

Evolution and Structural Signature of the Cadherin Domain

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Keywords: cadherin, phylogeny, adhesion

The cadherins are transmembrane glycoproteins that mediate cell-cell adhesion in a calcium dependent manner[1]. Cadherins enable the development of distinct tissues during morphogenesis and the maintenance of tissue integrity. Aberrant cadherin expression correlates to the invasion and metastasis of many cancers[2]. Members of the cadherin superfamily differ in the number of cadherin repeats present in their ectodomain and in the functional roles of their cytoplasmic domains. Classical cadherins have five cadherin repeats and conserved cytoplasmic tails that are linked to the cytoskeleton, while protocadherins have six repeats and function in the brain[3]. For classical cadherins, cell-cell adhesion is achieved by the formation of a strand-swapped interface between the N-terminal repeat of cadherins present on the surfaces of neighboring cells[4].

The common signature of the cadherin domain is comprised of the conserved calcium binding motifs. Using available structural and sequence data, we show that a conserved set of hydrophobic residues forms a structural signature that characterizes the domain. We demonstrate that the unique structural features of the N-terminal domain that form the strand swapping interface are derived from a conserved internal motif present in the other domains. To probe the evolution of cadherin proteins from an ancestral single domain to diverse multidomain families, we examine the phylogenetic relationships of different classical and protocadherin domains. We show that cadherins and protocadherins probably diverged from a shared ancestral domain prior to separate duplication of the domain in each lineage. In the classical cadherin lineage, recurring duplications of cadherin repeat EC2 may have generated the multidomain protein, while in the protocadherin lineage, duplication of different domains occurred. We also compare the rate of evolution of the various repeats and show that due to its direct adhesive function, the classical N-terminal domain has evolved more slowly than the other classical domains. We present a possible model of cadherin and protocadherin evolution that accounts for these analyses.

References

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