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Review

Neuronal territory formation by the atypical cadherins and clustered protocadherins

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ABSTRACT

Spatial patterns of neuronal connectivity are critical for neural circuit function and information processing. For many neuron types, the development of stereotyped dendritic and axonal territories involves reiterative contacts between neurites and successive re-calibration of branch outgrowth and directionality. Here I review emerging roles for members of the atypical cadherins (Fmi/Celsrs) and the clustered Protocadherins (Pcdhs) in neurite patterning. These cell-surface molecules have shared functions: they engage in homophilic recognition and mediate dynamic and contact-dependent interactions to establish reproducible and space-filling arborization patterns. As shown in genetic and molecular studies, the atypical cadherins and clustered Pcdhs serve in multiple contexts and signal diverse actions such as neurite repulsion or selective adhesion. In some cell types, they regulate the non-overlapping arrangement of branches achieved through homotypic interactions, such as in self-avoidance or tiling. In others, they promote dendritic complexity through cell–cell interactions. With critical roles in both the fine-scale arrangement of axonal and dendritic branching and the large-scale organization of axon tracts and neuronal networks, the atypical cadherins and clustered Pcdhs are key regulators of neural circuit assembly and function.

Contents

Abbreviations: Celsr, cadherin EGF LAG seven-pass G-type receptor; CTCF, CCCTC binding factor; da, dendritic arborization sensory neurons; Dnmt3b, *de novo* DNA methyltransferase 3b; EC, extracellular cadherin motifs; Fmi, flamingo; FAK, focal adhesion kinase; IgSF, immunoglobulin superfamily; md, multidendritic sensory neurons; MARCKS, myristoylated alanine-rich C-kinase substrate; Pcdh, clustered Protocadherin; PCP, planar cell polarity; Pyk2, proline-rich tyrosine kinase 2; RGC, retinal ganglion cell; SETDB1, SET domain binding protein 1, Histone-lysine N-methyltransferase.

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1. Introduction

Neurons develop dendritic and axonal territories that are characteristic for their cell type and critical for their function. Features that define a neuron's territory include arbor size and geometry, branch placement and complexity, and the types and distributions of synaptic contacts. These features also shape a neuron's function because branch patterns influence the ways in which neural information is received, processed and contributes to circuit output. Despite their stereotyped features, neuronal arborizations typically develop from dynamic and at times stochastic processes of branch addition, growth, and retraction. Neurite trajectories are shaped by repulsive and attractive interactions with cues on other neurons and in the extracellular environment. The specificity of these interactions depends on the repertoires of cell-surface molecules. While many neuronal receptors and adhesion molecules have been identified, the next challenge is to determine how these molecules link cell recognition with neurite patterning, and how they contribute to the precise wiring and function of neural circuits. This review focuses on the roles for the atypical cadherins and the clustered Protocadherins (Pcdhs) in neuronal morphogenesis and territory formation.

2. The cadherin superfamily

2.1. Overview of the cadherin superfamily and neuronal patterning

Members of the cadherin superfamily are implicated in neuronal patterning through regulation of dynamic and highly selective neurite–neurite interactions. Cadherins are a group of transmembrane molecules defined by the presence of extracellular cadherin 'EC' domains containing conserved Ca2+ binding sequences. This superfamily comprises more than 100 members and is further divided into subfamilies based on extracellular and cytoplasmic domain composition: 1) the major cadherins (Cdhs), which include the type I and II classical cadherins; 2) the Flamingo/Celsr proteins; 3) the Protocadherins, including the clustered and non-clustered (or delta) protocadherins; and 4) the cadherin-related family, which includes diverse members such as Fat, Daschous, and Calsyntenin [1].

