Gene regulation behind the choice of the correct receptor for olfaction

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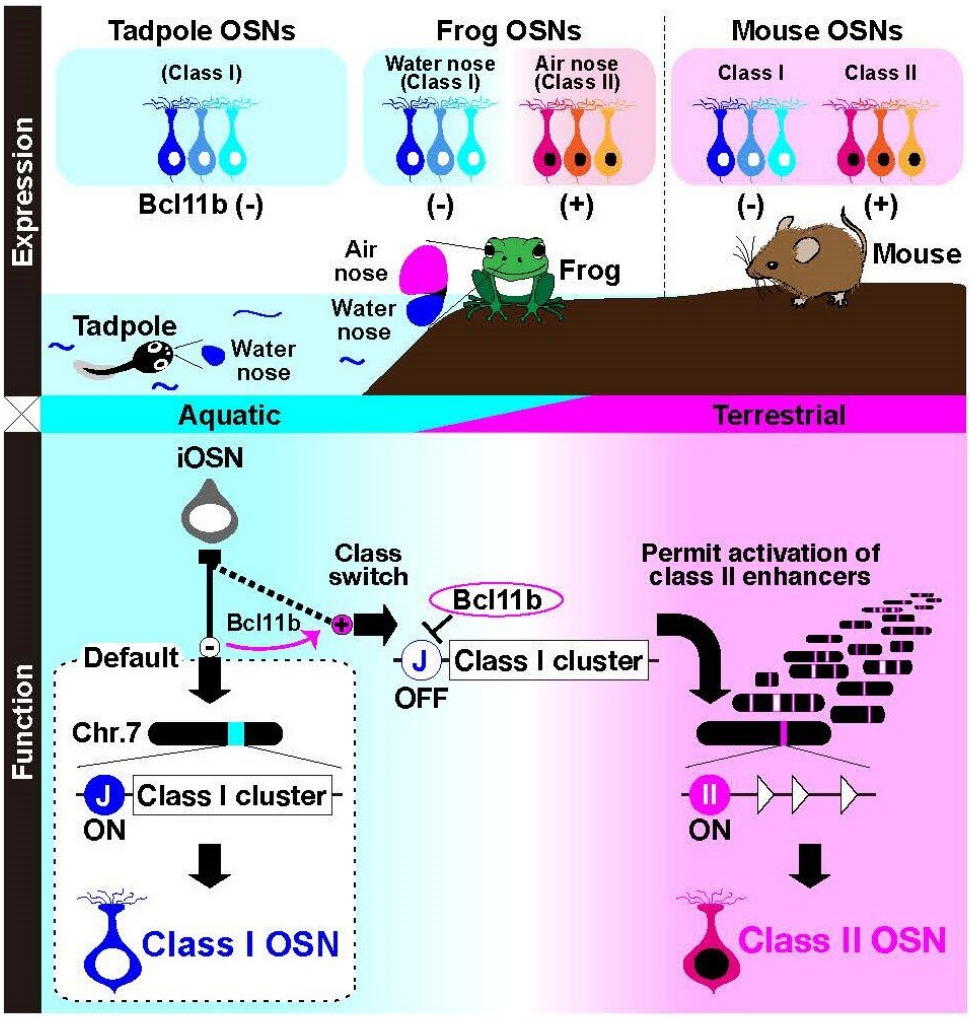


