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Chapter 2: Olfaction

Development of the olfactory system: from sensory neurons to cortical projections

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Abstract

The olfactory system detects airborne chemicals as odorants. While visual and auditory sensory stimuli are continuous physical quantity, odorants detected by the olfactory system are extremely diverse and discontinuous in nature. The olfactory system utilizes a large repertoire of odorant receptors (ORs) to detect and discriminate a diverse kind of odorants in the environments. After the discovery of ORs in 1991, there has been progress in understanding of the olfactory system. ORs are found in most of vertebrate species and chordates, while there are considerable species-specific variations. In addition, specific additional receptors are known to exist for olfactory subsystems in some species. In mice, there are ~1,000 types of functional OR genes in the genome and each olfactory sensory neuron (OSN) expresses just one type of OR out of ~1,000. OSNs expressing a given type of OR converge their axons to a specific set of glomeruli in the olfactory bulb. The glomerular map formed in the olfactory bulb is the basis for odor discrimination. In glomeruli, sensory inputs are relayed to second-order neurons, mitral and tufted (M/T) cells, which project axons to the olfactory cortex. The olfactory system mediates not only stereotyped innate behaviors, such as attraction and aversion, but also more flexible learned behaviors. For this purpose, projections from the olfactory bulb to the olfactory cortex are stereotyped in some, but divergent in other areas. For example, neurons in the piriform cortex receive divergent inputs from multiple glomeruli and mediate learned odor recognition, whereas neurons in the cortical amygdala receive inputs from specific glomeruli and mediate innate odor responses. Olfactory information is further conveyed to the orbitofrontal cortex, insula, and hippocampus, where it interacts with non-olfactory information.

1. Introduction: organization of the mammalian olfactory system

In mammals, the olfactory system detects airborne chemicals as odorants. Environmental odorants have to be actively delivered to the olfactory epithelium (OE) in the nasal cavity by rhythmic inhalation or sniffing. Odorants generated by food intake can be delivered by the exhalation process (retronasal smell) in humans (Shepherd, 2006). Odorants are then dissolved into the olfactory mucus, which is secreted from the Bowman's gland in the OE. The dissolved odorants are then detected by the odorant receptors (ORs) expressed by olfactory sensory neurons (OSNs). OSNs extend multiple olfactory cilia into the olfactory mucus from their dendritic knobs. ORs are localized at the olfactory cilia and subsequent signal transduction occurs within this compartmentalized structure. ORs in the main olfactory system are G-protein coupled receptors (GPCRs) with seven transmembrane domains. The crystal structures of various GPCRs have been reported to date; however, the crystal structure of vertebrate ORs have yet to be determined and remains as the major challenge in the field. All the ORs are considered to activate a heterotrimeric G-protein, G_{olf}, which then stimulates adenylyl cyclase type III. The cAMP then gates cyclic nucleotide-gated (CNG) channels, which contains CNGA2 as an essential subunit. Calcium influx through the CNG channels gate chloride channels to mediate chloride efflux, and together depolarizes membrane potentials (reviewed in: (Firestein, 2001)). Action potentials generated in OSNs are propagated along axons to the glomeruli of the olfactory bulb (OB), in which glutamatergic neurotransmission occurs between OSNs and mitral and tufted (M/T) cells (**Figure 1**). M/T cells project axons to various areas of the brain, including the anterior olfactory nucleus, piriform cortex, lateral entorhinal cortex, olfactory tubercle, cortical amygdala, tenia tecta, etc., which are collectively called the olfactory cortex (reviewed in: (Imai, 2014; Mori and Sakano, 2011)).

Odorants emitted from the environment or conspecifics are functionally and chemically diverse. Moreover, unlike visual or auditory stimuli, chemical information is discrete in nature. ORs have evolved to cover a huge variety of chemicals, resulting in the largest gene family of up to 2,000 genes among vertebrates: There are ~1,000 types of functional ORs in mice and ~390 in humans. In addition, there are hundreds of OR pseudogenes, reflecting the dynamic expansion and shrinkage of the OR gene repertoire during evolution (Niimura and Nei, 2007; Zhang and Firestein, 2002). After the discovery of ORs in 1991 (Buck and Axel, 1991), molecular, cellular, and circuit logics of the olfactory system have been extensively studied in mice. Importantly, odor information detected by ~1,000 sets of ORs is processed in discrete parallel circuits in the olfactory system. To ensure parallel processing, there are three important principles in the organization of the olfactory system (**Figure 2**).

Firstly, each OSN expresses just one type of OR out of ~1,000 repertoires, which is known as the "*one neuron – one receptor rule*" (Malnic et al., 1999; Serizawa et al., 2004). In other words, there are 1,000 distinct types of OSNs, each of which expresses just one type of OR. This is a stark contrast to the taste system, in which all the tastants are detected and categorized by just 5 types of taste receptor cells (for sweet, umami, bitter, sour, and salty) (Ache and Young, 2020; Roper and Chaudhari, 2017).

Secondly, OSNs expressing the same type of ORs converge their axons onto a common glomerulus in the olfactory bulb, known as the "*one glomerulus – one receptor rule*" (Mombaerts et al., 1996). This enables segregated sensory inputs to the OB. In mice, there are mirror-symmetric glomerular maps in the medial and lateral surface of the olfactory bulb, each of which is comprised of ~1,000 sets of glomeruli. The location of glomeruli for a given OR is largely stereotyped, while there are local permutations among individuals.

Thirdly, each M/T cells receives direct excitatory inputs from just one glomerulus through its primary dendrite, which could be designated here as "*one M/T cell – one glomerulus rule*". As a result, distinct chemical information detected by an OR will be processed in a segregated pathway from OSNs to a specific set of M/T cells. Each glomerulus is innervated by 20-50 M/T cells, which are called "sister" M/T cells (Ke et al., 2013; Kikuta et al., 2013; Sosulski et al., 2011).

In this chapter, I will describe the odor coding mechanisms at different stages of the olfactory system based on the above three principles (Section 2). The evolutionary aspects will be discussed based on the olfactory receptor genes (Section 3 and 4). I then describe developmental mechanisms that establish the three principles in the mammalian olfactory system (Sections 5-10). I will mainly describe our knowledge in the most extensively studied mammalian model organism, mouse, but some aspects will be compared with other vertebrate species with an evolutionary viewpoint.

2. Physiology and coding logics at different stages of the olfactory circuits

In mice, nearly 5% of genes in the genome are dedicated to ORs. However, this number is still much smaller than the total number of possible odorants animals would encounter in their life, which is estimated to be at least hundreds of thousands. A key to understanding this discrepancy is the ligand specificity of ORs. Each OR typically interacts with multiple types of odorants. Similarly, each OR is recognized by multiple types of ORs (Malnic et al., 1999). Some ORs are narrowly tuned but others are more broadly tuned to a variety of odorants in a heterologous assay system (Saito et al., 2009). While it has been previously considered that odorants "activates" ORs and

OSNs, recent studies have demonstrated that ORs have variable levels of basal activities and an odorant can act as an inverse agonist for some ORs (Inagaki et al., 2020). Thus, each odorant is represented as the combinatorial activation and inhibition patterns of ORs at the level of OSNs (combinatorial receptor code).

In nature, an odor is often comprised of multiple odorants. When multiple odorants are presented, some odorants can suppress OSN responses to other odorants, known as antagonism (Inagaki et al., 2020; Oka et al., 2004; Pfister et al., 2020; Xu et al., 2020; Zak et al., 2020). Moreover, some odorants can enhance the responses to other odorants, known as synergy (Inagaki et al., 2020; Xu et al., 2020). As a result, OSN responses to a mixture of odorants can be smaller or larger than the linear sum of responses to its components. Thus, the perception of natural odors is already extensively modulated at the most peripheral level (Kurian et al., 2021).

In physiological conditions, OSNs respond not only to odorants but also to mechanical stimuli produced by the nasal airflow, i.e., sniffing (Grosmaitre et al., 2007). In mammals, one sniff is a unit for odor information processing in the brain (Kepecs et al., 2006), and the mechanosensory signals serve as an important pacemaker (Iwata et al., 2017).

