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Review

Control of tangential/non-radial migration of neurons in the developing cerebral cortex

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Abstract

Projection neurons in the developing cerebral cortex of rodents are basically born near the ventricle and migrate radially to beneath the marginal zone, whereas their cortical interneurons are generated in the ventral telencephalon and migrate tangentially to the cortex. The origins and migratory profiles of each interneuron subtype have been studied extensively in the last decade, and an enormous effort has been made to clarify the cellular and molecular mechanisms that regulate interneuron migration. More recently, the interaction between projection neurons and migrating interneurons, including how they are incorporated into their proper layers, has begun to be analyzed. In this review, I outline the most recent findings in regard to these issues and discuss the mechanisms underlying the development of cortical cytoarchitecture.

Keywords: Interneuron; Tangential/non-radial migration; Cerebral cortex; Ganglionic eminence; Cajal-Retzius neurons; Layer formation

Contents

1. Introduction

The functions of our central nervous system are based on a balance and interactions between excitatory neurons and inhibitory neurons. The neural networks in the cerebral cortex are basically composed of pyramidal projection neurons, which primarily contain the excitatory neurotransmitter glutamate, and interneurons, which are mostly inhibitory and produce γ-aminobutyric acid (GABA). Although GABAergic interneurons make up only 20–30% of the entire population of cortical neurons, they are extremely heterogeneous and diverse in morphology, physiology, and molecular properties (Kawaguchi and Kubota, 1997; Kawaguchi and Kondo, 2002; Monyer and Markram, 2004; Markram et al., 2004; Flames and Marin, 2005; Blatow et al., 2005).

The importance of interneurons in cortical function is well recognized, and the term ‘‘interneuronopathies’’ has been proposed as the name for interneuron disorders involving a

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defect in their tangential/non-radial migration (Kato and Dobyns, 2005). X-linked lissencephaly with abnormal genitalia (Kato and Dobyns, 2005), schizophrenia (Benes and Berretta, 2001; Levitt et al., 2004; Lewis et al., 2005; Woo and Lu, 2006), autism (Levitt et al., 2004), and Miller–Dieker syndrome (Pancoast et al., 2005) are some examples of interneuronopathies. Mutations in *Sonic hedgehog (Shh)*, which is required to maintain *Nkx2.1* expression and cortical interneuron fate determination by progenitors in the medial ganglionic eminence (MGE) (Xu et al., 2005), are manifested by microcephaly and behavioral abnormalities, and these abnormalities may also result from interneuron deficits (Wonders and Anderson, 2006).

In this review I discuss recent findings regarding how cortical interneurons migrate from their origins to the cortex and how they are incorporated into the cortical layers. Since the most important findings regarding these issues have recently been reviewed extensively (Marin and Rubenstein, 2003; Wonders and Anderson, 2005, 2006; Metin et al., 2006), I will focus on the more recent studies.

