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Without BIG-2, odor maps stink

RIKEN researchers identify a protein that guides the formation of brain circuit networks essential for processing olfactory information.

Among sensory modalities, olfaction remains relatively cryptic. Recently, it has become clear that the brain utilizes a 'topographical atlas' approach for distinguishing different smells. Now, a new study, headed by Yoshihiro Yoshihara of RIKEN's Brain Science Institute, and published online in the March 27, 2008, issue of *Neuron*, improves our understanding of how this 'odor map' is guided into a functional form.

Many animals have sophisticated olfactory capacities to decipher the bewilderingly complex cornucopia of volatile odor molecules called odorants. Even the humble mouse possesses about 1,000 genes coding for receptor proteins that recognize specific odorants. These receptors sit on the surface membranes of olfactory sensory neurons (OSNs) - electrically excitable nerve cells - situated in a thin layer of tissue, the olfactory epithelium, within the nasal cavity. Each OSN expresses only one of these odorant receptors, which can recognize multiple odorants; conversely, each odorant can also be identified by multiple receptors.

When odorants in the nose dock in the appropriate, matching receptor, a cascade of molecular events is triggered, culminating in an electrical signal transmitted to the brain's olfactory bulb (OB) - a 'relay station' in the circuitry connected to higher brain regions, where the conscious perception of the odor, as well as emotional and stimulatory reactions to it, are effected. Neurons use a primary extension of the cell body called an axon to communicate with other neurons, via special junctions called synapses. Nasal OSN axons extend into the OB, eventually converging in clearly visible and anatomically distinct domains called glomeruli, which house dense synaptic connections between input OSNs and output neurons.

The mouse OB contains approximately 2,000 glomeruli, each of which receives axons only from sensory neurons that express the same type of odorant receptor. In effect, each glomerulus translates and captures the chemical signature of odorant molecules - smells can then be ciphered as a combinatorial code of glomeruli representing an assemblage of receptors. The brain uses this special olfactory code - the activation of

some specific array of glomeruli - to recognize a smell and the stage is set for a veritable actualization of a topographical map of smells.

Axons utilize abstruse guidance systems - the intricacies of which are still being unraveled - to accurately reach out to their correct target contact locations while traversing long, labyrinthine obstacle courses. Yoshihara's group was interested in expanding what little is known about the precise molecular mechanisms by which OSN axons target specific glomeruli. The scientists focused on BIG-2, a protein that Yoshihara had characterized years earlier as being important in the developing nervous system, mainly because a subpopulation of mouse OSNs was found to express BIG-2.

Detailed analyses involving elaborate fluorescent-based visualization assays revealed that BIG-2 expression levels within OSNs correlated strikingly with the presence of specific odorant receptors, and that BIG-2 has an intriguing mosaic expression pattern within glomeruli. These findings indicate a major role for BIG-2 in olfactory information processing. More convincing proof followed, using mice genetically engineered - by disrupting the *BIG-2* gene - to not produce BIG-2 protein; without BIG-2, the glomerular mapping process went awry, suggesting that BIG-2 is required for accurate axonal guidance and glomerular targeting. Other discoveries point to an unidentified protein binding partner, within the target glomeruli, for BIG-2, consistent with the latter's proposed role as an axon guidance molecule.

Because this topographic logic mapping appears to be widely conserved in nature, BIG-2 very likely plays similar roles in humans and mice. The BIG-2-deficient mice may also provide clues on several human disorders linked with the *BIG-2* gene. BIG-2 may well live up to its epithet and turn out to be a 'big' deal in more ways than 'one.'

Original work:

Kaneko-Goto, T., Yoshihara, S., Miyazaki, H., Yoshihara, Y.
BIG-2 Mediates Olfactory Axon Convergence to Target Glomeruli. *Neuron*, published online on Mar. 27, 2008

For more information, please contact:

RIKEN Public Relations Office
Email: koho@riken.jp