OSN responses in the OE are then converted to the odor map in the glomerular layer of the OB (Johnson and Leon, 2000; Mombaerts et al., 1996; Mori et al., 2006; Wachowiak and Cohen, 2001). Odor information is represented by spatial patterns of activity, as well as both activation and inhibition, in glomeruli (Inagaki et al., 2020). Similar odorants tend to activate glomeruli in similar areas of the OB (Rubin and Katz, 1999; Uchida et al., 2000). Therefore, there is a chemotopic representation in the OB, even if chemotopy is not necessarily evident at a finer scale (Chae et al., 2019; Ma et al., 2012). Different parts of the OB mediate distinct innate behaviors. For example, the dorsal domain of the OB mediates innate fear responses (Kobayakawa et al., 2007), while other parts of the OB can mediate learned fear responses. Furthermore, some pheromone signals are mediated by the ventral OB (Lin et al., 2005).

Inputs from OSN axons are then relayed to the second-order neurons in the OB. However, the odor map in the OB is more than just a spatial map. Due to the sniff-coupled mechanosensation of OSNs (Grosmaitre et al., 2007), M/T cells show rhythmic neuronal activity without odors (Iwata et al., 2017). Odor stimuli change not only the firing rate but also the timing of activity within a sniff cycle in M/T cells (Dhawale et al., 2010; Shusterman et al., 2011; Spors and Grinvald, 2002). In particular, the temporal patterns of activity in M/T cells is important for the concentration-invariant representation of an odor “identity” (Iwata et al., 2017). A recent study using

optogenetic activation of glomeruli indicated that the temporal sequence of glomerular activation within a sniff cycle is critical for odor identity coding (Chong et al., 2020; Smear et al., 2013). Indeed, the temporal patterns of activity, but not the response amplitude, is concentration-invariant in M/T cells (Imai, 2020; Iwata et al., 2017). It is also suggested that glomeruli which are activated earlier within the sniff cycle are invariant and have more impacts in odor identity coding, known as primacy code hypothesis (Chong et al., 2020; Hopfield, 1995; Wilson et al., 2017).

In the OB, ~99% of neurons are interneurons. Interneurons play important roles to reformat odor inputs in the OB (Imai, 2014; Wilson and Mainen, 2006). For example, gain control is mediated by juxtaglomerular interneurons and parvalbumin-expressing interneurons. Periglomerular short axon cells mediate lateral inhibition among glomeruli and granule cells mediate lateral inhibition among individual M/T cells (Economo et al., 2016; Yokoi et al., 1995). Periglomerular neurons and granule cells regulate theta and gamma oscillations, respectively (Fukunaga et al., 2014). Many of them are also regulated by the excitatory top-down inputs from the olfactory cortices (Boyd et al., 2012; Markopoulos et al., 2012).

Mitral and Tufted cells are anatomically and functionally distinct. Single-cell RNA sequencing indicated that there may be more subtypes within mitral and tufted cells (Zeppilli et al., 2020). Tufted cells receive direct glutamatergic inputs from OSNs and have relatively low-threshold, short-latency odor responses, fire strongly in phase with sniff cycles, and are less influenced by OB interneurons. On the other hand, Mitral cells receive more indirect sensory inputs via tufted cells and show higher-threshold and longer-latency responses, possibly due to more inhibitory modulations (Fukunaga et al., 2012; Gire et al., 2012; Igarashi et al., 2012). Moreover, responses of M/T cells are extensively modulated by various types of interneurons (i.e., juxtaglomerular interneurons, short axon cells, and granule cells), centrifugal feedback from the olfactory cortex, and neuromodulations (Imai, 2014).

The activity of M/T cells is transmitted to a variety of brain regions (e.g., anterior olfactory nucleus, olfactory tubercle, tenia tecta, piriform cortex, lateral entorhinal cortex, and cortical amygdala), which are together called the olfactory cortex (**Figure 3**). Each of these areas seems to have distinct functions. For example, the anterior olfactory nucleus mediates the coordination between two hemispheres (Kikuta et al., 2010; Yan et al., 2008); the cortical amygdala mediates innate olfactory behaviors (Root et al., 2014); the amygdalo-piriform transition area mediates stress hormone responses to predator odors (Kondoh et al., 2016); and the piriform cortex mediates olfactory discrimination and learning (Giessel and Datta, 2014; Wilson and Sullivan, 2011).

The axonal projection profiles of mitral and tufted cells are segregated: Tufted cells project to the anterior olfactory nucleus (AONpE) and the cap region of the olfactory tubercle, while mitral cells project to all the other regions (Hirata et al., 2019; Igarashi et al., 2012). The axonal projection profiles of M/T cells are different in different cortical areas. Only in the AONpE, Tufted cells are arranged into a topographic projection, which may be important for the glomerulus-specific precise coordination and unity between left and right OBs (Grobman et al., 2018; Yan et al., 2008). In the cortical amygdala, inputs from different glomerulus are segregated, possibly representing distinct valence and stereotyped innate behaviors produced by these regions (Sosulski et al., 2011). In the piriform cortex, axons from each M/T cell are highly scattered with no obvious topography (Igarashi et al., 2012; Sosulski et al., 2011). Inputs from multiple glomeruli converge onto individual pyramidal neurons (Apicella et al., 2010; Miyamichi et al., 2011). Moreover, responses of pyramidal neurons in the piriform cortex are sensitive to the temporal sequence of glomerular activation (Chong et al., 2020; Haddad et al., 2013). Thus, these neurons read out the specific combinations of the spatiotemporal patterns of glomerular activity. In the piriform cortex, the inputs from the recurrent network is another important source of activity in pyramidal neurons (Blazing and Franks, 2020; Wilson and Sullivan, 2011). The recurrent circuit implements some important features in odor perception, such as concentration-invariance (Bolding and Franks, 2018), pattern completion (Bolding et al., 2020), and odor categorization (Pashkovski et al., 2020). The auto-associative network may also be useful for olfactory working memory (Zhang et al., 2019).

Odor representation remains unchanged after learning in the piriform cortex; however, odor value affects the odor representation in the downstream regions, orbitofrontal cortex (OFC), and medial prefrontal cortex (mPFC) (Wang et al., 2020). Olfactory information is also conveyed from the lateral entorhinal cortex to the hippocampus for associative memory (Igarashi et al., 2014; Li et al., 2017). The olfactory tubercle is located in the ventral striatum and represents an odor-induced motivation for approach vs. avoidance behavior based on associative learning (Murata et al., 2015). Odor-induced innate and learned fear signals are integrated and processed in a part of central amygdala (Isosaka et al., 2015). In humans, the integration of olfactory and taste information occurs in the dorsal and anterior part of insular (Fadool and Kolling, 2020; Shepherd, 2006).

3. Receptor genes and evolution of the olfactory system

OR genes are present in all vertebrates including fish, amphibians, reptiles, birds,

and mammals, and the origin of OR genes can be traced back to the latest common ancestor of chordates, including amphioxus (Niimura, 2009). ORs are absent in ascidians, which is correlated well to the unique organization of the mouth (Kaji et al., 2016; Veeman et al., 2010) and the lack of clear olfactory organs (Holland, 2020). Insects have distinct types of olfactory receptors, but they are ionotropic receptors (Benton et al., 2009; Clyne et al., 1999; Sato et al., 2008; Vosshall et al., 1999), rather than GPCRs. Thus, a lot of similarities seen between vertebrate and insect olfactory systems are the results of convergent evolution (Imai et al., 2010).

Different aspects of olfactory function are linked to specific receptor types with different evolutional traits. ORs can be divided into class I and class II based on the sequence similarity (Niimura and Nei, 2007; Zhang and Firestein, 2002). Class I genes were first identified in fish and frog that have persisted throughout the evolution of most vertebrate taxa. In contrast, class II genes are specific to terrestrial animals and account for ~90% of the mammalian OR repertoires. It is, therefore, suggested that class I and class II ORs are utilized for water-soluble and more volatile odorants, respectively (Bear et al., 2016; Nei et al., 2008).

While OR genes are preserved in all vertebrates, the number of receptors ranges from ~10 to ~2,000. Primates have 300-400 functional OR genes. In humans, 840 OR genes were found but among them only ~390 genes have intact coding sequences. Even within humans, various polymorphisms are found for ORs, many of which may be evolved under different selective pressure in different geographic areas (Mainland et al., 2014). OR genes are dispersed in the genome, except for chromosomes 20 and Y. (Nei et al., 2008) and 40% of human OR are found in chromosome 11. African and Asian elephants have the largest number of coding genes (~2000) and pseudogenes (~2,200) that is twice as many when compared to dogs and five times as many when compared to humans (Niimura et al., 2014). On the other hand, marine mammals typically have <100 functional ORs as a result of the evolutional loss. Dolphins do not smell and no longer maintain OR genes: They only have 12 intact OR genes and ~100 pseudogenes (Kishida et al., 2015; Niimura et al., 2014). Rodents have 1000-1500 ORs (Nei et al., 2008; Zhang and Firestein, 2002).

