Molecular Basis of Odor Perception in the Mouse

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In the mammalian olfactory system, odorants are detected with ~1000 odorant receptors (ORs) expressed by olfactory sensory neurons (OSNs) in the olfactory epithelium (OE). Since the discovery of OR genes, it has remained entirely elusive how each OSN expresses only one functional OR gene, and how OSNs expressing the same type of OR converge their axons to a specific set of glomeruli in the olfactory bulb (OB).

Singular OR gene choice appears to be ensured by the combination of a rate-limiting enhancer-promoter interaction and negative-feedback regulation by OR proteins\(^1\). For the OR-instructed axonal projection, OR molecules at axon termini have been assumed to recognize guidance cues on the OB. However, our recent studies demonstrated that the axonal projection is regulated by OR-derived cAMP signals\(^2\). The levels of cAMP establish the anterior-posterior (A-P) topology of axonal projection via cAMP-dependent protein kinase (PKA) at an early stage of development. For the dorsal-ventral (D-V) arrangement of glomeruli, anatomical locations of OSNs in the OE determine the target sites of OSN axons. This positional information is represented by the expression levels of axon guidance molecules, for example, Neuropilin 1 forming a gradient along the A-P axis and Neuropilin 2 along the D-V axis. After axons are guided to approximate destinations in the OB, axon termini are further sorted based on the expressed OR species in an activity-dependent manner\(^3\). A unique combination of axon sorting molecules, e.g., homophilic adhesion molecules Kirrel2/3 and repulsion molecules ephrin A/EphA, constitute the neuronal identity code for the expressed OR species.

The mouse olfactory system mediates various responses, including aversive behaviors to spoiled foods and fear responses to predator odors. In the OB, each glomerulus represents a single species of ORs. Since a single odorant can interact with many different OR species, the odor information received in the OE is converted to a topographic map of multiple glomeruli activated in distinct areas in the OB. In order to study how the odor map is interpreted in the brain, we generated mutant mice in which OSNs in a specific area of the OE are ablated by targeted expression of the diphtheria toxin gene\(^4\). In the dorsal zone-ablated mice, the dorsal domain of the OB was devoid of glomerular structures. The mutant mice lacked innate responses to aversive odorants, even though they were capable of detecting them and could be conditioned for aversion with remaining glomeruli. It was thought that glomeruli in the OB would contribute equally to the processing of odor information in the glomerular map. However, our study indicates that the mouse main-olfactory system may be composed of two functional modules: one for innate odor responses, and the other for discrimination and associative learning of complex odorous information.

References