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Protocadherins branch out: Multiple roles in dendrite development

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Abbreviations: Pcdh, Protocadherin; Celsr, Cadherin EGF LAG 7-pass G-type receptor 1; EC, extracellular cadherin; TM, transmembrane; CNR, Cadherin related neuronal receptor; PSD, Post-synaptic density; FAK, Focal adhesion kinase; PKC, Protein kinase C; MARCKS, Myristoylated alanine-rich C-kinase substrate; RNAi, RNA interference; PYK2, Protein tyrosine kinase 2; Rac1, Ras-related C3 botulinum toxin substrate 1; DSCAM, Down syndrome cell adhesion molecule; SAC, starburst amacrine cell; CTCF, CCCTC-binding factor; Dnmt3b, DNA (cytosine-5-)-methyltransferase 3 β; RGC, Retinal ganglion cell; TAF1, Template-activating factor 1; TAO2β, Thousand and one amino acid protein kinase 2 β; p38 MAPK, p38 mitogen-activated protein kinase; MEK3, Mitogen-activated protein kinase kinase 3; MEF2, Myocyte enhancer factor 2; FMRP, Fragile X mental retardation protein; Ds, Dachsous; PCP, planar cell polarity; EGF, Epidermal growth factor; Fjx1, Four jointed box 1; Fj, Four jointed; fmi, Flamingo; GPCR, G-protein-coupled receptor; S2 cells, Schneider 2 cells; md neuron, multiple dendrite neuron; da neuron, dendritic arborization neuron; Gogo, Golden Goal; LIM domain, Lin11, Isl-1 & Mec-3 domain; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II.

The proper formation of dendritic arbors is a critical step in neural circuit formation, and as such defects in arborization are associated with a variety of neurodevelopmental disorders. Among the best gene candidates are those encoding cell adhesion molecules, including members of the diverse cadherin superfamily characterized by distinctive, repeated adhesive domains in their extracellular regions. Protocadherins (Pcdhs) make up the largest group within this superfamily, encompassing over 80 genes, including the ~60 genes of the α-, β-, and γ-Pcdh gene clusters and the non-clustered δ-Pcdh genes. An additional group includes the atypical cadherin genes encoding the giant Fat and Dachsous proteins and the 7-transmembrane cadherins. In this review we highlight the many roles that Pcdhs and atypical cadherins have been demonstrated to play in dendritogenesis, dendrite arborization, and dendritic spine regulation. Together, the published studies we discuss implicate these members of the cadherin superfamily as key regulators of dendrite development and function, and as potential therapeutic targets for future interventions in neurodevelopmental disorders.

Introduction

The development of functional neuronal circuitry is a key step in the formation of all nervous systems. Neurons, uniquely among metazoan cell types, interact directly in a point-to-point wiring fashion through synapses, which allows neural circuits to encode and constantly modify vast amounts of information. Each neuron is estimated to make thousands of synapses with partner neurons, and studies in a wide variety of model systems have shown that these connections are formed with a high degree of specificity. Because the synapse is, in many ways, a specialized type of adhesive junction, it is not surprising that many of the molecular cues thus far shown to influence the formation of neural circuits are cell adhesion molecules.

The establishment of a proper dendritic arbor is a critical component of neuronal circuit formation, and is linked to synaptogenesis as well, both morphologically and in terms of molecular mechanisms.[1-3] Dendrites represent the "input" side of the neuron (axons typically represent the "output" side), and as dendritic arbor size and pattern varies widely among distinct neuronal types,[4] aberrations from these normal parameters should have major effects on the development of proper circuitry. Consistent with this, disrupted dendrite development, including defects in the dendritic spines onto which most excitatory synapses are made, is associated with autism spectrum disorders and intellectual disabilities, both in available human patient samples and in the brains of transgenic mice engineered to model these disorders.[5-8]