In addition to the OR family, there is another type of receptor family, TAARs, in the main olfactory system (Liberles and Buck, 2006). TAARs are specialized for the detection of volatile amines (Dewan et al., 2013; Li et al., 2013; Pacifico et al., 2012). ORs and TAARs are expressed in a restricted area within the OE, thus forming zones in the OE (Miyamichi et al., 2005; Ressler et al., 1993; Vassar et al., 1993). Class I ORs and TAARs are only expressed in the dorsal zone of the OE, while class II ORs are

expressed in both dorsal and ventral zones. OSNs in the dorsal and ventral zones of the OE project axons to the dorsal (D) and ventral (V) domains of the OB, respectively. Within the dorsal domain of the OB, OSNs expressing different types of receptors have distinct glomerular territories: DI for class I ORs, DII for class II ORs, and DIII for TAARs (Kobayakawa et al., 2007; Pacifico et al., 2012). Different domains of the OB may be linked to distinct innate olfactory behaviors (Inokuchi et al., 2017; Kobayakawa et al., 2007).

The overall structure of olfactory circuits is conserved across vertebrate species. In zebrafish, different classes of OSNs, namely ciliated OSNs expressing OMP and microvillar OSNs expressing Trpc2, project axons to distinct domains of the OB (Sato et al., 2005). Majority of OSNs express just one OR, and OSNs expressing the same type of OR converge their axons to common glomeruli (Sato et al., 2007). As a result, the odor map is formed in the glomerular layer of the OB (Friedrich and Korsching, 1997). Taking advantage of its small size, the connectome of mitral cells is beginning to be elucidated (Miyasaka et al., 2014; Wanner and Friedrich, 2020). Like mice, zebrafish mitral cells receive inputs from single glomerulus and send stereotyped projection to some, but more divergent projection to other cortical regions. In the lamprey, mitral-like and tufted-like cells show segregated projections to distinct regions or the pallium, suggesting that parallel odor information processing is a conserved feature of the vertebrate olfactory system (Suryanarayana et al., 2021).

In summary, ORs (class I and class II) and TAARs mediate odor detection in the main olfactory system in mice. There is a zonal organization in the OE and OB, based on the receptor class and the expression zones of the receptors. This may be linked to distinct innate behaviors mediated by these receptors.

4. Vomeronasal Receptors and olfactory subsystems

The rodent olfactory system has additional chemosensory receptor families and olfactory subsystems (Bear et al., 2016; Munger et al., 2009). The vomeronasal organ (VNO) and its projection target, accessory olfactory bulb (AOB), constitute the accessory olfactory system. Vomeronasal sensory neurons (VSNs) in the VNO express three different types of chemosensory receptors, V1Rs, V2Rs, and formyl peptide receptors (FPRs)(Dulac and Axel, 1995; Herrada and Dulac, 1997; Matsunami and Buck, 1997; Riviere et al., 2009). The VNO also shows a zonal organization: VSNs in the apical layer of the VNO express V1Rs or FPRs, G_{i2}, and project axons to the rostral half of the AOB, whereas VNSs in the basal layer express V2Rs, G_o, and project to the caudal AOB. Unlike the main olfactory system, VSNs expressing a given receptor

project axons to multiple glomeruli in the AOB (Belluscio et al., 1999; Del Punta et al., 2002). As many of the glomeruli are composed of heterogeneous VSNs, inputs from different receptors may be partially converged at the level of mitral cells. Some of V1Rs are known to detect volatile and non-volatile small molecular-weight compounds, whereas some V2Rs detect peptide and protein ligands, such as MUPs, ESPs, and MHC peptides (Chamero et al., 2007; Kimoto et al., 2005; Leinders-Zufall et al., 2004). FPRs detect formyl peptides and may mediate avoidance of sick conspecifics (Bufe et al., 2019). The sensitivity and selectivity of vomeronasal receptors seems to be higher than those for ORs (Leinders-Zufall et al., 2000).

Many V2R-expressing VSNs express members of another multigene family, H2-Mv, which is known as a non-classical class I MHC (Ishii et al., 2003; Loconto et al., 2003). Together with its co-receptor, β2-microglobin, H2Mv facilitates the functional expression of V2Rs (Leinders-Zufall et al., 2009).

Some atypical sensory neurons in the OE express non-GPCR receptors, such as GC-D and MS4As, and project axons to the "necklace glomeruli" that are located at the posterior end of the main OB (Greer et al., 2016; Hu et al., 2007). GC-D and MS4As are exceptions to the *one neuron – one receptor rule*. They are expressed in the same neurons and respond to carbon dioxide, carbon disulfide, fatty acids, and volatile pheromones (Greer et al., 2016; Hu et al., 2007; Munger et al., 2010).

The receptor repertoire and olfactory subsystems demonstrate extensive species-specific diversification under various environmental challenges (Nei et al., 2008). V1Rs and V2Rs are entirely lost in some species. The accessory olfactory system seems to be non-functional in primates, as most of the V1R/V2Rs and a key transduction channel, Trpc2, are missing. In bony fish and amphibians, ORs, V2Rs and TAARs comprise the major components of the olfactory system (Korsching, 2020; Nei et al., 2008).

So far, only a small subset of receptors has been deorphanized for olfactory receptors (ORs, TAARs, V1Rs, V2Rs, and FPRs). New deorphanization strategies *in vitro* and *in vivo* are being developed, and a comprehensive description of receptor-ligand interactions should facilitate our understanding of olfactory physiology, behavior, and evolution (Dey and Matsunami, 2011; Jiang et al., 2015; Lee et al., 2019; Saito et al., 2009; von der Weid et al., 2015).

In summary, GPCR and non-GPCR chemosensory receptors mediate a variety of species-specific chemosensory functions in both the vomeronasal and olfactory subsystems. The identification of their ligands should facilitate our understanding of animal behavior and hormonal regulation based on chemical communication.

5. Generation of OSNs and singular OR gene choice

A remarkable feature of the mammalian olfactory system is that receptor-specific neuronal circuits are constructed from the periphery to the central brain, despite the dynamic changes of receptor repertoire that occurred during evolution. From this section, I will describe developmental mechanisms to achieve this goal, which has been unveiled in mice during the past 30 years.

During development, OE and OB develop from different parts of the embryo. The OE is derived from the olfactory placode, whereas the OB is a part of the central nervous system. The olfactory placode is one of the cranial sensory placodes that give rise to several specialized sensory organs (anterior pituitary gland, OE, lens, auditory and vestibular organs) and sensory ganglia of the trigeminal, facial, glossopharyngeal, and vagus cranial nerves. A set of transcription factors, including *Eya1/Six1, Otx2, Pax6, Emx2,* and *Ebf2*, regulate the induction of olfactory placode. Additionally, retinoic acid (*RA*), *Fgf8, Shh*, and *BMP4* secreted from adjacent mesenchymal cells define the axis of the OE and induce nasal cavity formation (Moody and LaMantia, 2015). These factors together allow for the upregulation of specific genes required for the generation of OSNs (e.g., *Sox2*, *Ascl1*, *Neurog1*, *Neurod1*, and *Foxg1*)(Cau et al., 2002; Dvorakova et al., 2020; Kawauchi et al., 2009; Panaliappan et al., 2018; Tucker et al., 2010). In addition, microRNA plays several critical roles in neuronal induction (Kersigo et al., 2011). The OE and VNO develop from the olfactory placode that also gives rise to a set of gonadotropin-releasing hormone (GnRH)-positive neurons that migrate into the hypothalamus (Wierman et al., 2011; Wray, 2010). Hypothalamic GnRH neurons play crucial roles in reproduction and are also modified by olfactory inputs (Boehm et al., 2005; Yoon et al., 2005). In some fish species, GnRH neurons in the olfactory system project to the retina (Crapon de Caprona and Fritzsch, 1983).

The OE is composed of multiple cell types. In addition to mature and immature OSNs, there are two types of basal stem cells, the horizontal basal cells (HBCs) and globose basal cells (GBCs), sustentacular (supporting) cells in the apical surface of the OE, and cells comprising the bowman's gland. All of these cells are generated from HBCs, a common multipotent stem cell type (Schwob et al., 2017). Wnt signaling plays a critical role to make a neuronal fate choice from HBCs to GBCs (Fletcher et al., 2017). OSN lineage develops from transit-amplifying cells ($GBC_{TA\text{-}OSN}$; Ascl1+) through a second transit-amplifying progenitor and the intermediate precursor (GBC_{INP}; *Neurog1*$^{+}$ and/or *Neurod1*$^{+}$). Daughter cells from GBC_{INP} differentiate into immature OSNs (GAP43^{+}) and then mature OSNs (OMP^{+}). OSNs are regenerated and replaced throughout the life of animals. The renewal of OSNs is enhanced by OSN injury,

following the same differentiation trajectory (Gadye et al., 2017).

