Molecules and Cells

Minireview

Distinct Developmental Features of Olfactory Bulb Interneurons

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The olfactory bulb (OB) has an extremely higher proportion of interneurons innervating excitatory neurons than other brain regions, which is evolutionally conserved across species. Despite the abundance of OB interneurons, little is known about the diversification and physiological functions of OB interneurons compared to cortical interneurons. In this review, an overview of the general developmental process of interneurons from the angles of the spatial and temporal specifications was presented. Then, the distinct features shown exclusively in OB interneurons development and molecular machinery recently identified were discussed. Finally, we proposed an evolutionary meaning for the diversity of OB interneurons.

Keywords: development, diversity, interneuron, olfactory bulb, spatio-temporal specification

INTRODUCTION

Identification of the neuronal components in the brain provides important insight for understanding high-order and complicated behaviors, including logical thinking, emotional sensation, and interaction with external signals (Ramón y Cajal et al., 1988). Specifically, interneurons control neurotransmission by the intricate modulation of information processing (Bartolini et al., 2013; Paredes et al., 2016). To adapt these diverse neuronal functions, interneurons are developed into morphologically, molecularly, and electrophysiologically diverse subtypes and are continuously generated from embryonic to even adult stages (Bartolini et al., 2013; Batista-Brito and Fishell, 2009; Kepecs and Fishell, 2014). Malformation of the interneurons during early development can lead to neurodevelopmental disorders, such as autism spectrum disorder (ASD) and Tourette's syndrome (Ashwin et al., 2014; Marco et al., 2011). Thus, defining neuronal properties and classifying the myriad of diverse interneurons are essential for understanding complex brain physiologies (Maccaferri and Lacaille, 2003), as well as neurodevelopmental disorders (Fang et al., 2014).

Mammalian OB express the most abundant and varied interneurons in the brain, but they have received little attention compared to cortical interneurons. Approximately 90% of ASD patients having mental retardation have a high sensitivity to external auditory stimuli and some of patients are suffered from hallucinations of olfaction (Galle et al., 2013; Gomes et al., 2008; Tonacci et al., 2017). Furthermore, the abnormal structural development of OB interneurons in the early stage induces olfactory impairments (Kim et al., 2020; Yoshihara et al., 2014). These facts indicated that research on the development of interneurons in the OB is critical and fundamental. In this review, we introduced the distinct characteristics of OB interneuron development by comparing them to the common developmental features of other interneurons. We also

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discussed the recently identified mechanisms underlying OB interneurons development and their physiological functions.

AMAZING CELL TYPE: INTERNEURON

The mammalian brain contains dozens of distinct types of interneurons with very diverse morphologies, molecular markers, electrophysiological properties and connectivity that modulate and refine neuronal circuits (Bandler et al., 2017; Hu et al., 2017). Broadly, GABAergic cells in the forebrain are classified based on their progenitor origins, and which has been studied well in mice (Fertuzinhos et al., 2009; Hansen et al., 2013). In the progenitor zones of the three subcortical regions of the brain, the medial ganglionic eminence (MGE), the caudal ganglionic eminence (CGE), and the lateral ganglionic eminence (LGE), many inhibitory cell subtypes are produced during embryonic stages and migrate along stereotyped streams, then finally disperse throughout the forebrain. MGE and CGE-derived interneurons which are mainly generated during embryonic days 11-15 predominantly migrate into the cortex, hippocampus, amygdala, and striatum, whereas LGE-derived interneurons, which are generated from mid embryonic days 13.5-15.5 become the olfactory bulb (OB)- or striatum-interneurons (Bandler et al., 2017; Torigoe et al., 2016). To more detail, cortical interneurons are divided into up to 50 different types, which are characterized by a combination of molecular markers or other intrinsic factors (Lim et al., 2018; Wamsley and Fishell, 2017). The subdivided regions of ganglionic eminence can generate more specialized and differentiated interneurons (Rubenstein et al., 1994). That is, these regional domains are specified by transcriptional factors with a spatial bias for the generation of specific interneuron types (Puelles and Rubenstein, 1993). For instance, Nkx2.1 highly expressed in MGE, determines MGE-derived cell fate, and the MGE-derived cells become somatostatin (SST)- or parvalbumin (PV)-expressing interneurons. In the case of CGE, Pax6, Prox1, and Sp8 are predominantly expressed and the CGE-derived cells become vasoactive intestinal peptide (VIP)- or cholecystokinin (CCK)-expressing interneurons. These observations strongly indicate that spatial specification critically contributes to the diversification of interneurons.