Over the past decade, many cell adhesion molecules, including members of the cadherin superfamily, have been implicated in developmental brain disorders (see recent reviews refs. 9–11). At the same time, recent publications have demonstrated increasing evidence of major roles for the diverse group of cell adhesion molecules known as the protocadherins (Pcdhs), which represents the largest group within the cadherin superfamily, in the regulation of dendrite arborization and function. For the purposes of this review, we confine our focus to recent work that has demonstrated functions for the clustered (α-, β-, and γ-) Pcdhs, the

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non-clustered δ-Pcdhs, and the atypical cadherins such as Fat and Flamingo/Celsr, in dendrite development. These molecules all have interesting expression patterns and functional roles in many other aspects of neural development, such as apoptosis, axon outgrowth and targeting, and migration; though we will not discuss these here, information can be found in several other recent reviews (see refs. 12–18).

Protocadherin Classification

The Pcdhs include more than 80 members of the cadherin superfamily: a diverse collection of cell-surface molecules defined by the presence of several ~110 amino acid extracellular cadherin (EC) motifs.[19-21] The canonical members of the superfamily, the "classical" cadherins, are type I transmembrane (TM) proteins that contain 5 EC repeats and a conserved cytoplasmic domain that interacts with the armadillo repeat proteins, β-catenin and p120 ctn, and that mediate calcium-dependent, primarily homophilic, adhesion via the EC domains.[22-25] Shintaro Suzuki and colleagues used degenerate PCR to search for additional cadherin molecules, and discovered and named the first protocadherins in the early 1990's.[26] The initial molecules to be cloned were structurally quite similar to the classical cadherins, with a single TM domain and 6 or 7 EC repeats, though lacking catenin-binding sites in their cytoplasmic domains.[26-29] Such "typical" Pcdhs can be divided into 2 classes: 1) the clustered α-, β-, and γ-Pcdhs, which are encoded by, respectively, the *Pcdha, Pcdhb,* and *Pcdhg* gene clusters, together encompassing ~60 genes in mammals with differing arrangements in other vertebrates; and 2) the non-clustered δ-Pcdhs (**Fig. 1**).[12,15,19,21,30-33] The molecules initially reported by Suzuki and colleagues included both clustered Pcdhs and δ-Pcdhs.

In addition to these Pcdhs, there are also several molecules with larger numbers of EC domains that are referred to in the literature as either Pcdhs or as "atypical cadherins;" because of their many roles in dendrite development, we will include these in our review, but refer to them as atypical cadherins. We discuss 2 groups of these, both of which are found in invertebrates as well as vertebrates: 1) the Fat and Dachsous cadherins, which have 27–34 EC domains and a single TM domain;[16] and 2) the 7 TM cadherins, which include Flamingo in *Drosophila* and its mammalian homologues Celsr1–3 (**Fig. 2**).[17,18]

Clustered Protocadherins

In mammals, the clustered Pcdh genes are situated in 3 sequential arrays (termed *Pcdha, Pcdhb,* and *Pcdhg*) encompassing about 1 MB on human chromosome 5q31 and mouse chromosome 18.[30,31,34] Within the *Pcdha* and *Pcdhg* clusters, large "variable" exons (14 for *Pcdha* and 22 for *Pcdhg* in the mouse) encoding 6 EC domains, a TM domain, and a ~90 amino acid cytoplasmic domain are each expressed from their own promoters and spliced to 3 small "constant" exons that encode a shared 125 amino acid C-terminal domain (the mouse *Pcdhb* locus contains 22 variable exons but no constant exons; **Fig. 1**). To generate transcripts encoding individual clustered Pcdh isoforms, a given variable exon promoter is "chosen," through mechanisms that are only now being elucidated,[35-37] and transcription through the remaining portion of the cluster proceeds. For the *Pcdha* and *Pcdhg* clusters, intervening variable exons are removed when the 5′ variable exon is spliced to the 3 constant exons.[38,39] The *Pcdhg* cluster is further divided into subfamilies based on sequence similarity of the variable exons: *Pcdhg A* (12 exons), *B* (7 exons), *and C* (3 exons) subfamilies, with an additional 2 exons closely

