Cell Recognition and Wiring the Fly Brain

How neurons form precise patterns of synaptic connections remains a mystery. Studies in vertebrates and invertebrates have revealed that neural circuitry is established in a stepwise fashion: neurons extend axons, growth cones at the leading edge of the axon navigate stereotyped pathways to target regions, and, finally, within target regions neural processes select appropriate partners and form synapses. Secreted signals acting at a distance, components in the extracellular matrix and molecules expressed on the surface of cells act at short range provide growth cones with the instructions for neural circuit formation. The complexity of neural circuits with vast numbers of cells interconnected in complex yet highly specific ways suggest that very special solutions at the molecular and cellular level would be needed to promote connection formation.

The Drosophila Dscam gene provides a fascinating example of how molecular complexity encoded at a single genetic locus contributes to the complexity of neural circuit organization. Through extensive alternative splicing, the Dscam gene potentially encodes 38,016 different isoforms of a single pass transmembrane protein of the immunoglobulin (Ig) superfamily. This includes 19,008 extracellular domains linked to the membrane through one of two alternative transmembrane domains. The extracellular domains of all isoforms share the same domain structures with multiple Ig and fibronectin type III domains. Of these three Ig domains are variable with 12, 48, or 33 different flavors. Dscam isoforms exhibit homophilic binding specificity, binding to themselves but rarely, if ever, to other isoforms; binding partners must share the same three variable domains. Biochemical and structural studies have demonstrated that each variable Ig domain binds to its counterpart in the opposing molecule and that stable binding occurs only if all three domains match. Genetic studies demonstrate that diversity is essential for neural circuit assembly throughout the fly peripheral and central nervous system.

Dscam provides the molecular basis of self-avoidance. This poorly understood and under appreciated aspect of neural development was discovered by Kramer and Stent in the early 1980s while studying the development of the leech nervous system. In Drosophila, as in the leech, neuronal processes distinguish between self and non-self. Self-processes repel each other and this provides a crucial mechanism for patterning the branches of axons and dendrites. Each neuron expresses a unique combination of Dscam isoforms such that only branches of the same neuron recognize each through homophilic binding. Binding in turn activates a repulsive response and as a consequence processes extend away from each other.

Reference