TIMELY DEVELOPMENT AS A DETERMINANT OF INTERNEURON DIVERSITY

The temporally defined development of interneurons is also a key factor in the diverse specifications of interneurons (Kao and Lee, 2010; Osterhout et al., 2014). The temporally defined expression of CoupTF2 determines the cell fate of progenitor cells derived from the MGE in SST- and PV-expressing cortical interneurons (Hu et al., 2017). Even interneurons with the same molecular cell fates can form different functional circuits dependent on their temporally defined birth. In the hippocampus, early-born and late-born PV-expressing basket cells form synapses with different subpopulations of pyramidal neurons in CA1 and play differential roles in memory and learning (Donato et al., 2015). Especially, the timely development of interneurons is more closely correlated with their final positioning in the brain (Fairen et al., 1986; Rymar and Sadikot, 2007). Interneurons with similar fates determined by their same birthdate assemble with each other to form laminar structures and cooperate in modulating the signal responses of excitatory neurons (Bartolini et al., 2013). For example, early- and late-born MGE-derived interneurons predominantly settled in infragranular layers and supragranular layers of the neocortex, respectively (Ma et al., 2006; Rymar and Sadikot, 2007), establishing distinct neuronal innervated circuits. Furthermore, it has been reported that the final positioning of interneuron was not determined by their clonality or lineage, rather, it might be affected by birthdates or migration machinery (Mayer et al., 2015). However, integrative studies on the temporal specifications of interneurons are still lacking.

DISTINCT CHARACTERISTICS OF THE OLFACTORY BULB INTERNEURONS

The OB, like the cortex, striatum or hippocampus, is a recipient of the massive generation of GABAergic interneurons from the telencephalon. Although each region shares common features for interneuron development, OB has a few unique properties (Fig. 1): a) the OB has an extremely higher proportion of interneurons (I) to excitatory neurons (E), at a 100:1 ratio, compared to other brain regions at a 1:5 ratio (Bayer, 1983). The reason for the high conserved ratio of OB interneurons remains a mystery; b) neurogenesis for OB interneurons occurs not only in the embryonic stages but also in the adult stages. Cortical interneurons are primarily produced from the MGE or CGE from embryonic days 9.5-17.5. However, OB interneurons are continuously generated from the LGE or subventricular zone (SVZ) throughout life (Alvarez-Buylla et al., 2001). Specifically, approximately 73% of the interneurons are generated from the SVZ during the postnatal first or second week, 25% are born during the embryonic stage from the LGE (Bayer, 1983; Hinds, 1968), and only 2% are generated from adult neurogenesis; and c) in the migration of LGE or SVZ-derived cells into the OB, the interneuron precursors (neuroblast) tangentially migrate through the RMS (Lledo et al., 2008; Lois and Alvarez-Buylla, 1994; Mirich et al., 2002; Rall et al., 1966), whose distance is relatively very long. This implies that LGE- or SVZ-derived precursors might have distinct migratory machinery, unlike the MGE- or SGZ-derived precursors traveling short distances (Lepousez et al., 2015). Lastly, GABAergic interneurons in OB rarely express SST or PV, which are representative markers in cortical or hippocampal interneurons, implying that the molecular markers identified before are not sufficient to fully define or understand the diversity of the OB interneurons. Given these distinct developmental features of OB interneurons, different approaches or criteria should be considered to analyze OB interneurons.

