SCIENCE & SCILIFELAB PRIZE

Assembly of a Neural Circuit

Differential expression of cell-surface molecules instruct the precise assembly of a neural circuit.

Weizhe Hong

Precise connections established between synaptic partners are essential for the proper function of neural circuits. To explain the striking target specificity of the optic nerve during regeneration, Roger Sperry proposed the chemoaffinity hypothesis 50 years ago, which posits that developing neurons must carry "individual identification tags," presumably cytochemical in nature. By this means, they can almost be distinguished in many regions, to the level of the single neuron (*1*). Since then, many molecules have been identified that guide axons to their final target area, but little is known about molecules that mediate mutual selection and matching between individual pre- and postsynaptic partners among many possible alternatives at the target area (*2*–*4*).

The olfactory system detects environmental odorants and processes the information in a precisely connected neural circuit. In *Drosophila*, the axons of olfactory receptor neurons (ORNs) expressing the same odorant receptor converge onto an anatomically discrete glomerular unit in the antennal lobe, the first olfactory processing center in the brain (*2*, *5*). The antennal lobe consists of ~50 glomeruli, which are uniquely identifiable by their stereotypical size, shape, and relative position. In each glomerulus, a single class of ORN axons makes synaptic connections with dendrites of a single class of second-order olfactory projection neurons (PNs). This one-to-one organization principle is highly conserved from insects to mammals. The fly olfactory circuit thus offers us an attractive model system to study the mechanisms underlying synaptic partner matching.

My graduate thesis focused on the identification of the developmental mechanisms underlying the wiring specificity of the fly olfactory system. Targeting of PN dendrites and ORN axons is presumably achieved by differential expression of cell surface receptors in different classes of PNs and ORNs. Prior studies showed that graded expression of transmembrane Sema-

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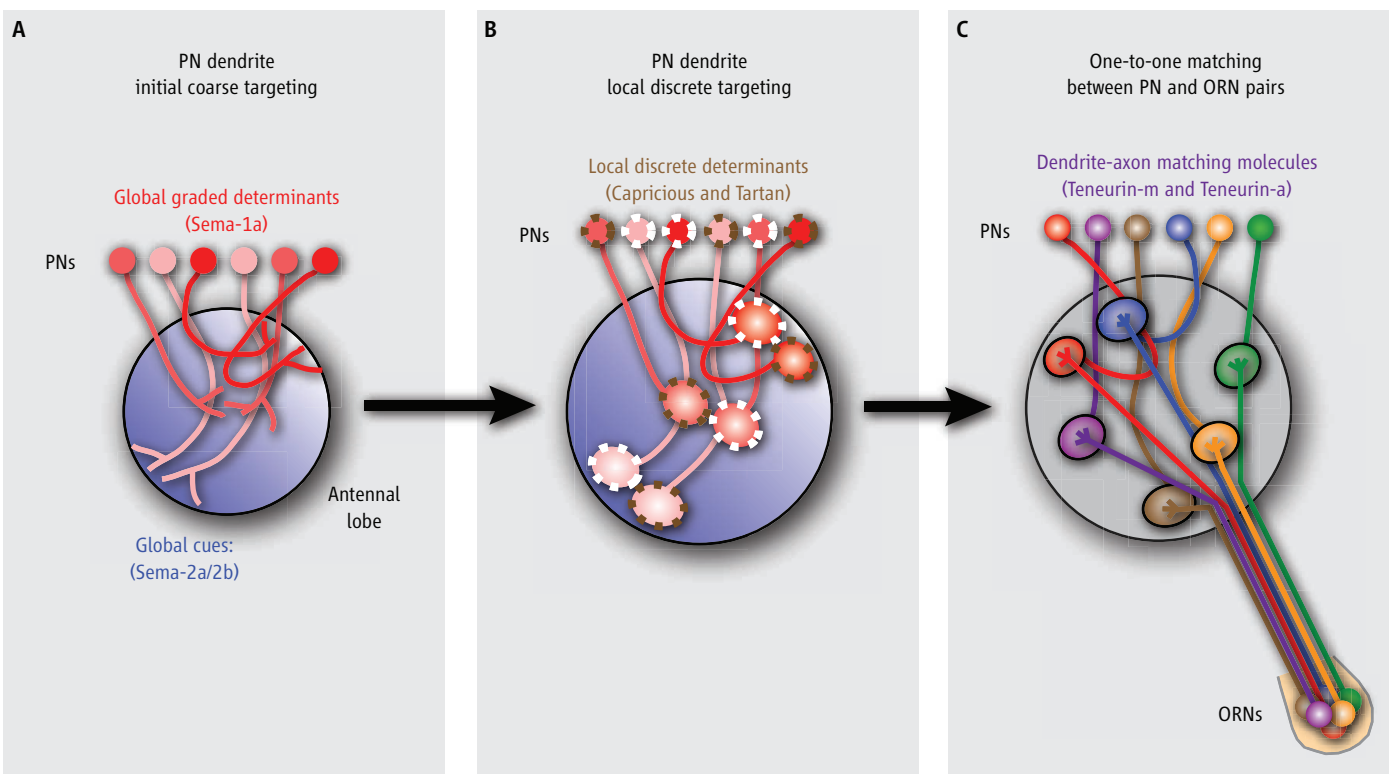

