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Research Focus

Putting smell on the map

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The vertebrate olfactory system must cope with a staggering developmental problem: how to connect millions of olfactory neurons expressing different odorant receptors to appropriate targets in the brain. Recent studies demonstrate remarkable plasticity in integrating novel olfactory sensory neurons into this circuitry.

The olfactory system permits animals to recognize and discriminate a vast number of different odorous molecules. This sensitivity is achieved by the selective expression of a single odorant receptor, specific to a small subset of the universe of odors, in each olfactory sensory neuron [1,2]. The topography of synaptic connections at the first relay in the olfactory system is organized according to the type of odorant receptor a particular olfactory sensory neuron expresses. All neurons expressing a given member of the odorant receptor gene superfamily extend axons that synapse in one medial and one lateral glomerulus in the olfactory bulb [3,4]. The position of the glomerulus is sensitive to the particular odorant receptor a neuron expresses, as shown by experiments that exchanged the coding region of odorant receptors and produced predictable distortions in the olfactory bulb map [5,6]. These experiments have led to the model that the odorant receptor itself plays a role in organizing the connectivity of olfactory map. A recent article by Belluscio *et al.* [7] demonstrated for the first time that olfactory neurons expressing a novel odorant receptor not only target a novel glomerulus, but also functionally engage the circuitry of the olfactory bulb. This is the first direct evidence that a glomerulus identified by the molecular properties of the olfactory sensory neurons that innervate it responds to a given odorant. Therefore, these results serve as a starting point to unify the molecular and functional maps of the olfactory bulb.

Insights into how the olfactory map forms

Using mouse knock-in technology, Bozza *et al.* [8] created mice in which the M71 receptor was replaced with the rat I7 receptor ('rI7 → M71'). The rI7 → M71 axons targeted glomeruli that were intermediate between I7 and M71 glomeruli (Fig. 1). Because olfactory sensory neurons have a propensity to form glomerulus-like structures even in the absence of olfactory bulb target neurons [9,10], Belluscio *et al.* asked the important question of whether such an rI7 → M71 glomerulus was functional [7]. I7 is known to be sensitive to octanal and heptanal [11–13], and in the rI7 → M71 mice the novel glomerulus was selectively activated by these two odorants, as visualized by the technique of intrinsic signal imaging [14]. Anatomical analysis of the rI7 → M71 glomerulus showed it to be richly innervated by postsynaptic mitral and tufted cell dendrites, and a number of mitral cells with I7-specific response profiles were found in the region surrounding the rI7 → M71 glomerulus. Finally, the novel glomeruli were found to be specifically linked to one another through an intrabulbar associational network that connects the medial and lateral hemispheres of the olfactory bulbs [15,16]. This intrabulbar association network had been inferred by the work of previous authors but the precision with which it wires cognate medial and lateral glomeruli together was shown for the first time by Belluscio *et al.* [7]. These results suggest a remarkable plasticity in the olfactory bulb that is induced by the arrival of novel olfactory sensory neurons. The postsynaptic targets of these sensory neurons are therefore unlikely to be prespecified and instead seem to be instructed and organized by their presynaptic partners. It remains an open question whether these selective connections form through the influence of odorant-evoked synaptic activity or whether the in-growing axons respond to local positional cues that are genetically encoded. Whether genetic or activity-dependent cues are dominant in this process, it is clear that the cues which organize these connections must be present throughout the life of the animal – not just