DIVERSITY OF OLFACTORY BULB INTERNEURONS

OB interneurons are grouped into four classes by their soma locations (Nagayama et al., 2014) (Fig. 2). First, granule cells (GC) represent the most abundant populations (~94%) and are highly heterogeneous in their morphologies, connectiv-

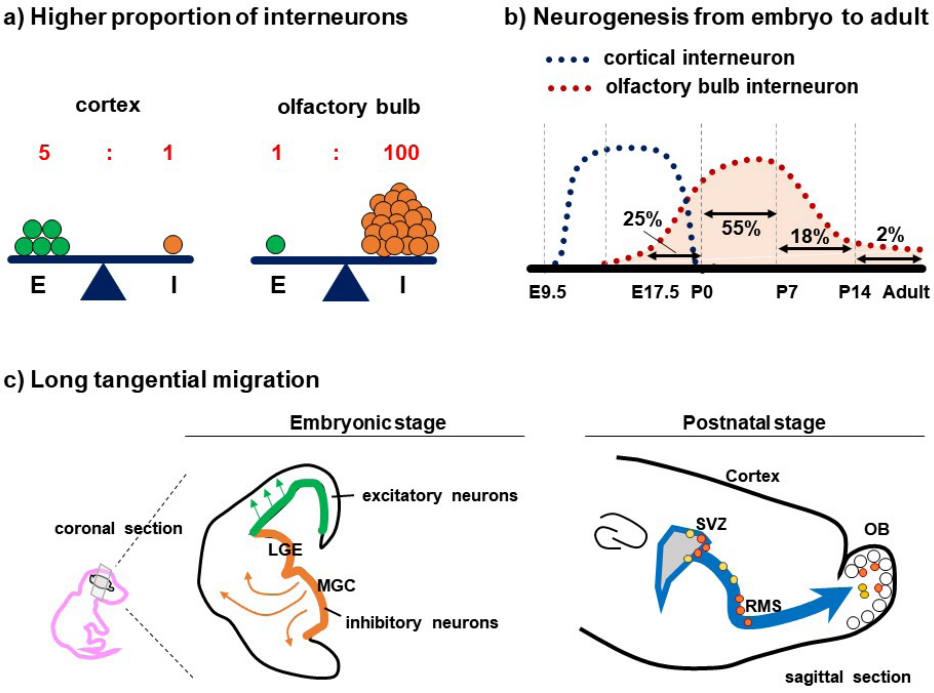
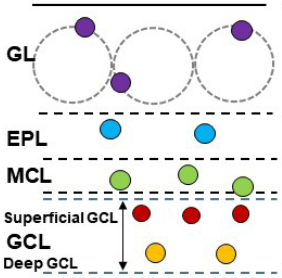


Fig. 1. Distinct features of OB interneurons development. Developmental characteristics of OB interneurons. a) OB has a higher conserved ratio of interneurons (I; orange) to excitatory neurons (E; green). b) Neurogenesis of OB interneurons throughout life. The red graph indicates the production timeline of OB interneurons. The blue graph indicates that of cortical interneurons. c) Long migration from the SVZ into the OB. Left: The MGE (orange line) mainly produces cortical interneurons. They migrate longer than excitatory precursors (green line). Right: During the postnatal stage, OB interneurons are consistently generated from the SVZ and migrate a very long distance into the OB. Orange circles: early-born interneurons, Yellow circles: late-born interneurons.

4 classes of OB interneuron by their soma locations



	%	Marker	Production time		Production origin		References
					Embryo (E)	Postnatal (P)	
PGC	4	TH	E12.5-15.5		**Cortical VZ**	Dorsal V-SVZ	1),2)
		CB			**Striatal/LGE-VZ**	Ventral V-SVZ	
		CR	Postnatal (P)		Septal VZ	**Middle V-SVZ**	
EPL-IN	2	PV, CRH	Late E-P7		?		3),4)
MCL-IN	94	5T4	Consistent		?		5)
GC		CR	sGC	Late E-P7	Cortical VZ	**Dorsal V-SVZ**	6)-9)
			dGC	Postnatal	Striatal/LGE-VZ	**Ventral V-SVZ**	

1) Batista-Brito et al., 2008; 2) Nagayama et al., 2014; 3) Garcia et al., 2014; 4) Liu et al., 2019; 5) Yoshihara et al., 2012; 6) Fuentealba et al., 2015; 7) Fujiwara and Cave, 2016; 8) Lemasson et al., 2005; 9) Mori, 1987.