Stepwise assembly of the *Drosophila* olfactory circuit. The olfactory circuit is assembled in three major developmental steps. In the first step (**A**), PNs first extend their dendrites to create the proto-antennal lobe. Secreted Sema-2a/2b proteins are distributed in gradients opposing the gradient of the cell surface receptor Sema-1a and repel Sema-1a–expressing dendrites to regulate the targeting along the dorsolateral-ventromedial axis. In the second step (**B**), differential Capricious and Tartan expression instructs the segregation of PN dendrites into class-specific, discrete glomeruli through dendrite-dendrite interaction. In the third step (**C**), the appropriate PN-ORN connections are established through the one-to-one class-specific matching between ORN axons and PN dendrites. Teneurin-m and Teneurin-a instruct synaptic partner matching specificity between PNs and ORNs through homophilic attraction. [Modified after Hong *et al.* (*10*)]

2013 Second Runner-Up

For his essay in the category of Developmental Biology, Weizhe Hong is a second runner-up. Dr. Hong is a Helen Hay Whitney Fellow at California Institute of Technology, working on neural mechanisms underlying social and emotional behaviors in David Anderson's laboratory. Dr. Hong received a B.Sc. degree in biological sciences at Tsinghua University and a Ph.D. degree from Stanford University, where he worked in Liqun Luo's laboratory and studied the cellular and molecular mechanisms of wiring specificity in olfactory system development. Dr. Hong received the Genetics Society of America's Larry Sandler Memorial Award for the best Ph.D. dissertation on *Drosophila*-related research and presented the Larry Katz Memorial Lecture at the Cold Spring Harbor Conference for the best Ph.D. dissertation on neural circuit research.

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phorin-1a regulates targeting of PN dendrites to coarse subregions during the initial formation of the antennal lobe (*6*) (see the figure, A). This single continuous molecular gradient, however, is not sufficient for each of the 50 classes of PN dendrites to select class-specific glomerular targets and form a three-dimensional discrete neural map.

To search for instructive molecules that specify targeting of PN dendrites to class-specific areas, I conducted a genetic screen to identify genes involved in this process. I identified Capricious, a leucine-rich repeat transmembrane protein that is differentially expressed in different PN classes (*7*). Loss- and gain-of-function studies indicate that Capricious instructs the segregation of Capricious-positive and -negative PN dendrites to discrete glomerular targets. Moreover, I also found that the closely related protein Tartan plays a partially redundant function with Capricious. Therefore, these leucine-rich repeat proteins instruct targeting of PN dendrites to class-specific, discrete glomeruli in the antennal lobe (see the figure, B). This discrete dendrite-targeting mechanism mediated by Capricious represents a novel strategy for PNs to select proper targets (see the figure, B).

The function of Capricious in regulating PN dendrite targeting is independent of presynaptic ORNs. The class-specific expression of Capricious and Tartan appears to regulate only the targeting of dendrites through dendrite-dendrite interactions but is not involved in the direct recognition and matching between dendrites and axons. This left open the question of how different pairs of PNs and ORNs recognize each other and make class-specific one-to-one connections.

To address this question, we designed highly sensitive and robust assays to examine the matching and mismatching between specific pairs of PNs and ORNs. This allowed me to perform two unbiased screens, which identified two Teneurins, Teneurin-m and Teneurin-a, as synaptic partner-matching molecules (*8*). Teneurins are epidermal growth factor (EGF) repeat–containing transmembrane proteins that are evolutionarily conserved from worms to mammals. Several human Teneurins are located in chromosomal regions associated with neurological and psychiatric diseases. I found that *Drosophila* Teneurins, Teneurin-m and Teneurin-a, are highly expressed in select PN and ORN matching pairs. Loss- and gain-of-function of Teneurins cause specific mismatching of ORN axons and PN dendrites. Moreover, Teneurins promote homophilic interactions in vitro and mediate transcellular homophilic interactions to promote PN-ORN attraction in vivo. Therefore, Teneurins instruct synaptic partner-matching specificity between PNs and ORNs through homophilic attraction (see the figure, C). This homophilic attraction illustrates an intriguing strategy for synaptic partners to make connections at the level of individual synapses (see the figure, C).

Furthermore, Teneurin-m is also found to be involved in matching select motoneuron-muscle pairs in *Drosophila* (*9*). Teneurin-mediated target selection at the neuromuscular junction is analogous to its role in olfactory synaptic partner matching. Thus, the identification of Teneurins reveals a general mechanism for determining synapse specificity directly between pre- and postsynaptic partners.

In conclusion, my thesis work has identified two major mechanisms for the assembly of the olfactory circuit (see the figure) (*10*). After initial coarse positioning, PN dendrites target to class-specific, discrete glomerular locations in the antennal lobe through dendrite-dendrite interactions mediated by a pair of leucine-rich repeat transmembrane proteins, Capricious and Tartan (see the figure, B). Finally, late-arriving ORN axons recognize PN dendrites through homophilic attractions mediated by a pair of EGF repeat–containing transmembrane proteins, Teneurin-m and Teneurin-a (see the figure, C). The discrete targeting mechanism via dendrite-dendrite interactions and synaptic partner matching mechanism via axon-dendrite interactions act in a stepwise and complementary manner to wire the olfactory circuit and establish the class-specific one-to-one matching between synaptic partners. The identification of these molecules and the developmental mechanisms demonstrates that molecular determinants can instruct connection specificity of a moderately complex neural circuit at the level of individual synaptic partners. This work not only helps mechanistically understand the olfactory circuit assembly but also elucidates the general principles by which wiring specificity is established during neural development.

References and Notes

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