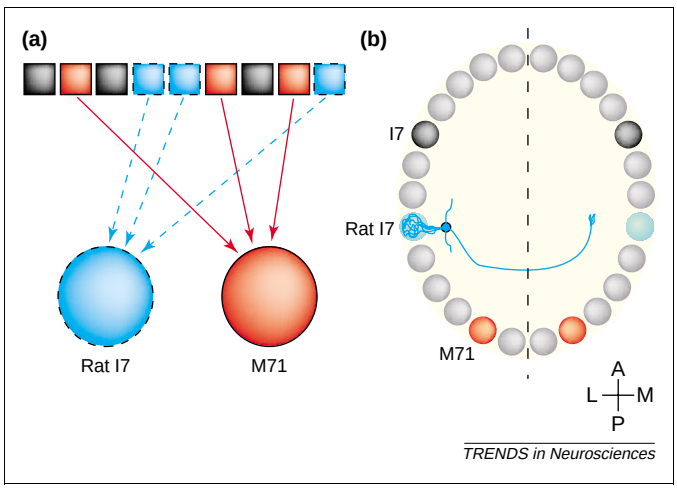

Fig. 1. Mouse olfactory circuitry modified to express a rat odorant receptor. (a) Olfactory sensory neurons (squares) each express a single odorant receptor and extend axons that converge on olfactory bulb glomeruli (circles). In 'rI7 → M71' mice, neurons engineered to express the rat I7 odorant receptor (blue) instead of the mouse M71 receptor (red) converge on a novel glomerulus that is distinct from the native M71 glomerulus. (b) The position of the rat I7 glomerulus (light blue circle) is intermediate to those of the native mouse I7 and M71 glomeruli (dark gray and red circles, respectively). Intrabulbar connections mediated by external tufted cells (blue neuron) connect to both the medial and the lateral rat I7 glomeruli. Abbreviations: A, anterior; L, lateral; M, medial; P, posterior.

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transiently present during the initial phases of olfactory system development – because the olfactory epithelium is subject to continual self-renewal [17].

Implications for evolution of smell

For the olfactory system to maintain its discriminatory power, a number of mechanisms have evolved to ensure that only a single odorant receptor is expressed per cell. Tight transcriptional control, regulated by an as yet unknown mechanism, results in the choice of one among a possible 1000 odorant receptor genes [2]. In the mouse, this extremely large repertoire of odorant receptors is undergoing rapid evolution, with at least 20% of the genes lost to frame-shift mutations, deletions and point mutations that are the hallmarks of pseudogenes [18]. This is likely to be the symptom of a gene family under pressure to diversify and generate large numbers of new receptors that might confer new selective advantage in the face of a changing olfactory environment. The rapid evolution of ligand specificity can be seen for the I7 receptor: mouse and rat I7 differ only at 15 amino acid positions across their length of nearly 330 residues but have different ligand specificities (preferring heptanal and octanal, respectively) [12]. A further level of regulation imposes mono-allelic expression on this gene family, such that a given neuron will express only a single odorant receptor from either the maternal or the paternal chromosome [19]. Such a system could be crucial to avoid the co-expression of divergent alleles of the same odorant receptor within the same neuron. If the maternal and paternal receptors have diverged sufficiently to be responsive to different odorants, it would be essential to separate these receptors into different populations of olfactory sensory neurons to avoid profound olfactory confusion. The results of Belluscio *et al.* [7] suggest that the postsynaptic partners in the olfactory bulb cooperate with the olfactory epithelium to accommodate each new type of olfactory sensory neuron in the coding circuitry, including the extreme example here of a rat receptor being included in the mouse olfactory code.

Future directions

Key questions concerning this phenomenon remain unanswered. In the rI7 → M71 mouse, I7 is expressed under the early developmental control of the M71 regulatory region. Therefore, the target neurons in the olfactory bulb first encounter this new class of olfactory sensory neuron in embryonic life as the olfactory bulb connections are initially patterned, along with the thousands of other appropriate mouse receptor neuron populations. It would be of interest to determine whether plasticity of mitral and tufted cell connections could be induced by adult-onset expression of rI7 → M71, perhaps by the type of transcriptional trickery employed by Gogos *et al.* [17]. The results of Belluscio *et al.* further implicate the role of the odorant receptor in glomerular choice, but the exact mechanism by which seven-transmembrane-domain odorant receptors modulate axon guidance remains to be determined. And what is the functional importance of intrabulbar inhibitory connections, shown here to connect the medial and lateral glomeruli receiving input from a specific class of olfactory sensory neurons [15,16]? This phenomenon of dual, mirror-symmetric olfactory sensory maps has been well described [20] (Fig. 1) but a mechanistic explanation for its existence has been elusive. Further studies into the formation of these maps, through genetic manipulation of their underlying circuitry in the mouse, promise to provide further insight into these fascinating problems.

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