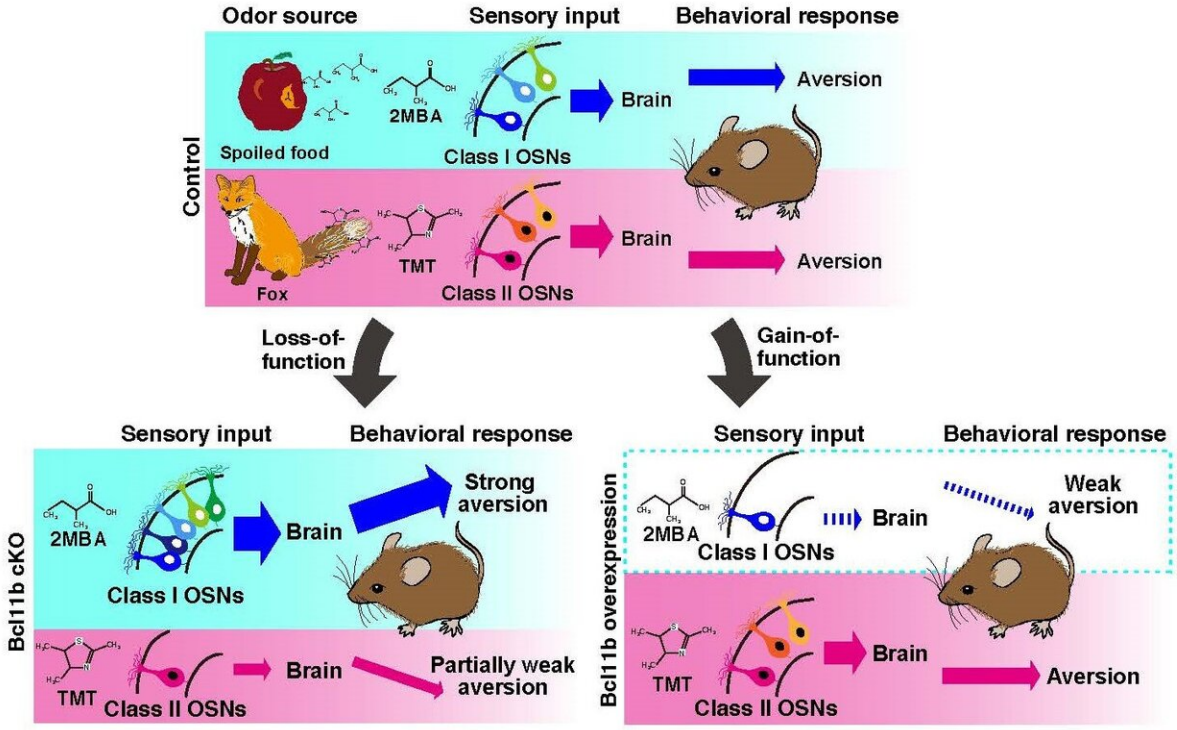
Tadpoles, which express the so called "water-nose" class I genes until they undergo metamorphosis. This this point, a part of their olfactory epithelium

starts expressing Bcl11b, resulting in the expression of class II, or "air-nose" genes, as well. Mice, on the other hand, expresses Bcl11b and leads to class II OR expression. Credit: Communications Biology, Dr. Junji Hirota

Scientists at Tokyo Institute of Technology (Tokyo Tech) have uncovered the genetics behind two distinct types of olfactory sensory neurons; the so-called class I olfactory neurons, conserved from aquatic to terrestrial animals, and class II olfactory neurons that only terrestrial animals possess. But how does the olfactory sensory neuron know which class of OR to express?

"Decision between two classes of ORs is critical to both the anatomical and functional organization of olfactory system," explains Prof. Junji Hirota from the Tokyo Institute of Technology. "However, while we have known that two classes of ORs exist for more than 20 years, the mechanisms that regulate the OR class choice have remained an open question." To understand the OR selection process, he and a group of investigators set out to unveil the factors that determine the expression of the two classes of ORs.

The researchers discovered for the first time that Bcl11b, a transcription factor, determines which class of OR gene is expressed in olfactory neurons. In the absence of Bcl11b, olfactory neurons are fated to class I. But the fate can be switched to class II in the presence of Bcl11b. This also corroborates the idea that class I OR is the default OR, which undergoes a transcriptional switch in the presence of Bcl11b.



Because the two different OR classes are linked to the entire odor perception mechanism of the animal, the mutant mice perceived aversive odors (i.e. the smell of predators [TMT] and spoiled food [2MBA]) differently. Credit: Communications Biology, Dr. Junji Hirota

A similar mechanism takes place in frogs. In tadpoles, olfactory neurons express class I ORs in the so called "water nose" until they undergo metamorphosis, when a part of their olfactory epithelium starts expressing Bcl11b, and thus starts expressing class II ORs, which become the "air-nose" in adult frogs.

Further, the scientists demonstrated that genetically manipulating Bcl11b expression in mice not only altered the class of the OR gene, but it also changed the corresponding neural wiring, altering odor perception in the

animals.

By manipulating the expression of this gene in mice, the researchers generated mice with "class I-dominant" and "class II-dominant" noses. Interestingly, because these two different OR classes are linked to the entire odor perception mechanism of the animal, the mutant mice perceived aversive odors differently, i.e., class I-dominant mice become hyper-sensitive to decayed food odor, but less sensitive to predator's odor.

"Our findings unveil a longstanding mystery in OR gene regulation, a molecular mechanism of the OR class choice as well as an essential role of Bcl11b for the functional organization of olfactory system by integrating genetic, cellular, and behavioral analyses, and provide important insights on the terrestrial adaption of olfaction during evolution," concludes Prof. Hirota.

More information: Takayuki Enomoto et al, Bcl11b controls odorant receptor class choice in mice, *Communications Biology* (2019). DOI: 10.1038/s42003-019-0536-x

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