The first important event after the terminal cell division is the OR gene choice (Hanchate et al., 2015). In the OE, expression of each OR gene is restricted within a zone, which are continuous and overlapping from dorsomedial to ventrolateral (Miyamichi et al., 2005; Ressler et al., 1993; Vassar et al., 1993). However, an OR is expressed in a punctate pattern within a zone. A mature OSN expresses a single functional OR gene in a mono-allelic manner, forming the basis of odor coding (*one neuron – one receptor rule*) (Chess et al., 1994; Malnic et al., 1999). This is also an important basis for the OR-instructed axonal projection in the OB. Singular OR gene expression was also observed among OR transgenes having the same regulatory sequences (Serizawa et al., 2000; Vassalli et al., 2002), suggesting that OR gene expression is a result of stochastic choices from 2,000 possible alleles in the genome. This is useful to accommodate new and/or polymorphic OR genes generated during evolution. The molecular mechanisms of the singular OR gene choice have been extensively studied during the last two decades (Monahan and Lomvardas, 2015).

OR genes are distributed throughout most chromosomes, but many of them are located close to each other, forming OR gene clusters. Cis-regulatory enhancer elements were found in many of the OR gene clusters (Serizawa et al., 2003). These are required for the expression of multiple OR genes in the cluster in cis. A typical OR gene promoter has two conserved sequences: O/E motifs for the Olf/EBF family of transcription factors (Olf1-4) and homeodomain sites for *Lhx2* and *Emx2*. These motifs are essential for the OR gene expression (Vassalli et al., 2002).

To ensure the singular OR gene choice, it is important to silence all the other OR genes. Prior to the OR gene choice, heterochromatin compacts and silence the entire OR genes in the genome. OR gene loci are decorated with histone H3 lysine 9 trimethylation (H3K9m39) and H4K20me3, which are characteristic of constitutive heterochromatin (Magklara et al., 2011). However, after OR gene choice, the heterochromatin mark is absent only at the chosen OR gene allele. The chosen OR gene locus instead has H3K4me3, a hallmark of the transcriptionally active euchromatin.

The singular OR gene choice is ensured by the combination of stochastic activation and the subsequent feedback regulation (Serizawa et al., 2003) (**Figure 4**). To stochastically activate an OR gene, a histone demethylase, LSD1, plays a critical role. LSD1 mediates the demethylation of H3K9 in the OR gene locus. Knockout experiments indicate that LSD1 is required for the activation but not the maintenance of the OR gene expression (Lyons et al., 2013). Once a functional OR gene is activated, feedback regulation prevents further activation process to ensure the singular

expression. The feedback signal does not require G-protein signals from ORs (Imai et al., 2006). Due to the poor folding of the OR proteins, the translated OR proteins triggers an unfolded protein response (UPR), activating a kinase, Perk, which in turn phosphorylates the translation-initiation factor eIF2a (Dalton et al., 2013). The phosphorylated eIF2a halts translation of most transcripts, but facilitates the translation of ATF5, which then stabilizes the expression of the chosen OR, prevents further activation of other ORs, and facilitates OSN maturation. Due to dynamic evolutional changes, significant fractions of OR genes in the genome are pseudogenes. If the first choice was a pseudogene, the UPR does not occur, and gene choice continues until a functional OR gene is activated (Serizawa et al., 2003).

It remains elusive how chromatin demethylation occurs exclusively at just one OR gene allele at a time. As a cis-regulatory enhancer can interact with one OR gene within a cluster at a time, this may limit the chance of co-activation (Lomvardas et al., 2006; Serizawa et al., 2003). It is also known that enhancers from different OR gene clusters in different chromosomes can physically interact with a chosen OR gene locus in trans (Markenscoff-Papadimitriou et al., 2014), suggesting a possible role for trans-chromosomal interactions in the singular OR gene choice.

In summary, the *one neuron – one receptor rule* in the olfactory system is ensured by stochastic activation of OR genes via histone demethylation and feedback regulation by the translated OR protein via UPR.

6. Coarse targeting of OSN axons

Odor information detected by ~1,000 types of OSNs is then sorted into ~1,000 sets of glomeruli in the OB (*one glomerulus – one receptor rule*). Thus, a major challenge in the OSN axonal projection is how to sort OSN axons based on the expressed OR type. In the retinotopic visual map formation in the tectum or superior colliculus, axon guidance molecules expressed in a graded manner (e.g., ephrin-A and B) regulate the coarse targeting of axons. This is then further refined based on spontaneous neuronal activity generated in the retina (Feldheim and O'Leary, 2010; Huberman et al., 2008). Similarly, the formation of the discrete olfactory map is also controlled by the combination of coarse axon targeting and local axon sorting.

One parameter that defines the coarse targeting of axons is the cell type and positional information of the OSNs in the OE. OSNs in the dorsomedial and ventrolateral zones project axons to the D and V domains of the OB, respectively. The D domain of the OB is comprised of three subdomains, DI, DII, and DIII, for class I ORs, class II ORs, and TAARs, respectively (Kobayakawa et al., 2007; Pacifico et al., 2012;

Tsuboi et al., 2006). Within the V domain of the OB, dorsal-ventral locations of the glomeruli are correlated with the dorsomedial-ventrolateral expression zones of the ORs in the OE (Miyamichi et al., 2005).

Neuropilin-2 and Robo2 are expressed in a graded manner in the OE and play key roles in the OSN projection along the D-V axis of the OB (**Figure 5**). Nrp2 is expressed in a ventrolateral-high and dorsomedial-low gradient, whereas Robo-2 is expressed in a counter gradient (Cho et al., 2007; Nguyen-Ba-Charvet et al., 2008; Norlin et al., 2001). During development, OSNs in the dorsomedial zone project axons earlier than the ventrolateral ones (Takeuchi et al., 2010). At this stage, Slit1, a repulsive ligand for Robo2, is expressed in the septum and ventral OB. As a result, the early-arriving dorsomedial OSNs axons are confined to the D domain of the OB. At a later stage, Nrp2-high OSNs in the ventrolateral zone project axons to the OB. Sema3F coding for a repulsive ligand for Nrp2 is expressed in the dorsomedial OSNs, but not in the OB. A conditional knockout experiment indicates that Sema3F secreted from early-arriving OSN axons is important to guide Nrp2-positive late-arriving OSN axons to the ventral OBs. As a result, the temporal sequence of the OSN projection is converted to the dorsal-ventral gradient in the OB with the aid of OB-derived Slit1 and OSN-derived Sema3F (Takeuchi et al., 2010).

Contrary to D-V patterning, the anterior-posterior (A-P) positioning of glomeruli is independent of expression zones of the ORs in the OE. The first mechanistic insight came from OR swapping experiments: When an OR coding sequence was replaced with that of another OR gene, OSN projection sites shifted, often along the A-P axis (Feinstein et al., 2004; Mombaerts et al., 1996; Wang et al., 1998). Thus, ORs have an instructive role in OSN projection. However, the OR-instructed OSN projection occurs independently of odor-evoked neuronal activity (Belluscio et al., 1998; Lin et al., 2000; Zheng et al., 2000). An OR mutant without G-protein coupling failed to form glomeruli in the OB, and this was rescued by a constitutively active G_s protein (Imai et al., 2006). Genetic manipulations to decrease and increase cAMP levels led to anterior and posterior shifts of glomeruli, suggesting that cAMP levels are a determinant of A-P projection position (Imai et al., 2006). Mice deficient for adenylyl cyclase type III show distorted topography of the glomerular map (Chesler et al., 2007; Dal Col et al., 2007; Zou et al., 2007). Basal activity, rather than ligand-dependent GPCR activity was correlated with the A-P positioning of glomeruli (Nakashima et al., 2013).

The OR-derived cAMP signals regulate transcriptional levels of Nrp1 positively and its repulsive ligand Sema3A negatively, forming complementary expression. Axon-axon interactions mediated by Sema3A and Nrp1 facilitate pre-target axon sorting, which can

occur without OB. Together with the OB-derived Sema3A, this mechanism establishes the anterior-posterior positioning of axons (Imai et al., 2009) (**Figure 6**). Nrp1-high OSNs project axons to the posterior OB and this pattern is perturbed in Sema3A knockout (Schwarting et al., 2000). Plexin-A1 is expressed in a complementary manner to Nrp1, suggesting its role in axonal projection to anterior OB (Nakashima et al., 2013).

