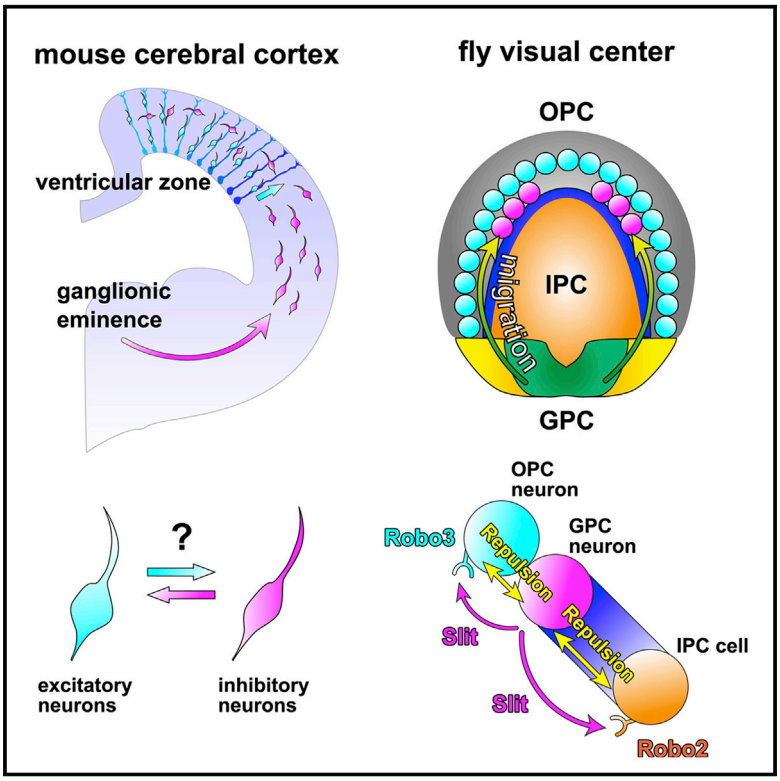
Report

Cell Reports

Formation of Neuronal Circuits by Interactions between Neuronal Populations Derived from Different Origins in the *Drosophila* Visual Center

Graphical Abstract



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In Brief

Suzuki et al. show that cell-cell interactions play an important role in establishing the precise arrangement of neurons of different origins in the *Drosophila* visual center. They suggest that the mechanism is conserved from invertebrates to vertebrates and involves repulsive Slit-Robo signaling.

Highlights

- Unique types of neurons from different origins migrate to the medulla in the fly brain
- Neural migration is regulated by Slit-Robo signaling and interactions with adjacent cells
- Interactions between neurons of distinct origins may be evolutionally conserved

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Formation of Neuronal Circuits by Interactions between Neuronal Populations Derived from Different Origins in the *Drosophila* Visual Center

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SUMMARY

A wide variety of neurons, including populations derived from different origins, are precisely arranged and correctly connected with their partner to establish a functional neural circuit during brain development. The molecular mechanisms that orchestrate the production and arrangement of these neurons have been obscure. Here, we demonstrate that cell-cell interactions play an important role in establishing the arrangement of neurons of different origins in the *Drosophila* visual center. Specific types of neurons born outside the medulla primordium migrate tangentially into the developing medulla cortex. During their tangential migration, these neurons express the repellent ligand Slit, and the two layers that the neurons intercalate between express the receptors Robo2 and Robo3. Genetic analysis suggests that Slit-Robo signaling may control the positioning of the layer cells or their processes to form a path for migration. Our results suggest that conserved axon guidance signaling is involved in the interactions between neurons of different origins during brain development.

INTRODUCTION

Various types of neurons are generated and properly positioned and connected with their partners to establish a complex neural circuit during development of a functional brain. In mammalian cerebral cortex, excitatory neurons are generated from the radial glial cells located in the ventricular zone of dorsal telencephalon and migrate radially to form the six-layered structure. In contrast, inhibitory neurons are produced from the ganglionic eminence located in ventral telencephalon (Anderson et al., 1997; Kriegstein and Noctor, 2004) and migrate tangentially from their birthplace into the cerebral cortex to establish precise neural circuits. Thus, mammalian cerebral cortex is composed of two types of populations derived from different sources, the ventricular zone and ganglionic eminence. It has been predicted that cell-cell interactions play important roles in the control of neuronal migration, and a recent report demonstrated that excitatory projection neurons control the distribution of inhibitory neurons (Lodato et al., 2011). However, the molecular mechanisms that orchestrate their migration remain unclear.

The fly visual center is regarded as a model for the study of brain development because it shares structural features with the mammalian brain, such as layered and columnar structures. The fly visual center is composed of four ganglia: the lamina, medulla, lobula, and lobula plate. Among them, the medulla is the largest component and is thought to contain approximately 100 types of neurons, with a total of 40,000 neurons. Our recent studies revealed that the developmental characteristics of the medulla are also similar to the mammalian cerebral cortex, such as subdivision into specific regions (Hasegawa et al., 2011; Sato et al., 2013) and birth-order-dependent neuronal specification (Li et al., 2013; Suzuki et al., 2013). Importantly, the medulla neurons extensively migrate during pupal development, similar to mammalian brains (Hasegawa et al., 2011; Morante et al., 2011).

During larval development, many neurons are produced from neuroblasts (NBs), the neural stem cells located on the surface of the medulla primordium, which is called the outer proliferation center (OPC). The NBs in the OPC (OPC-NBs) produce various types of medulla neurons in a birth-order-dependent manner, with a linear and radial orientation toward the center of the medulla primordium. Consequently, the larval medulla cortex is subdivided into concentric zones characterized by the expression of four conserved transcription factors: Homothorax (Hth), Brain-specific homeobox (Bsh), Runt (Run), and Drifter (Drf; Hasegawa et al., 2011; Suzuki and Sato, 2014; Figure 1A).

We demonstrated that at least four types of neurons, Mi1, Pm3, Lawf1, and Lawf2, are generated from the Hth domain, the innermost concentric zone in the larval medulla primordium (Hasegawa et al., 2011). Among these neurons, only Mi1 neurons co-express Bsh throughout development. In the present study, we show that a subset of Hth+/Bsh− cells express Eyes absent (Eya; Figures 1A and 1B). These Hth+/Eya+ cells differentiate into two types of lamina wide-field neurons, Lawf1 and Lawf2,