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Clustered protocadherin molecular assembly and implications for neuronal self-avoidance

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Abstract:

Subsets of clustered protocadherin isoforms (α-, β-, and γ-Pcdhs) are stochastically expressed in individual vertebrate neurons. These cell-surface proteins provide a basis for neuronal self-recognition and non-self discrimination, which underpin neuronal self-avoidance. Using cell aggregation assays, X-ray crystallography, cryo-electron microscopy, biophysical measurements, and computational modeling, we have determined much of the molecular logic by which Pcdhs mediate neuronal self-vs-non-self-discrimination. Pcdh isoforms mediate cell-cell recognition through strictly homophilic *trans*-interactions involving extracellular cadherin domains 1–4 (EC1–4). Crystal structures of multiple α-, β-, and γ-isoforms revealed the molecular basis of their homophilic specificity. Pcdh isoforms also associate promiscuously *in cis* via their membrane-proximal EC5–6 domains, generating *cis*-dimeric recognition units. Coupling of Pcdh *cis* and *trans* interactions results in the formation of a zipper-like assembly between contacting cell surfaces. Computational experiments showed that the size of this assembly is very sensitive to the presence of mismatched isoforms between contacting cell surfaces, suggesting a mechanism for self-vs-non-self-discrimination among vertebrate neurons.