In summary, coarse targeting of OSN axons depends on graded guidance cues and their receptors. The D-V axis is determined by the positional information of OSNs in the OE and the A-P axis is determined by OR-derived cAMP signals. Axon guidance is controlled not only by the axon-target interactions, but also by repulsive axon-axon interactions (Imai and Sakano, 2011).

7. Local sorting of OSN axons

After forming a coarse map in the olfactory bulb, OSN axons need to be further segregated to form discrete glomerular structures. Each OSN sends an unbranched axon into a glomerulus. A hallmark of glomerular organization is the coalescence of homotypic OSN axons expressing the same OR. However, this process occurs in the absence of the postsynaptic neurons (Bulfone et al., 1998).

When neuronal activity in OSNs was silenced, local axon sorting was perturbed forming multiple ectopic glomeruli (Imamura and Rodriguez Gil, 2020; Schwob et al., 2020; Yu et al., 2004; Zheng et al., 2000). As the silencing OSNs with Kir2.1 shows a more severe phenotype than CNGA2 knockout, spontaneous activity may play a more important role. In retinotopic map formation, the spontaneous neuronal activity generated in the retina mediates the refinement of the map based on the Hebbian mechanisms, in which neurons that fire together wire together (Huberman et al., 2008; Shatz, 1992). However, the olfactory system utilizes a distinct mechanism to control local axon sorting (**Figure 7**).

Neuronal activity in OSNs regulates the expression of a set of adhesion molecules, Kirrel2 and Kirrel3, positively and negatively, respectively. Different levels of OR-dependent neuronal activity define OR-specific levels of Kirrel2 and 3. Kirrel2 and 3 are homophilic but not heterophilic. Therefore, the complementary expression of Kirrel2/3 leads to the fasciculation of like axons (Serizawa et al., 2006). The neuronal activity also regulates the expression of EphA5 and ephrin-A5, positively and negatively, respectively. Axonal ephrin-A5 and EphA5 are assumed to mediate repulsive interactions. Therefore, EphA5/ephrin-A5 facilitates the segregation of heterotypic axons (Serizawa et al., 2006). There are additional types of cell surface molecules that

show glomerulus-specific expression patterns, e.g., BIG2, Pcdh10, and Sema7A (Kaneko-Goto et al., 2008; Nakashima et al., 2019). It is not just the firing rate of OSNs that determines the expression level of these molecules. Phasic and tonic firing regulate different sets of cell surface molecules. This may indicate that multiple signaling pathways tuned to different firing modes are engaged for different sets of cell surface molecules (Nakashima et al., 2019). As a result, each OSN type expresses a unique pattern of cell surface molecules. It remains to be determined how the OR define unique patterns of spontaneous activity in OSNs.

While sensory-evoked activity plays a limited role in the initial map formation, it plays an important role at a later stage. OSNs often mistarget axons and form ectopic glomeruli during the first two weeks after birth. However, the ectopic glomeruli are eliminated at later stages. Sensory-evoked signals mediate the elimination (Zou et al., 2004), possibly by facilitating activity-dependent competition among OSNs (Yu et al., 2004).

OSNs are continuously regenerated throughout life. Regenerated OSNs have to project axons to the pre-existing glomeruli. This process also involves various types of axon-axon interactions described above. Genetic perturbation of early-born OSNs impairs the projection of later-born OSNs (Ma et al., 2014; Wu et al., 2018), suggesting that the projection of later-born OSNs depends more on axon-axon interactions. This may be a reason for the poor recovery of the olfactory map after severe OSN injury (Costanzo, 2000; Murai et al., 2016; St John and Key, 2003).

In summary, the local sorting of OSN axons to form glomerular structures is also a result of axon-axon interactions, namely fasciculation and segregation mediated by axon sorting molecules. OR-specific patterns of axon sorting molecules are regulated by neuronal activity.

8. Neurogenesis, migration, and axonal projection of M/T cells

Unlike the OE that develops from the olfactory placode, the OB is a rostral part of the central nervous system. The most rostral part of the telencephalon starts to invaginate at E12.5 to form the OB. M/T cells develop in three different steps: neurogenesis, migration, and dendritic remodeling (Treloar et al., 2010). Similar to pyramidal neurons in the cerebral cortex, M/T cells are generated from stem cells, known as radial glial cells, that are located in the surface of the ventricle (ventricular zone). M/T cells are generated during E10-17. Like cortical pyramidal neurons, the birthdate is a determinant of the M/T cell types. The earliest-generated population become M/T cells in the AOB. Mitral cells in the OB are generated between E10-13,

and then tufted and external tufted cells are generated between E13-17 (Hirata et al., 2019). Within the mitral cell population, earlier and later-born neurons tend to locate in the D and V domains of the OB, respectively (Imamura et al., 2011). After neurogenesis, M/T cells start to migrate radially and then tangentially toward the surface of the OB. Radial migration of M/T cells is in part regulated by OSN-derived factors in the OB. In normal conditions, Nrp2-positive M/T cells are located in the posteroventral OB and mediate the attractive olfactory behavior via the medial amygdala. However, Nrp2-positive M/T cells mis-migrate to the more anterodorsal part when Sema3F is specifically knocked out in OSNs (Inokuchi et al., 2017), suggesting that Sema3F secreted from OSN axons regulate the correct migration of M/T cells and the formation of innate circuits.

M/T cells also start to extend axons soon after the neurogenesis. M/T cell axons fasciculate to form the lateral olfactory tract (LOT). There are guidepost cells called LOT cells that help guidance of M/T cell axons (Sato et al., 1998). Early-born and later-born M/T cells are segregated within LOT and project to different parts of the olfactory cortex (Hirata et al., 2019; Inaki et al., 2004). Several axon guidance molecules are involved in the formation of the LOT and the axonal projections of M/T cells (e.g., Sema3F-Nrp2, Slit-Robo, Netrin-Dcc) (de Castro, 2009; Fouquet et al., 2007; Inokuchi et al., 2017; Kawasaki et al., 2006). At a later stage, M/T cells extend multiple dendrites toward the surface of the OB. Dendritic remodeling occurs at an early postnatal stage as will be discussed in more detail (Malun and Brunjes, 1996). In the cerebral cortex, neurons generated from the same progenitor tend to share the cortical columns; however, cell lineage is not a determinant for the dendrite wiring specificity of M/T cells (Sanchez-Guardado and Lois, 2019).

In the OB, ~99% of neurons are interneurons, among which 95% are granule cells. The generation of OB interneurons starts during embryonic stages but persists throughout life. Embryonically generated OB interneurons are derived from the lateral ganglionic eminence (LGE) and dorsal telencephalon, whereas postnatally they are derived from the subventricular zone (SVZ) of the lateral ventricle (Lledo et al., 2008). Different types of interneurons are generated from progenitors located in distinct microdomains and are defined with specific sets of transcription factors (Emx1, Gsh2, Nkx2.1, Nkx2.6, Gli1, and Zic). In the embryo, different subtypes of interneurons are generated at different timing (Batista-Brito et al., 2008). In parallel, a subpopulation of embryonically generated progenitors give rise to neural stem cells for postnatal neurogenesis, while retaining their subtype specificity (Fuentealba et al., 2015). Newly generated OB interneurons migrate toward the OB through the rostral migratory stream

(RMS) and then radially toward the appropriate destination within the OB. In the adult, a significant fraction of OB interneurons have postnatal origins (Imayoshi et al., 2008). Adult-born OB interneurons are required for flexible olfactory behavior based on cortical feedback (Sakamoto et al., 2014; Wu et al., 2020a).

In summary, M/T cells are generated from the ventricular zone of the rostral part of telencephalon, whereas OB interneurons are supplied from LGE and dorsal telencephalon during development and from the SVZ in the adult. OSN-derived factors (e.g., Sema3F) play important role for correct migration of some OB neurons.

