Genetic 'reset switch' enables signaling pathway to induce multiple developmental outcomes for olfactory neurons

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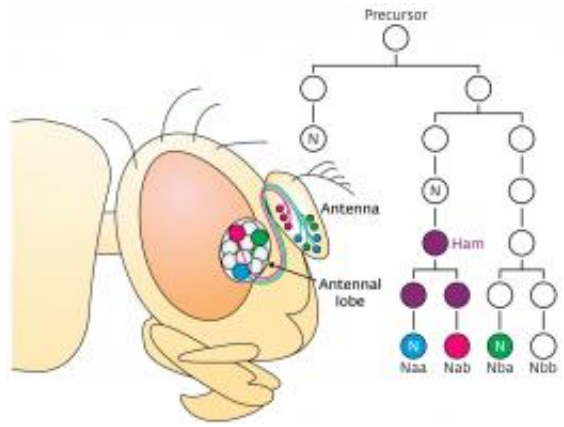

Figure 1: Interplay between Notch signaling and Hamlet activity gives rise to diverse olfactory receptor neurons (ORNs), each with distinct structures and subsets of olfactory receptors (left). The precursor cell (right) divides to yield two daughter cells, one of which undergoes Notch (N)-mediated gene activation. Hamlet (Ham) subsequently resets Notch's genetic effects, and the absence or subsequent restoration of Notch signaling determines which type of ORN (Naa or Nab) will result from differentiation. Credit: 2012 Adrian Moore, RIKEN Brain Science Institute

Within the nervous system, a handful of signaling pathways modulate development of a cornucopia of different neuronal subtypes. "Even small alterations in neuron differentiation pathways can disrupt subsequent circuit organization and catalyze the genesis of neurological

disorders," explains Adrian Moore of the RIKEN Brain Science Institute in Wako.

Recent work from Moore's team, which includes Keita Endo of the University of Tokyo, has revealed mechanisms governing this complexity in the fruit fly olfactory system. Within the antennae—the fly equivalent of the nose—it was known that cells called neuronal precursors undergo multiple rounds of 'asymmetric division', wherein each resulting daughter cell follows a distinct developmental path, yielding different combinations of olfactory receptor neurons (ORNs). Moore's team showed specifically that ORN precursors undergo two rounds of division, yielding four different cellular subtypes, three of which will typically mature into ORNs.

Earlier work from Endo showed that the activation or suppression of signaling by the Notch protein helps differentiate these cellular fates, but other factors were clearly involved. Their joint research demonstrated that a second protein, Hamlet, modulates the effects of Notch.

"This [process] provides an important foundation for all future studies of odorant receptor expression and axon targeting control on the olfactory system," says Moore. The researchers found that presence or absence of Notch and Hamlet activity plays a central role in establishing the identity of these subtypes, and this in turn determines both the connections formed by the resulting ORNs as well as the subset of olfactory receptor proteins that will be expressed (Fig. 1).

Moore and Endo's study also revealed a surprising mode of action for Hamlet. Chromosomal DNA is wrapped around clusters of protein, and chemical changes to those proteins profoundly alter local gene activity—a mechanism called 'epigenetic regulation'. They found that Hamlet selectively deactivates genes activated by Notch by triggering such changes. This means that immature ORNs produced by division of

a Notch-activated cell can essentially be 'reset' by Hamlet. The ultimate developmental fate of those cells is then determined, in part, by whether or not they subsequently undergo a new round of Notch activation.

Moore and colleagues also observed that, beyond simply switching off active Notch genes, Hamlet may define subsets of target genes that can subsequently be reactivated by Notch signaling. "The modifications induced by Hamlet may help establish cell fate by marking gene promoters for use later during differentiation," says Moore. "This could prove fundamental to understanding the process of neuronal diversification."

More information: Endo, K., et al. Chromatin modification of Notch targets in olfactory receptor neuron diversification. Nature Neuroscience 15, 224–233 (2011).

Endo, K., et al. Notch signal organizes the Drosophila olfactory circuitry by diversifying the sensory neuronal lineages. Nature Neuroscience 10, 153–160 (2007).

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