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Development of Wiring Specificity of the *Drosophila* Olfactory System

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The central problem of neural circuit assembly is how wiring specificity is achieved. The *Drosophila* olfactory neural circuit presents a fascinating system to attack this problem. As in mammals, the *Drosophila* olfactory receptor neurons (ORNs) that express a given receptor converge their axons onto a common glomerulus in the antennal lobe, creating an odor map in this first olfactory structure of the central nervous system (Ressler *et al.*, 1994; Vassar *et al.*, 1994; Mombaerts *et al.*, 1996; Gao *et al.*, 2000; Vosshall *et al.*, 2000). Antennal lobe projection neurons (PNs) send their dendrites into glomeruli and axons to higher brain centers including the mushroom body and the lateral horn (Stocker, 1994). Using MARCM-based systematic clonal analysis, we found that PNs are prespecified by lineage and birth order to send dendrites to specific glomeruli and thereby carry specific olfactory information (Jefferis *et al.*, 2001). Further, we demonstrated that according to glomerular class, PNs have stereotyped axon branching patterns and terminal fields in the lateral horn (Marin *et al.*, 2002; Wong *et al.*, 2002). Thus during the construction of the fly olfactory system, a given ORN must target its axons to one of ~50 glomeruli, while a given PN must also target its dendrites to one of ~50 glomeruli and furthermore the PN must coordinate its dendritic target choice with its axon terminal arborization pattern in higher olfactory centers.

Our developmental and genetic analyses have begun to shed light on how wiring specificity in the antennal lobe is achieved. Surprisingly, PN dendrites and ORN axons appear to have substantial self-organizing properties. For instance, we found that, before ORN axon arrival, PN dendrites have already created a prototypic dendritic map by virtue of their selective and stereotyped localization of dendritic processes within the developing antennal lobe (Jefferis *et al.*, 2004) and that dendrite-dendrite interactions are essential for the formation and refinement of the PN dendritic map (Zhu and Luo, 2004). On the ORN side, genetic mosaic analyses revealed cooperative interactions between axon terminals of the same ORN classes and hierarchical interdependence among different ORN classes (Komiyama *et al.*, 2004). Thus the precise wiring of the olfactory system likely relies on extensive PN–PN and ORN–ORN interactions to create two prototypic maps, which then come into register through ORN–PN interaction.

We are using both a candidate gene and forward genetic approach to identify genes that direct the establishment of wiring specificity of the olfactory system. For example, we have identified a set of POU-domain transcription factors that are expressed in a lineage-specific fashion in PNs and instruct lineage-specific dendritic targeting (Komiyama *et al.*, 2003). One of these POU factors also control ORN axon targeting (Komiyama *et al.*, 2004). We are also analyzing a number of candidate cell-surface proteins such as N-cadherin (Zhu and Luo, 2004) for their contribution to wiring specificity. Our ongoing forward genetic screen has yielded a number of interesting mutants that block different aspects of dendritic targeting, including glomerular choice, terminal elaboration and uni-glomerular restriction. By continuing these approaches, we expect to make substantial progress in the near future in deciphering the molecular logic that underlies the development of wiring specificity in the antennal lobe.

Many of these genes may be used in projection neurons for both dendritic targeting and axon terminal arborization (e.g. Komiyama *et al.*, 2003; Zhu and Luo, 2004), providing a means to coordinate the wiring specificity in two olfactory centers.

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