2. Origins and migratory paths of cortical interneurons

In contrast to the cortical projection neurons, which are generated in the dorsal telencephalon (pallium) and migrate radially toward beneath the marginal zone (MZ), GABAergic neurons have been found to migrate tangentially in the lower intermediate zone (IZ) beyond area boundaries in the embryonic rat cortex (DeDiego et al., 1994). de Carlos et al. (1996) have reported that cells in the ganglionic eminence (GE) of the ventral telencephalon (subpallium) cross the corticostriatal boundary and migrate to the developing cortex (pallium) (de Carlos et al., 1996). The cells that migrate trangentially from the GE to the cortex in mice turned out to include GABAergic interneurons (Tamamaki et al., 1997; Anderson et al., 1997), and their migration was found to depend on the transcription factors distal-less homeobox 1 and 2 (Dlx1/2) (Anderson et al., 1997). Although the cortical interneurons of rodents are primarily produced in the ventral telencephalon (Tamamaki et al., 1997; Anderson et al., 1997; Lavdas et al., 1999; Wichterle et al., 1999; Wichterle et al., 2001), two lineages of interneurons have been reported in the human neocortex (Letinic et al., 2002). One lineage, which expresses *mammalian achaete-schute homolog 1 (Mash1),* represents 65% of neocortical interneurons, and is born from Mash1-positive progenitors in the neocortical ventricular zone (VZ) and subventricular zone (SVZ). The other lineage, which does not express *Mash1*, forms 35% of cortical interneurons and originates from the GE (Letinic et al., 2002). One possible explanation for the difference between rodents and humans is that some of the Mash1-positive progenitors in the human neocortical VZ/SVZ may have arrived from the GE at earlier embryonic stages and then continued to divide locally. However, retroviral labeling of the proliferative VZ/SVZ cells in slice cultures of human fetal forebrain has shown that these cells divide several times before starting radial migration, supporting their cortical origin (Letinic et al., 2002). Interestingly, expression of *Nkx2.1*, which is required for the specification of the MGE-derived interneurons (Sussel et al., 1999), in the proliferative zone has been found to spread dorsally from the GE to the cortical areas in humans, whereas *Nkx2.1* is not expressed in the rodent cortex (Rakic and Zecevic, 2003).

A number of studies have revealed the existence of multiple pathways of tangential migration in the developing mouse cortex (reviewed by Metin et al. (2006)). Briefly, in the early stages (∼embryonic day ⟨E⟩12 in mice), the tangentially migrating cells enter the preplate, where at least some of them differentiate into Cajal-Retzius neurons (described below). In the intermediate stages of corticogenesis, the cells travel through the IZ as well as through the MZ. In the late stages, the cells migrate tangentially, mainly in the lower IZ/SVZ, subplate (SP), and MZ. After the GABAergic interneurons reach the cortex through the IZ/SVZ stream, about 70% dive down to the surface of the ventricle (‘‘ventricle-directed migration’’), make contact, and, after a pause in this proliferative zone, they migrate radially to the cortical plate (CP) (Nadarajah et al., 2002). It has been speculated that these neurons may seek the cortical VZ to receive some layer information. Within the cortex, GABAergic neurons exhibit multidirectional tangential migration, at least in the MZ and VZ, and probably also in the CP and SP (Tanaka et al., 2006). These findings indicate that after reaching the cortex by tangential migration from the GE cortical interneurons undergo a second phase of tangential migration in all directions. Migrating interneurons that have initially traveled through the MZ or the SP/IZ/SVZ then enter the CP radially from either location to reside in their proper layers (described below) (Polleux et al., 2002; Ang et al., 2003; Tanaka et al., 2003, 2006; Hevner et al., 2004).

The three-dimensional migratory profiles of interneurons derived from the GE, especially from the caudal ganglionic eminence (CGE), has been described by Yozu et al. (2005), who developed a technique involving focal electroporation into a small, defined portion of the telencephalic hemisphere. By using this technique in combination with whole-mount telencephalic hemisphere culture, they found that, while the MGE cells migrated laterally and spread widely throughout the cortex, the majority of the CGE cells migrated caudally toward the caudal-most end of the telencephalon (Fig. 1A). Time-lapse imaging and an *in vivo* immunohistochemical study confirmed the existence of a migratory stream depicted by a population of CGE cells directed caudally that eventually reached the hippocampus, and it has been dubbed the ‘‘caudal migratory stream (CMS)’’ (Yozu et al., 2005) (Fig. 1A).

The various subtypes of cortical interneurons are generally specified by different combinations of transcription factors and derived from distinct regions of the ventral telencephalon. Since the mechanisms of cell type specification have been thoroughly reviewed recently (Wonders and Anderson, 2006) and are not the main topic of this review, I will only briefly outline the recent findings regarding the origin of each subtype of cortical interneurons (Fig. 1B).

Two of the neurochemically defined subpopulations of interneurons, parvalbumin (PV)-containing interneurons and