Cadherins are classically regarded as cell adhesion molecules that regulate stable, Ca2+ dependent homophilic adhesion. In addition cadherins regulate dynamic events such as cell sorting and coordinated movements, and that the properties responsible for cell recognition and differential adhesion are also utilized for neural circuit formation [2,3]. Mutual expression and homophilic matching of type II cadherins have been shown to regulate synapse specificity, consistent with a model in which a cadherin adhesion code specifies connectivity [4]. The clustered Protocadherins (Pcdhs) and the atypical cadherins Flamingo and CESLRs have also emerged as important regulators of neuronal morphogenesis. These molecules shape arbor development by regulating processes such as neuronal tiling, neurite self-avoidance, and axon sorting. Although these patterning strategies are diverse, I will discuss how the Pcdhs and atypical cadherins implement them through common functions: 1) engage in homophilic recognition; 2) mediate dynamic neurite–neurite interactions that can be repulsive, attractive, or stabilizing; 3) fill the available territory. I will also discuss how Fmi/Ceslrs and Pcdhs pattern neuronal territories at the level of individual and populations of neurons, and how patterning at both levels is critical for circuit function.

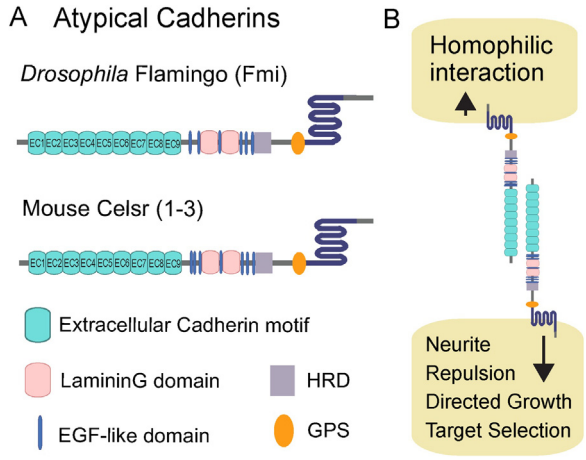

Fig. 1. Molecular organization of the atypical cadherins and the clustered Protocadherins.
(A) *Drosophila* Flamingo (Fmi) and Mouse Celsrs are large seven-pass transmembrane proteins. Fmi and Celsr extracellular regions comprise nine Extracellular Cadherin repeats (EC), EGF-like and laminin globular-like domains, a hormone receptor domain (HRM), and the GPCR proteolytic site (GPS), which is conserved in many adhesion GPCRs. The cytoplasmic region does not contain recognizable domains.
(B) Fmi and Celsrs mediate homophilic interactions to produce various outcomes such as neurite repulsion and target selection.

2.2. The atypical cadherins, Flamingo and Celsr

Flamingo and the mammalian homologs Celsr1-3 are atypical cadherins with a seven-pass transmembrane domain similar to G protein–coupled receptors, a feature unique to this subfamily (Fig. 1). They are large proteins composed of nine extracellular cadherin repeats, three cysteine-rich motifs, several EGF-like repeats, and two laminin globular domains [5,6]. Analysis of the *Drosophila Fmi* mutant and the *Celsr1* mouse mutant revealed central roles in planar cell polarity (PCP) and in neuronal patterning [6,7]. Flamingo induces homophilic binding in cell aggregation assays [6], suggesting that Fmi/Celsrs mediate homophilic adhesive or dynamic cell–cell interactions.

2.3. The clustered protocadherins

The clustered Protocadherins are members of the Protocadherin subfamily and the largest subgroup within the cadherin superfamily. Pcdhs are defined by a single transmembrane domain and by 6 EC domains. They differ from the classical cadherins by the absence of the beta-catenin and P120-catenin binding motifs [8]. Clustered Pcdhs genes are also distinguished by their complex organization of ~60 tandemly arrayed genes and their potential to generate enormous cell-surface diversity. In mice, the clustered Pcdhs comprise 58 genes subdivided into the *Pcdh-alpha (Pcdha)*, *–beta (Pcdhb)*, and *–gamma* (*Pcdhg)* clusters, which encode 14, 22, and 22 isoforms respectively (Fig. 2A) [9,10]. β-Pcdh isoforms are encoded by single exon genes and have a relatively short cytoplasmic region. α-Pcdh