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The trailblazers' guides in olfactory development

A well-developed sense of smell is more essential to the survival of most animals than any of the other senses. Animals use smells to negotiate social interactions, access environmental situations, find food and determine threats. This sense of smell guides the animal's progress through life. Researchers at RIKEN Brain Science Institute have found that scent sense neurons also have guides-at least in the early development of the olfactory system. When those first, pioneering axons set off for their synaptic connections, they are assisted by a pair of genes that detect chemical signals along the way.

Dr. Yoshihiro Yoshihara, head of the Laboratory for Neurobiology of Synapse at RIKEN Brain Science Institute, and his team of researchers discovered that the Robo/Slit receptor-ligand signalling process is crucial to the earliest stages of development of the olfactory system in zebrafish. Robo2 and Slit signalling ensures that axons of olfactory sensory neurons find the correct path to the olfactory bulb and make all the right connections.

In vertebrates, olfactory sensory neurons distributed along the olfactory epithelium detect smell-producing chemicals and send messages via their axons. These axons project to specific locations on the olfactory bulb to create an olfactory map. A series of molecular processes during development send attractive or repulsive messages to the foraging axonal projections to guide them to the proper locations. Here, a small number of pioneering olfactory axons push out of the olfactory epithelium, heading toward the olfactory bulb where the cluster of axons unbundle and proceed to more precise regions within the bulb to make synaptic connections in glomeluri with target neurons.

The repulsive signalling activity of Roundabouts (Robo) and Slits mediates axon pathfinding for various neurons, and therefore is a likely candidate for this process with

olfactory neurons. Using *astray* mutant (lacking Robo2) and Slit2-overexpressing zebrafish, Dr. Nobuhiko Miyasaka at Yoshihara's laboratory investigated the possible role of Robo and Slit signalling in this system. A lack of Robo2 as the first axons are trying to find their way to and when the clusters of axons unfold in the olfactory bulb region impairs pathfinding and screws up the glomerular map. This suggests that Robo2 is needed to bundle and direct the axons as they venture out of the epithelium. Axon pathfinding was also misguided when Slit2 was ubiquitously overexpressed to neutralize its local function, indicating that Slit is able to prevent axons from going off-course by sending repulsive signals. They also found that once the first axons have cut the path, the signalling shuts down and new connections develop without these messages.

Robo2/Slit signalling guides the first axonal projections of olfactory sensory neurons to the olfactory bulb, determines the spatial arrangement of this development, and form the olfactory map. Just as smell helps some animals blaze new trails, Robo2 and Slit help axons of early scent sensory neurons traverse unknown terrain to establish that sense of smell.

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