9. Dendrite remodeling of M/T cells

As mentioned in the previous section, newly generated M/T cells initially extend multiple primary dendrites toward the protoglomerular structure. During the first postnatal week, however, each M/T cell strengthen one winner and weaken all the other primary dendrite to form singular connectivity to a glomerulus (*one M/T cell – one glomerulus rule*) (Malun and Brunjes, 1996) (**Figure 8**). In the *Drosophila* olfactory system, matching between axons of sensory neurons and dendrites of projection neurons are defined by the cell surface molecules, e.g., Semaphorins and Teneurins (Hong and Luo, 2014). In mice, however, M/T cell connections can be newly allocated for OSNs expressing an artificially-introduced receptor (e.g., rat OR and β2-adrenergic receptor), suggesting a non-deterministic mechanism for OSN-M/T pairing (Belluscio et al., 2002; Feinstein et al., 2004). Thus, the postnatal dendrite remodeling process is critical to ensure the *one M/T cell – one glomerulus rule*. As somata of sister M/T cells are scattered in the mitral cell layer (Ke et al., 2013), the dendrite wiring is not just the connection to a nearest glomeruli. Even when multiple glomeruli are formed for an OR or OSN map is perturbed, each M/T cell still connects to just one glomerulus, excluding precise molecular matching between axons and dendrites as a possibility (Ma et al., 2014; Nishizumi et al., 2019).

Dendrite remodeling of M/T cells occurs without sensory-evoked nor spontaneous neuronal activity transmitted from OSNs (Fujimoto et al., 2019; Lin et al., 2000). Instead, the remodeling is controlled by the spontaneous activity generated within the OB. The dendro-dendritic glutamatergic neurotransmission among M/T cells is the origin of the spontaneous neuronal activity in the OB (Fujimoto et al., 2019). The remodeling is controlled by stabilization signals to strengthen the winner and destabilization signal to eliminate the loser dendrites. Stabilization is mediated by the concomitant inputs of BMP signaling and NMDAR-dependent Rac1 activity (Aihara et al., 2020). On the other hand, destabilization is mediated by activity-dependent RhoA

signaling (Fujimoto et al., unpublished data). During the remodeling process, activity-dependent competition between winner and loser dendrites establishes just one winner. The NMDA receptor is essential for the synaptic competition within an M/T cell (Fujimoto et al., 2019). Synapse formation between OSN axons and OB neurons occur in the absence of neuronal activity (Fujimoto et al., 2019; Lin et al., 2000; Ma et al., 2014), but its maturation requires neuronal activity (Aihara et al., 2020).

In summary, spontaneous neuronal activity is generated in the developing OB, and activity-dependent competition within a neuron establishes the *one M/T cell – one glomerulus rule*.

10. Modulation and plasticity of the olfactory system

While the overall architecture of the olfactory system is established by the early postnatal stages, various levels of plasticity persist throughout the life of animals to adapt to the ever-changing environment. Sensory stimuli affect the expression level of ORs and survival of OSNs (von der Weid et al., 2015; Zhao et al., 2013). In the vomeronasal organ, VSN responses to some male pheromones are suppressed by a female hormone, progesterone (Dey et al., 2015). Thus, hormonal regulation of olfaction might be an interesting topic for future study. In the OB, sensory-evoked activity modulates the excitability of M/T cells and short axon cells via axon initial segment (AIS) plasticity (Chand et al., 2015; George et al., 2021). In short axon cells, dopamine synthesis is modulated by the sensory-evoked activity (Baker et al., 1993). In the OB, the glomerulus-specific intrabulbar projection of tufted cell axons is controlled by the sensory-evoked activity (Marks et al., 2006). It will be important to investigate in the future how the sensory inputs modulate the cortical projection of M/T cells as well as odor-evoked innate and learned behaviors.

In the OB, learning-related plasticity has been extensively studied using chronic calcium imaging of awake behaving mice (Wu et al., 2020b). Chronic two-photon imaging during the learning process revealed that M/T cell responses are continuously updated to convey behaviorally relevant odor information to the olfactory cortex. For example, odor responses gradually decline over days when odors are passively presented to animals (Kato et al., 2012). In contrast, the representation of threatening stimuli is enhanced by experience (Kass et al., 2013). When mice perform fine or coarse odor discrimination tasks, odor representation changes in opposite ways to optimally separate the test odors (Chu et al., 2016; Doucette and Restrepo, 2008; Yamada et al., 2017). For this purpose, top-down inputs from the olfactory cortex and the plasticity of OB interneurons play key roles (Yamada et al., 2017). In the future, it will be important

to investigate how the experience affects the structure and function of the cortical circuits.

11. Summary and conclusion

This chapter, I first described how odor information is processed at different stages of the olfactory system. In the OE, the combinatorial receptor code for both excitatory and inhibitory responses are the basis for odor discrimination. Moreover, odor mixture responses can be tuned by antagonism and synergy. In the OB, odor information is spatiotemporally represented in the glomeruli. Particularly, temporal patterns may be a key to understand the concentration-invariant perception of odor identity. In the piriform cortex, convergent inputs from multiple glomeruli are used to learn and discriminate odors, whereas OR-specific stereotyped inputs to cortical amygdala drive innate behaviors. Odor information processing in higher brain regions are beginning to be elucidated. Secondly, I described various types of vertebrate olfactory receptors (ORs, TAARs, V1Rs, V2Rs, FPRs, etc.) that have dynamically evolved in a species-specific manner. Lastly, I described how the OR-specific neuronal circuits are constructed from the peripheral to the more central part of the brain. The "*one neuron – one receptor rule*" is established by the stochastic activation of an OR gene locus followed by the feedback regulation to prevent further activation. The "*one glomerulus – one receptor rule*" is the result of the coarse axon targeting (D-V and A-P axes) and subsequent local axon sorting. Remarkably, axon-axon interactions play important roles in every aspect of OSN projections. The "*one M/T cell – one glomerulus rule*" is established during the dendrite remodeling process: Intracellular competition between winner and loser dendrites establishes the single winner. These mechanisms enable the flexible acquisition and loss of OR-specific circuits in the brain upon OR gene gain/loss during evolution. The OR-specific parallel discrete circuits enable the transformation of the molecular world to the neuronal ensembles to mediate stereotyped and flexible behaviors.

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Figures

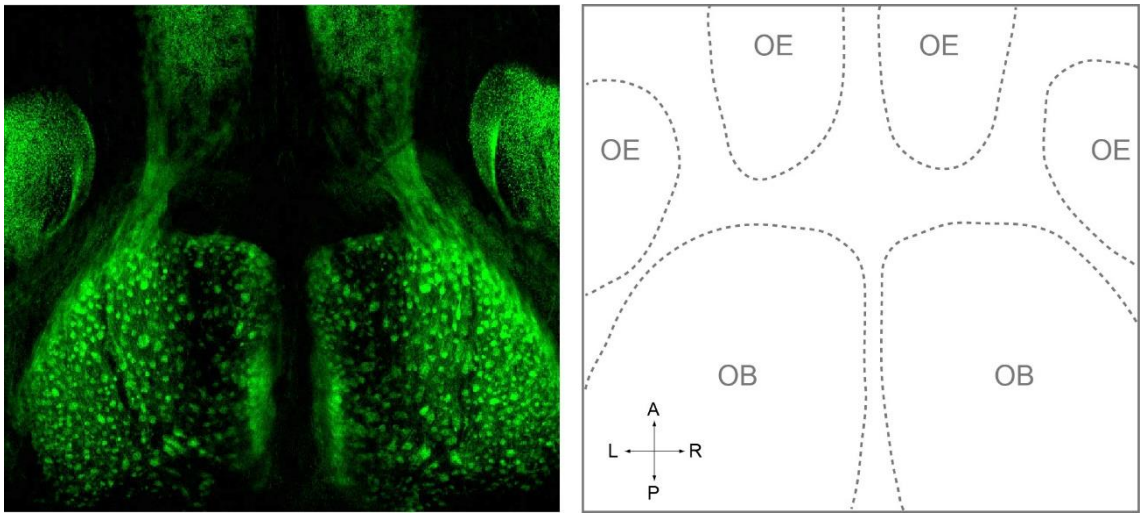

Figure 1

The mouse olfactory system. An OMP-GFP knock-in mouse, in which all mature OSNs are labeled with EGFP. OE and OB were cleared with BABB and imaged with a confocal microscope. OSN somata are scattered in the OE. OSN axons converge onto ~1,000 sets of glomeruli in the medial and lateral surface of the OBs. Dorsal view of the OE and OB. A, anterior; P, posterior; L, left; R, right. Image modified from Imai (2011).

