

Once migration is under way, 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 the distinct origins of interneurons help to 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 lateral GE (LGE)-derived interneurons and E13.5 for medial GE (MGE) and caudal GE (CGE)-derived interneurons [15–18]. The intrinsic migratory fate of interneurons is specified by the combinatorial expression of several key transcription factors that are expressed within the progenitor domains of the subpallium [19–24]. These transcription factors not only define subpallial patterning and interneuron differentiation, but also provide migratory route instructions for the newborn interneurons [19–26]. One of these transcription factors is Nkx2.1. Its expression is maintained in newborn interneurons migrating into the striatum, but is downregulated in interneurons destined for the cortex. This differential Nkx2.1 expression is necessary for interneurons to migrate into the cortex and serves as a sorting mechanism for directional migration of cortical and striatal interneurons [25]. By contrast, COUP transcription factor II (COUP-TFII), preferentially expressed in the CGE, is required for CGE-derived interneuron migration in the caudal direction [27]. Notably, overexpression of COUP-TFII in MGE