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Review

Mechanisms of odorant receptor gene choice in *Drosophila* and vertebrates

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ABSTRACT

Odorant receptors are encoded by extremely large and divergent families of genes. Each receptor is expressed in a small proportion of neurons in the olfactory organs, and each neuron in turn expresses just one odorant receptor gene. This fundamental property of the peripheral olfactory system is widely conserved across evolution, and observed in vertebrates, like mice, and invertebrates, like *Drosophila*, despite their olfactory receptor gene families being evolutionarily unrelated. Here we review the progress that has been made in these two systems to understand the intriguing and elusive question: how does a single neuron choose to express just one of many possible odorant receptors and exclude expression of all others?

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Abbreviations: LCR, locus control region; OB, olfactory bulb; OE, olfactory epithelium; OR, vertebrate olfactory receptor; Or, insect odor receptor; ORN, insect olfactory receptor neuron; OSN, vertebrate olfactory sensory neuron.

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Introduction

A fundamental principle in the organization of the olfactory system that is conserved from insects to mammals is the precise functional specification of sensory receptor cells. Individual neurons choose to express only one (and sometimes two) odorant receptor from a genomic repertoire that can be as large as 1500 genes (Buck, 2000; Hallem et al., 2006). Olfactory sensory neurons send axonal projections to an olfactory processing center in the brain where axons of cells expressing the same receptor converge onto one or a few stereotypical glomeruli. In the peripheral olfactory system expression of each receptor is restricted to a subregion of the sensory surface with different olfactory receptors expressed in distinct but overlapping domains (Fig. 1).

Although other types of sensory neurons may also follow a 'one receptor rule' (Mazzoni et al., 2004), the regulatory challenge confronted by the olfactory system represents an extreme amongst gene regulation problems (Mombaerts, 2004). Similarly, B- and T-lymphocytes of the immune system also face the problem of selecting a single antigen receptor from a multitude of possibilities. It has been several years since the identification of olfactory receptor genes (>18 years in mammals, and >11 years in *Drosophila*), yet little is known about the mechanisms regulating their expression. Here we review the progress made in understanding the elusive problem of odorant receptor gene choice in vertebrates and *Drosophila*.

Various models that invoke either stochastic or deterministic mechanisms have been proposed to underlie olfactory receptor gene choice. At least five basic mechanisms, which are not mutually exclusive, are conceivable (Fig. 2). (1) Olfactory neurons could be specified in a "one-to-one" manner by specific transcription factors that are expressed in a distinct neuronal cell type and drives expression of only one receptor. However, such a model simply transfers the problem of odorant receptor gene choice up to the level of establishing specific expression patterns for transcription factors. (2) Receptor expression could be specified by a 'combinatorial' code of transcription factors, expressed in overlapping domains or combinations of gradients, rather than a battery of unique regulatory factors for each receptor. (3) Limiting factors may stochastically initiate expression of a single or a few receptors per cell; expression of a functional receptor may then exclude expression of others by a 'negative-feedback' mechanism. (4) Exclusive receptor expression could be controlled by a single locus control region (LCR), present either in *cis* or *trans*, which stochastically selects and activates the promoter of only one out of several odorant receptor promoters in an individual neuron. (5) Lastly, DNA recombination events could lead to expression of a single receptor by juxtaposing the promoter of a chosen receptor with an enhancer region. We will discuss the experiments that have explored these models.