Fig. 2. Four classes of OB interneurons by their soma locations. Left: Representation of the OB layers. GL: glomerulus layer, EPL: external plexiform layer, MCL: mitral cell layer, GCL: granule cell layer. Right: PGC: periglomerulus cell (purple), EPL-IN: interneuron located in the EPL (blue), MCL-IN: interneuron located in the MCL (green), sGC: superficial granule cell (red), dGC: deep granule cell (yellow). A dominant developmental period is typeset in bold font.

ity, and intrinsic factors (Lledo et al., 2008). In 1987, Greer reported three morphological subpopulations of mouse OB GCs through Golgi qualitative analyses (Greer, 1987). Specifically, Type 2 cells have cell bodies in the deep granule cell layer (dGCL) and extend their dendrites into the mitral cell layer (MCL) and lower layer of the external plexiform layer (EPL). However, Type 3 cells have cell bodies located in the superficial GCL (sGCL) or proximal MCL and extend their apical dendrites through the entire EPL. The differences in soma location and the range of the extending dendrites in each subpopulation suggest that they are distinct subtypes of GCs with different functional circuits. One GC makes connec-

tions with about 200-300 mitral or tufted cells (TC), causing dendro-dendritic inhibition (Burton, 2017; Price and Powell, 1970). In particular, interneurons integrated into the sGCL form neural circuits with TC. In contrast, interneurons integrated into the dGCL form synaptic connections mainly with mitral cells (MC) (Lemasson et al., 2005; Mori, 1987; Orona et al., 1983). The distinct anatomical connectivity by the depth of the GCL implies differential functionality, but little is known about the physiological olfactory functions of each layer. In fact, different subtypes of OB GCs originate from regionally specified origins expressing specialized transcriptional factors (Fujiwara and Cave, 2016). For instance, sGCs are generated from dorsal SVZ and highly express Emx1, SP8, and Pax6, whereas dGCs are born from the ventral SVZ and express Gsh1/2 or Nkx2.1 (Fuentealba et al., 2015). However, little is known about the precise diversification of GCs and their physiological circuits.

Second, periglomerular cells (PGC), accounting for 4% of the total OB interneurons and surrounding glomerulus, can directly make connections with axons of olfactory sensory neurons (OSN) and dendrodendritic synapses with MCs or TCs (Lledo and Valley, 2016). PGCs consist of three types, tyrosine hydroxylase (TH)-, calbindin (CB)-, or calretinin (CR)-expressing cells. Whereas the TH- and CB-expressing cells are predominantly born at embryonic days 12.5-15.5, CR-expressing cells are generated during the postnatal stage (Batista-Brito et al., 2008).

Third, EPL-interneurons, which account for only 2% of the total interneurons, are characterized by PV or corticotropin-releasing hormone (CRH) (Garcia et al., 2014; Liu et al., 2019). They are produced in the late embryonic to early postnatal stages (Batista-Brito et al., 2008). Of great interest, one EPL-interneuron connects with over 1,000 MCs or TCs, although the occupying ratio of EPL-interneurons in the entire OB interneuron populations is extremely rare (Burton, 2017). Furthermore, EPL-interneurons weight their synapses more specifically to TCs than MCs (Liu et al., 2019). This suggests that each interneuron contributes to a distinct circuit by forming its preferred synapses depending on the interneuron types.

Lastly, glycoprotein 5T4-expressing interneurons are located above the MCL and are consistently generated until adulthood (Yoshihara et al., 2012). Although 5T4 knockout mice displayed dysfunctions in the firing of excitatory TCs and defective olfactory behaviors (Takahashi et al., 2016), little is known about the precise characteristics of MCL-interneurons themselves.

