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Structure and Bi-functionality of Dscam Headpiece: One stone for Two Birds. Jia-huai Wang, Dana-Farber Cancer Inst., Harvard Medical School.

Dscam is a highly diverse cell surface receptor expressed in the nervous system as well as the immune system of insects. Mutually exclusive splicing of exons arranged in three clusters results in extensive sequence variability in three immunoglobulin-like ecto-domains. It has been proposed that homophilic and heterophilic interactions involving thousands of Dscam isoforms provide recognition specificity for neuronal wiring and immune responses. X-ray structures of the N-terminal four Ig-like domains of two different Dscam isoforms have been determined, both encompassing variable domains D2 and D3. Both isoforms assume a horseshoe configuration. The most variable residues of D2 and D3 constitute two independent surface-epitopes presented as unique structural elements at opposite faces of the horseshoe. Epitope I is engaged in homophilic dimer formation, involving symmetric, antiparallel pairing of identical peptide segments within $D2^A/D2^B$ and $D3^A/D3^B$ interfaces. This suggests an exclusive homophilic interactions of Dscam isoforms. In contrast, epitope II does not contribute to homophilic interactions and is likely involved in heterophilic recognition.