Zonal expression of vertebrate *OR* genes

The family of vertebrate olfactory receptor (*OR*) genes was initially discovered based on the prediction that they may encode seven-transmembrane G-protein coupled receptors (Buck and Axel, 1991). With *ORs* comprising up to 3% of genes in mammals, they constitute the largest gene family in vertebrate genomes, where they are

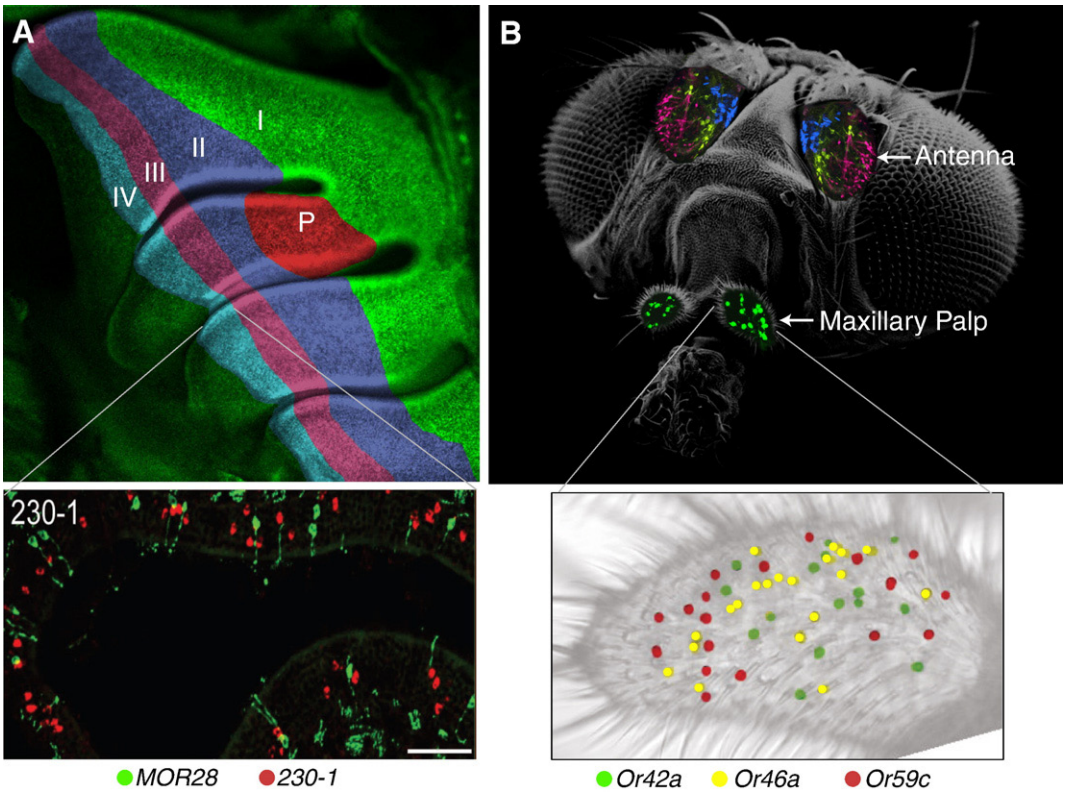

Fig. 1. Olfactory receptor expression. (A) In the mouse olfactory epithelium individual *ORs* are expressed in distinct banded expression zones (top) indicated by different colors. The numbers refer to the classical 4 zone distinction, p denotes the patch region, an exception from the otherwise elongated parallel organization of zones (adapted from Vassalli et al., 2002). Within a given region of the OE multiple *ORs* are expressed in distinct neuronal cell population (bottom) as shown for MOR28 and MOR230-1 (taken from Serizawa et al., 2003). (B) Representation of *Drosophila* head, labeled for expression of *Or22a* (blue, large basiconic), *Or47a* (yellow, small basiconic), *Or23a* (magenta, trichoid), and *Or71a* (green, palp basiconic) (taken from Ray et al., 2008). The two *Drosophila* olfactory organs are marked, the 3rd antennal segment and the maxillary palp, which express distinct, non-overlapping sets of *OR* genes. The seven *Or* genes expressed in the maxillary palp are distributed in three distinct functional types of sensilla. The schematic (bottom) shows the positions of nuclei of neurons that have been differentially stained for one receptor from each of the three sensilla classes. The three receptors appear randomly distributed within the maxillary palp (adapted from Ray et al., 2008).