It is intriguing that the same progenitor regions in the VZ produce different types of interneurons depending on the developmental stages (Fig. 2). For example, TH-expressing PGCs are predominantly generated in cortical progenitor-producing VZ cells (cortical-VZ) during embryonic days 12.5-15.5. During development, cortical VZ gradually mature into dorsal V-SVZ where sGCs are mainly produced. This might be because of changes in the LGE lineage specification during embryonic days 13.5-15.5 (Fuentealba et al., 2015). However, an integrative understanding of the diversity of OB interneurons is still lacking.

DIVERSITY OF OB INTERNEURONS CLASSIFIED BY TEMPORAL SPECIFICATION

Recent studies have reported that GCs having the largest population of OB interneurons can be divided into two distinct populations by their birth dates, postnatal early- and postnatal late-born interneurons. They have properties different from each other in functional connectivity of their final positioning and survival rates (Bovetti et al., 2007; Lemasson et al., 2005; Tseng et al., 2017). For example, postnatal early-born interneurons are located in the sGCL and mainly form inhibitory circuits with excitatory TCs. In contrast, almost all postnatal late-born interneurons are integrated into the dGCL and form circuits mainly with excitatory MCs (Lemasson et al., 2005; Mori, 1987). Furthermore, excitatory TCs and MCs are directly innervated into the brain without thalamus relay and transmit integrated olfactory information into different regions. MCs project their axons into the entire piriform cortex, including the amygdala and entorhinal cortex, and their synapses with GCs display more plasticity from the sensory inputs (Huang et al., 2016). TCs intensively project their axons into the anterior olfactory nucleus. The MCs exhibit intermediate-frequency firing, responding to relatively high concentration, whereas the TCs convey high-frequency firing with shorter latency, responding to even low odor concentration (Igarashi et al., 2012). These results indicate that the distinct neuronal circuits between postnatal early- and late-born OB interneurons can be translated into differential functions in olfactory information processing (Muthusamy et al., 2017). Additionally, postnatal early-born interneurons can survive until adulthood, but over 50% of the late-born interneurons undergo cell death after they reach the OB (Petreanu and Alvarez-Buylla, 2002). These different properties indicate that the OB GCs are diversified by their timely development into distinct subtypes with distinct extrinsic or intrinsic profiles.

TIMELY ACTION OF MOLECULAR MACHINERY FOR DIVERSIFICATION OF OB INTERNEURONS

To better understand the diverse OB interneurons, research on the molecular mechanisms underlying the diversification of interneurons has been conducted. Olfactory input dependently expressed transcription factors, such as c-fos and Npas4, modulated the survival rate of postnatal early-born interneurons and doublecortin (Dcx)-mediated structural development of OB GCs, respectively (Tseng et al., 2017; Yoshihara et al., 2014). In addition, a recent study identified the specific signaling in postnatal early-born interneurons that facilitated the temporal development of early-born related circuits for regulating innate olfactory functions (Kim et al., 2020). Abelson tyrosine-protein kinase 1 (Abl1), a proto-oncogene involved in chronic myelogenous leukemia (Wang et al., 1984) is highly expressed in postnatal early-born OB interneurons contributing to the stabilization of Dcx. This Abl1-mediated Dcx stabilization provides the driving force moving postnatal early-born interneurons to form OB circuits regulating innate olfactory behaviors, such as the detection of or sensitivity to odorants. These studies suggest that the differential profile between early-born or late-born OB interneurons is caused