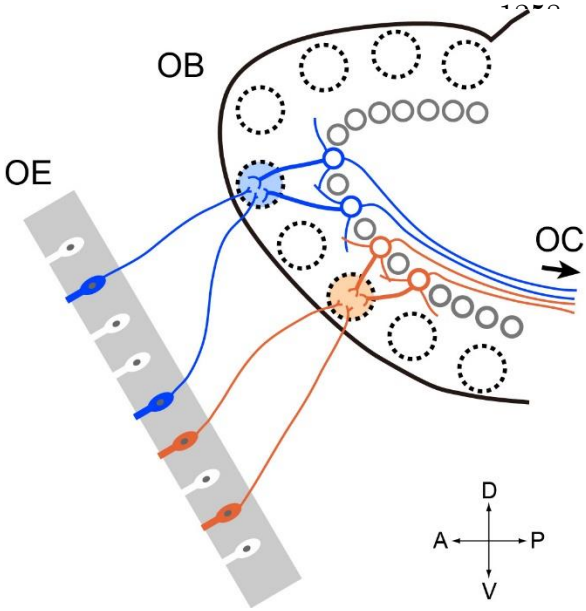

Figure 2

Organization of the olfactory system. Each OSN in the OE expresses just one type of OR in a mono-allelic manner (***one neuron – one receptor rule***). OSNs expressing the same type of OR converge their axons to a common set of glomeruli in the OB (***one glomerulus – one receptor rule***). In the OB, each M/T cell connect their primary dendrite to just one glomerulus to receive excitatory sensory inputs (***one M/T cell – one glomerulus rule***). M/T cells connecting to the same glomerulus are called sister M/T cells. M/T cell axons project to the olfactory cortex. Sagittal image. A, anterior; P, posterior; D, dorsal; V, ventral.

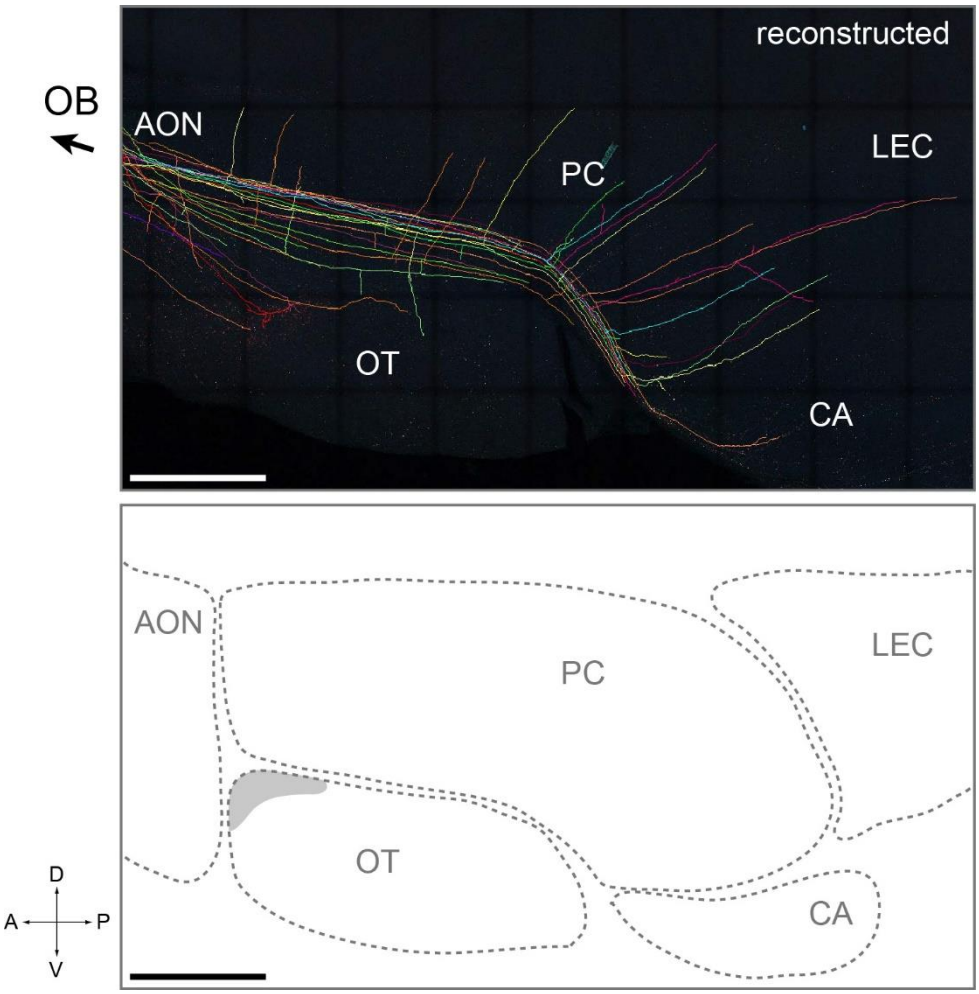

Figure 3

Axonal projections of M/T cells. Multicolor Tetbow AAV vectors were locally injected into the OB. Fourteen M/T cell axons were traced and reconstructed in the olfactory cortex. Tufted cells project axons to the AONpE and the cap region (shaded) of the olfactory tubercle. Topographic projection is seen in AONpE. Mitral cells project axons to all the other regions of the olfactory cortex. Mitral cells show differential patterns of axon collaterals, with no obvious topography. Image from the ventrolateral surface of the brain. AON, anterior olfactory nucleus; LOT, lateral olfactory tract; OT, olfactory tubercle; PC, piriform cortex; LEC, lateral entorhinal cortex; CA, cortical amygdala. A scale bar, 1 mm. Modified from Sakaguchi et al. (2018).

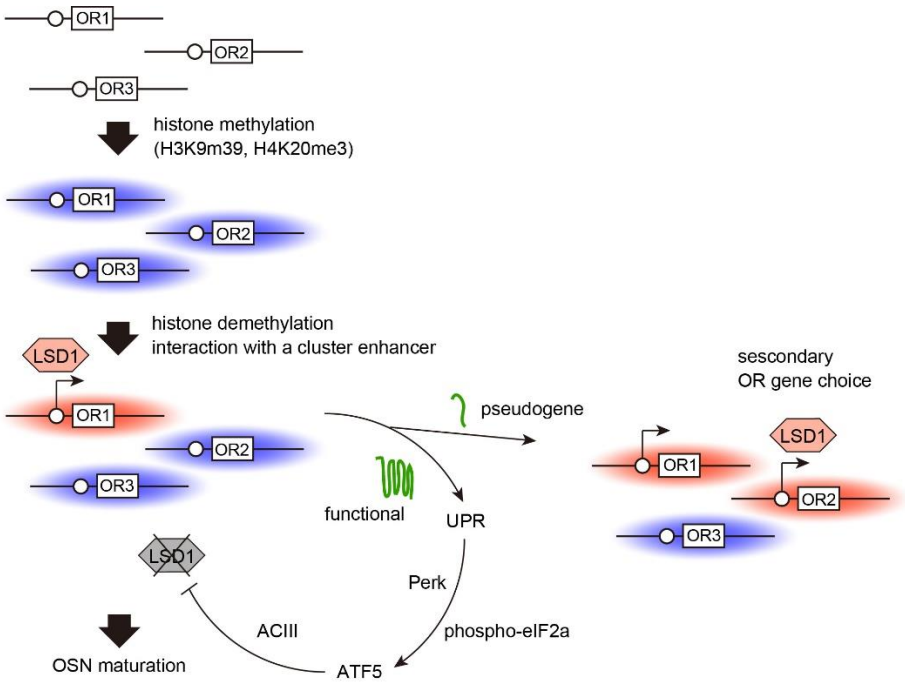

Figure 4

Singular OR gene choice. Prior to OR gene choice, OR gene loci in the genome are silenced by heterochromatin harboring H3K9m39 and H4K20me3 (blue). A histone demethylase, LSD1 mediates the stochastic activation of an OR gene locus. Physical interaction between a cluster enhancer and an OR gene promoter may also play an important role in the stochastic OR gene choice. Once a functional OR gene is activated (red), the translated OR proteins trigger an unfolded protein response (UPR), which mediates the feedback regulation. When an OR pseudogene is chosen, however, feedback regulation does not occur, and the gene choice continues until a functional OR gene is activated.

