Neuronal Development: Specifying a Hard-Wired Circuit

Lisa Stowers

The formation of neuronal circuits that relay distinct olfactory information is thought to depend on cues provided by pre-synaptic receptor neurons. But direct visualization of second order neurons in Drosophila now suggests that dendritic targeting occurs independently of interactions with incoming sensory neurons.

During sensory development, abundant neurons are created in the brain that become functional by precisely extending processes to synapse with determined targets. In contrast to the visual or somatosensory system, olfactory information is mediated by a large number of distinct receptor neurons, randomly intermingled in the olfactory epithelium, and the axons from cells expressing identical ligand receptors precisely converge on a defined second order neuron (Figure 1). This poses a number of molecular challenges to ensure that a stereotyped, hard-wired circuit properly develops so as to mediate perception. Work on development of the olfactory system in Drosophila is beginning to elucidate the principles that underlie this process.

Neuronal circuit formation has been well characterized in the visual system, where positional sensory information from neighboring neurons must be preserved at each synapse so as faithfully to represent the environment [1,2]. Gradients of ephrins and their receptors govern the position of synapse formation of individual neurons, which is then refined by coordinated neuronal activity [3]. This, however, does not appear to be the only strategy for specifying neuronal targets, as demonstrated in the mammalian olfactory system where activity is dispensable [4,5] and the only identified essential molecular components of this process are the olfactory receptor genes themselves [6,7]. One might assume that the olfactory receptors detect ligand cues which are important for correct wiring of the system, but at present no cues of this kind have been discovered.

Convergence of the sensory neurons is only half of this complex process. The dendrites of the second order neurons — mitral cells in vertebrates or projection neurons in invertebrates — are also targeted to this defined region to form glomeruli (Figure 1) [8]. Several studies on vertebrates and invertebrates have suggested that the wiring pattern at this level of the olfactory system is instructed by the incoming receptor neurons. Specifically, genetic ablation of the mitral cells in the mouse was found not to disrupt the convergence and stereotyped position of incoming receptor neurons [9]. In the moth, removal of the antennae, and thus the receptor neurons, prevented normal glomerular formation [10], while surgical dissection of projection neurons did not disrupt receptor neuron convergence [11]. And in Drosophila mutants where there is a failure to establish a proposed pioneer class of receptor neurons, the development of glomeruli is disrupted [12]. Together, these studies suggest that specific wiring at the first relay in the olfactory system is precisely patterned by receptor neurons which instruct the second order neurons to organize appropriately.

Liqun Luo and colleagues [13] recently reasoned that, to elucidate the mechanisms of stereotypic wiring, it is essential to identify the order of spatial patterning of the incoming receptor neurons and the outgoing projection neurons in the antennal lobe. To do this, they used a sophisticated genetic strategy [14] in which single cell clones or neuroblasts were labeled with a marker that allowed visualization of specific neurons. This strategy has now revealed [13] that projection neurons occupy their ultimate restricted and specific regions of the developing antennal lobe hours before the arrival of the axons of olfactory receptor neurons. This indicates that, in Drosophila at least, the dendrites of the projection neurons are capable of specific stereotyped targeting in the absence of any physical contact with olfactory receptor neurons.

Jefferis et al. [13] further investigated the origins of the cues that direct the dendritic patterning of the projection neurons. They hypothesized that the antennal lobe of Drosophila is so small (about 30 µm in diameter) that the approximately 50 different patterning domains within it — the glomeruli — are most likely established by cues within the developing lobe that are cell-surface bound, rather than freely diffusible or acting at long distances. Further genetic experiments allowed the authors to eliminate as sources of these putative cues the larval lobe, adult glial cells and a subset of local interneurons. They found that the position of each of these candidate cue sources remains distinct from projection neurons during the time of pattern formation.

Dendrites of projection neurons are the primary component of the developing antennal lobe, and different classes of projection neurons may have differential molecular profiles that depend on their cell lineage and birth order [8,15]. On the basis of their observations of cell location and the timing of projection neuron development, Jefferis et al. [13] suggest that patterning of projection neuron dendrites may have a significant self-organizing component, involving dendro–dendritic interactions. They propose that the mechanism may include homotypic attraction and/or heterotypic repulsion from surrounding dendrites to sort, pattern and specify the developing antennal lobe.

It is not immediately clear how this conclusion can be reconciled with the earlier observations suggesting that the axons of incoming olfactory receptors have an instructive role in development of the circuit [16–19].
These earlier studies, however, mostly relied on the formation of mature, discrete glomeruli to indicate the occurrence of patterning. Recently developed genetic techniques offer a superior resolution, making it possible to investigate the development of wiring specificity with a higher accuracy than previously possible. Jefferis et al. [13] propose that spatial patterning and glomerular formation may be two distinct processes. In the model proposed by Jefferis et al. [13], receptor neurons and projection neurons both have self-governing patterning mechanisms, each capable of forming a ‘proto-map’ that interacts to form the mature, coherent glomerular structure.

It will be of great interest to determine how the receptor neurons and projection neurons are directed to their destined targets (Figure 2). Do the pre-synaptic and post-synaptic cells use common intrinsic or extrinsic mechanisms to coordinate their specific patterning? Is activity dispensable for the refinement of connectivity? Interestingly, Jefferis et al. [13] observed that the projection neurons first extend axons to their targets prior to dendrite outgrowth. With this in mind, does the molecular landscape of the projection neuron axons direct dendritic patterning? Are the mechanisms that generate specific wiring conserved between the mouse and Drosophila? Recent technical advances should enable these issues to be clarified. The power of genetic analysis in Drosophila and mouse is providing a surprising picture of the development mechanisms which ensure that those neurons that generate olfaction perception are precisely wired.

References