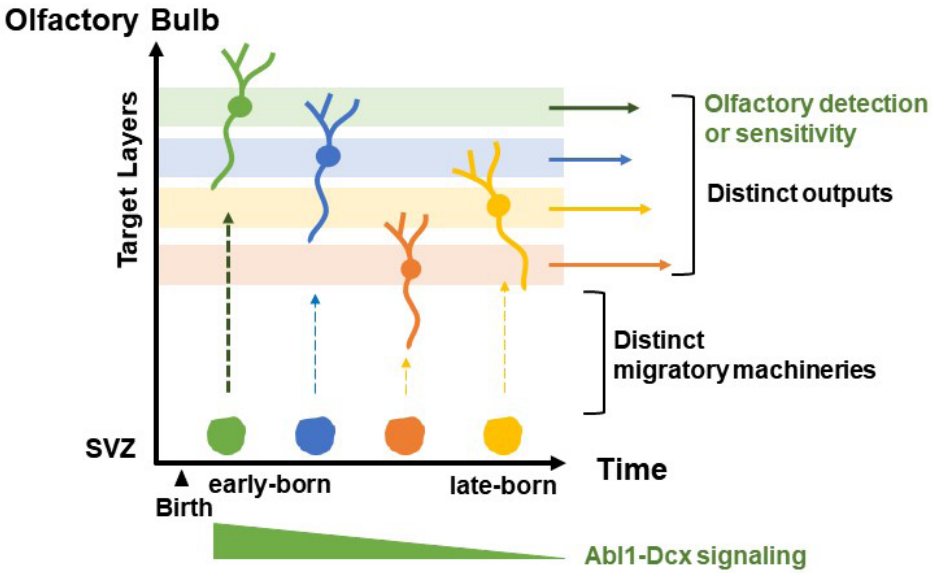


Fig. 3. Developmental factors identified for functional inhibitory circuits in OB. Schematic representation of the birthdate-order dependent interneuron final positioning in the OB. The X-axis represents the birthdate and the Y-axis represents the final positions from the SVZ to target layers in the OB. For the correct positioning, each neuron underlies the distinct molecular machinery. Postnatal early-born interneurons (green cell) have active Abl1-Dcx signaling as migratory machinery for integration into the sGCL (green layer). sGCL-specific circuits perform innate olfactory functions, such as detection or sensitivity.

by distinct molecular machinery, such as the action of transcription factors or Abl1-Dcx signaling, thereby playing a distinct role in olfactory information processing (Fig. 3). For more advanced understating of the distinct features of OB interneurons or functional circuits, integrative studies on other molecular mechanisms should be further investigated.

CONCLUSION AND PERSPECTIVES

The OB interneurons are extremely abundant and diverse. Here, we pointed out the unique characteristics of OB interneurons different from other interneurons. Most notably, OB interneurons are generated over a long period from the mid-embryonic to the adult stage, and migrate a long distance through the RMS into the OB. We also briefly summarized that special molecular machinery, such sensory input-mediated c-fos synthesis and Abl1-Dcx signaling, is reflected in the unique properties of postnatal early-born interneurons, including a high survival rate and integration into the sGCL forming the innate olfactory behaviors. Through our review, we suggest that OB interneurons might be diversified and clustered by a combination of their diverse and distinct properties, including precursor origins, developmental timing, sensory inputs, and migratory machinery.

Why OB interneurons are highly populated and diverse remains unsolved. This may be interpreted by some facts: 1) OB, as the first gating site of robust inputs from the external environment, tightly controls the E-I ratio (Anderson et al., 2000; D'Amour and Froemke, 2015). Furthermore, it must be associated with more tight or delicate modulation machinery, like interneurons, since the OB is a direct pathway for olfactory information processing to the cortex without thalamic relay (Kay and Sherman, 2007); 2) OB interneurons are continuously generated even during the adult stage (Alvarez-Buylla et al., 2001). During the development of OB interneurons, they are consistently exposed to various and unexpected sensory stimuli, implying that the diversity of OB interneurons might be evolutionary evidence of their adaptation to diverse environmental stimuli; and 3) despite the fact that there is a smaller odorant receptor repertoire than in other species, humans still can distinguish 1 trillion smells (Bushdid et al., 2014; Zozulya et al., 2001). This suggests that there must be other machinery for odor discrimination in the central nervous system beyond odor sensing by the odorant receptors. Based on the above facts, it is expected that the distinct developmental features of mouse OB interneurons might be conserved in human OB interneurons (Paredes et al., 2016; Zapiec et al., 2017).

In summary, considering these unanswered and intriguing questions about the diversity of OB interneurons, a deep focus on these issues would be of crucial importance. Furthermore, it may provide new insights into cures for neurodevelopmental disorder patients having sensory hallucination.

Disclosure

The authors have no potential conflicts of interest to disclose.

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