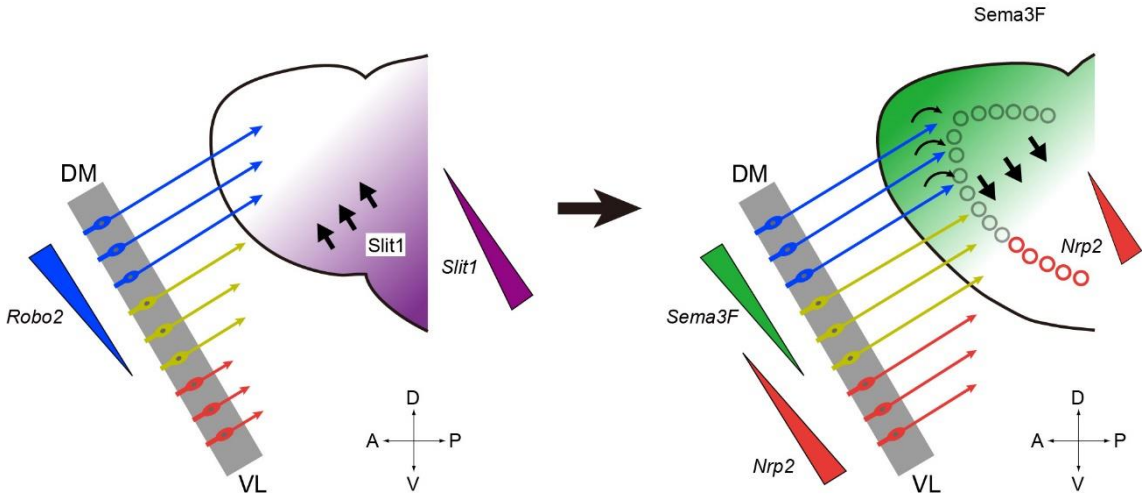

Figure 5

Dorsal-ventral (D-V) projection of OSN axons. During development, Robo2-high OSNs in the dorsomedial OE project axons, which are repelled by Slit1 in the ventral OB. These OSNs secrete Sema3F at their axon terminals. Nrp2-high OSNs in the ventrolateral OE project axons later, and are repelled by Sema3F. This sequential regulation of OSN projections establish the D-V pattern of glomeruli in the OB. Sema3F secreted from dorsomedial OSN axons are also important to localize Nrp2-high M/T cells to the ventral domain of the OB. Saggital view of the OB. DM, dorsomedial; VL, ventrolateral. Modified from Imai (2011).

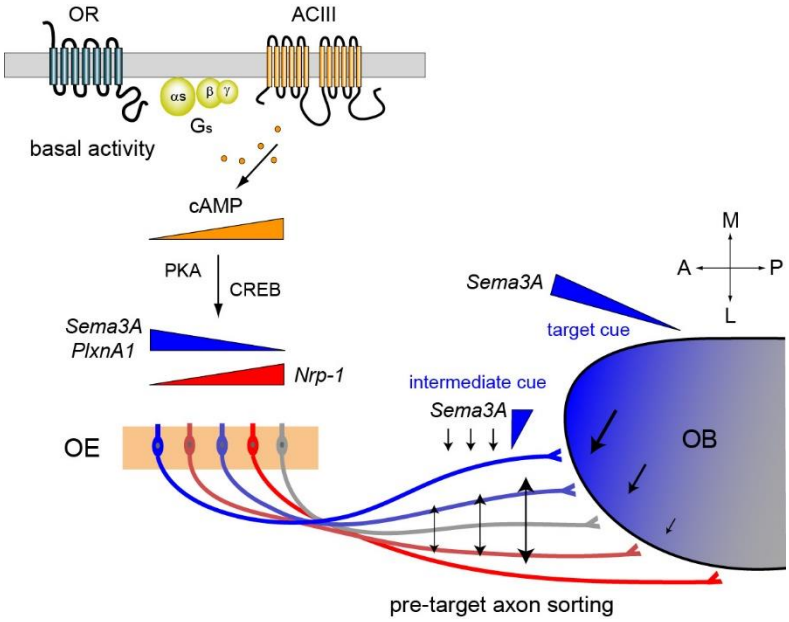

Figure 6
Anterior-posterior (A-P) projection of OSN axons. Each OR has a unique level of basal activity without odors. The basal activity positively regulates the transcriptional levels of Nrp1 via the cAMP pathway. Sema3A and PlxnA1 are negatively regulated by the basal activity. Repulsive axon-axon interactions mediated by Sema3A and Nrp1, together with the intermediate and target cues, establish the A-P positioning of glomeruli. Horizontal cartoon of the OB. A, anterior; P, posterior; M, medial; L, lateral. Modified from Imai (2011).

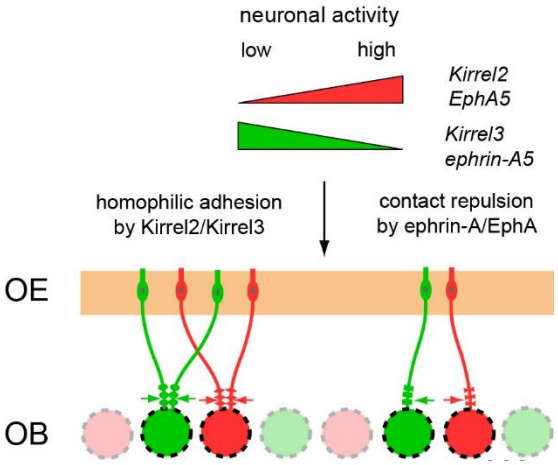

Figure 7
Local axon sorting to form a discrete glomerular map. At a later stage of OSN projection, neuronal activity regulates the expression of Kirrel2 and EphA5 positively, and Kirrel3 and ephrin-A5 negatively. Homophilic adhesion by Kirrel2 and Kirrel3 is thought to facilitate fasciculation of like axons. In contrast, repulsive interaction by ephrin-A5 and EphA5 is thought to facilitate the segregation of heterotypic axons. Note that this scheme may be too simplified: Different patterns of neuronal activity regulates different sets of cell surface molecules. Modified from Imai (2011).

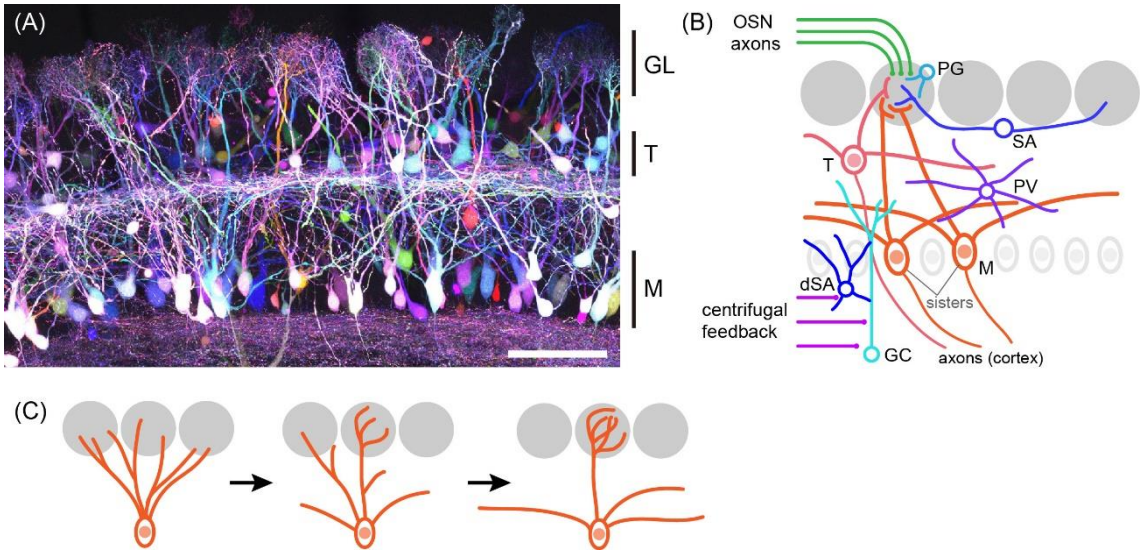

Figure 8

Development of the OB circuits. (A) Multicolor labeling of M/T cells in the OB. Tetbow plasmids were introduced to M/T cells using in utero electroporation. Note that each M/T cell connects to just one glomerulus. GL, glomerular layer; T, tufted cells; M, mitral cells. (B) A diagram of the OB circuits. In addition to M/T cells, there are various types of GABAergic interneurons, including periglomerular neurons (PG), short axon cells (SA), parvalbumin-positive interneurons (PV), deep short axon cells (dSA), and granule cells (GC). (C) Dendrite remodeling of M/T cells during the first postnatal week. An M/T cell initially extends multiple primary dendrites to the protoglomeruli. Later on, however, an M/T cell strengthens one winner dendrite and eliminates all the other loser dendrites to establish a single primary dendrite. (A) is modified from Sakaguchi et al. (2018). (B) and (C) are modified from Imai (2014).