Olfactory receptor expression transformations during neurogenesis

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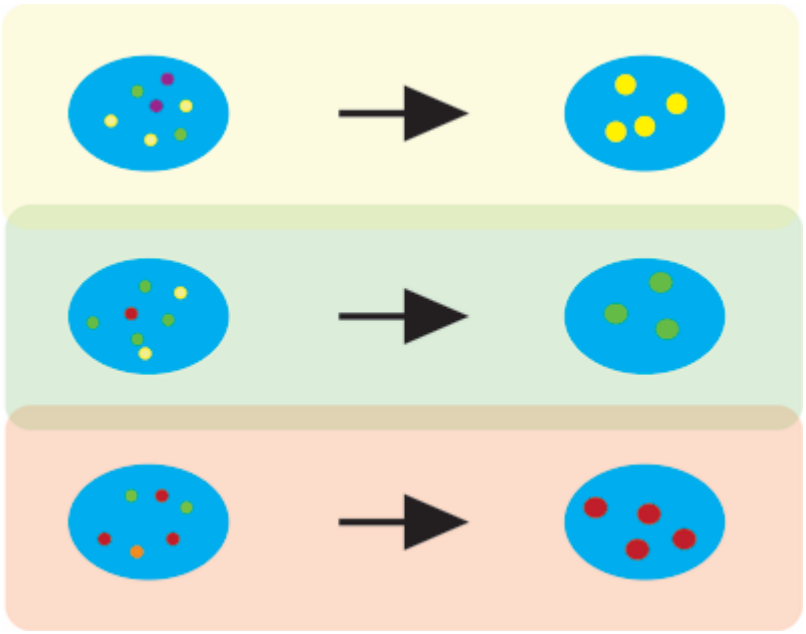

Early immature olfactory sensory neurons (left) co-express multiple olfactory receptors but once they reach maturity they are restricted to expressing a single olfactory receptor (right). Co-expression patterns in young neural tissue suggest that olfactory receptor gene expression in young neurons is restricted to a spatially determined set of genes.

Perhaps this holiday you were bombarded with many different scents: foods, people, and pets. You may have felt overwhelmed. The perception of scent, on a physiological and molecular level, is a complex process. The many chemicals that make up a scent are recognized by specific combinations of olfactory receptors that are present on the surfaces of olfactory neurons in the epithelium lining of the nasal cavity. The olfactory neurons project their axons to the olfactory bulb, a specialized region of the forebrain, where they synapse with projection neurons that then relay information to the olfactory cortex. This is the beginning of the neural circuit that will lead to the perception of scent.

Humans have around 350 intact olfactory receptor genes and mice have about 1,000 (DeMaria and Ngai, 2010). Intriguingly, research has suggested that each olfactory neuron expresses a single olfactory receptor gene (*Olfr*), a phenomenon that has been called the " one receptor, one neuron" rule (Dalton and Lomvardis, 2015). How is this exquisite patterning achieved? Based on previous evidence, the prevailing model has been that the expression of a single olfactory receptor allele

generates a feedback signal that prevents the expression of other olfactory receptor alleles within the neuron.

To carefully and precisely dissect this incompletely understood process, scientists in Linda Buck's Laboratory (Basic Sciences Division) and their collaborators in the Trapnell Laboratory at University of Washington, set out to isolate individual neurons from different stages of development and analyze how Olfr gene expression is regulated during neural development. Their findings were recently published in *Science*.

Naresh Hanchate, a postdoctoral fellow in the Buck Laboratory, isolated individual olfactory neurons from the nasal epithelium of mice at different stages of development and categorized the neurons based on the expression of cell stage markers using PCR. Next, cDNA libraries were prepared using mRNA transcripts from single neurons and Illumina sequencing was performed. Multiple neurons from each stage were analyzed. The authors found that olfactory receptor gene expression began in the late precursor stage of development and the level of expression of *Olfrs* increased with maturation. In confirmation of the one receptor-one neuron rule, most mature neurons expressed a single *Olfr*. Surprisingly, and in contrast to the prevailing model, they found that early immature neurons co-expressed low levels of multiple *Olfrs*. In order to validate their findings, they turned to a sensitive RNA-Fluorescent in situ hybridization (RNA-FISH) method to track *Olfr* expression in intact mouse tissue. Indeed, they were able to observe co-expressed *Olfrs* in cells that co-stained with markers of immature neurons. In contrast, they did not detect any cells co-expressing multiple *Olfrs* in adult tissue. Interestingly, they saw that the *Olfrs* that were co-expressed in immature neurons localized to neurons in overlapping and adjacent zones of the epithelium in adult tissue. This suggests that expression of specific sets of *Olfrs* in immature neurons is restricted spatially.

Considering the possibility that the early co-expression of multiple *Olfrs* in immature neurons could result from changes at a single genomic locus of grouped *Olfrs*, the authors investigated the chromosomal locations of the co-expressed *Olfrs* in individual neurons. Interestingly, they found that co-expressed *Olfrs* mapped to multiple different chromosomes and loci.

To investigate the hypothesis that olfactory receptor-induced neuronal activity is a feedback signal that leads to the expression of a single *Olfr*, the researchers analyzed the expression of olfactory sensory signaling transduction molecules in their sequencing data. They found evidence of olfactory sensory signal transduction molecules in immature neurons co-expressing multiple different *Olfrs* and they also observed mature neurons that were not expressing one of the transduction molecules that were analyzed. Based on these data, Naresh and colleagues concluded that olfactory receptor-

induced neuronal activity is neither necessary nor sufficient for the reduced co-expression of *Olfrs* during development.

Overall, their research provides important clues as to how olfactory receptor expression is patterned to specific neurons in the nasal epithelium during development. This process is an important part of understanding how smells are initially perceived and eventually processed by the brain.

Hanchate NK, Kondoh K, Lu Z, Donghui K, Ye X, Q X, Pachter L, Trapnell C, and Buck LB. 2015. "Single-cell transcriptomics reveals receptor transformations during olfactory neurogenesis." *Science*. 350(6265):1251-5. doi: 10.1126/science.aad2456.

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