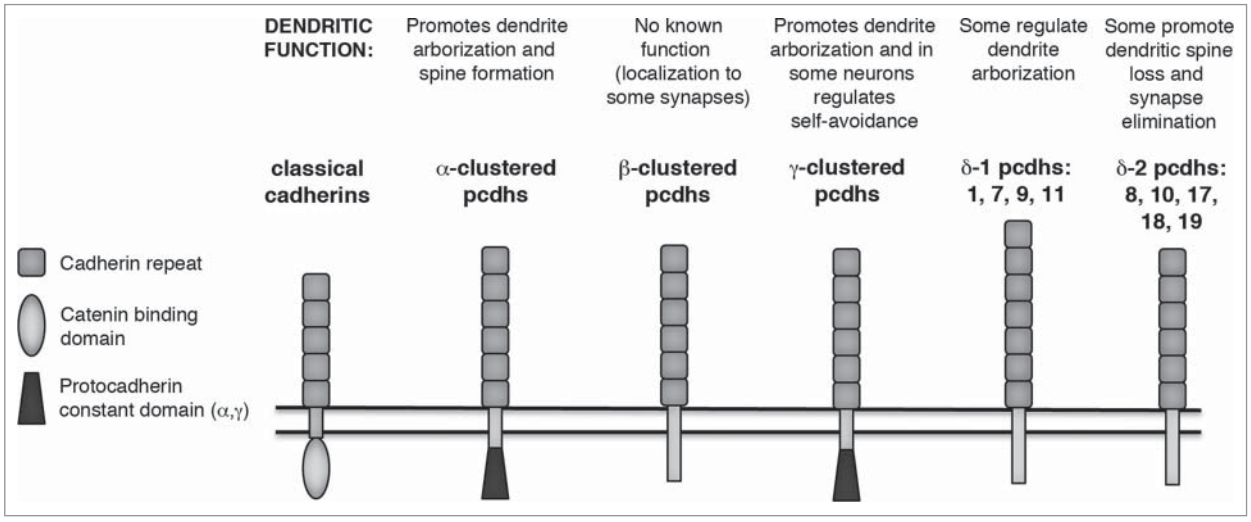

Figure 1. Clustered and Non-Clustered Protocadherins. Schematic domain structures of the clustered (α-, β-, and γ-) Pcdhs, and of the δ1- and δ2- non-clustered Pcdhs. Domains as indicated by legend; double horizontal line represents the plasma membrane. The domain structure of a classical cadherin is shown for comparison. A summary of known dendritic functions appears above each schematic.

homologous to *Pcdhg C* found at the 3′ end of the *Pcdha* cluster (αC1 and αC2).[30]

Based on extensive work from Takeshi Yagi's lab using RT-PCR on single cerebellar Purkinje cells from mice harboring maternal and paternal alleles from distinct mouse strains, most clustered Pcdh variable exons appear to be expressed monoallelically. While both alleles are transcriptionally active in any given neuron, each individual variable exon promoter appears to be active from only one of the 2 alleles. The exceptions to this rule are the ubiquitously-expressed *Pcdha C1* and *C2* exons, and the related *Pcdhg C3, C4,* and *C5* exons, all of which are biallelically expressed. Each Purkinje cell expresses ~4 *Pcdha* isoforms (2 of the monoallelically expressed exons plus the ubiquitous C1 and C2), ~2 *Pcdhb* isoforms and ~7 *Pcdhg* isoforms (~4 of the monoallelically expressed exons plus the ubiquitous C3, C4, and C5).[13,40-43] Our own studies indicate that γ-Pcdh proteins form *cis*-multimers that interact in a strictly homophilic manner in *trans*.[44] Because *cis*-interaction occurs promiscuously, while *trans* interaction requires isoform matching, the *Pcdhg* cluster could encode between 10^4 and 10^5 distinct adhesive interfaces.[44,45] As γ-Pcdhs form complexes with α- and β-Pcdhs, which can also mediate homophilic interactions,[46-48] clustered Pcdhs could provide vast combinatorial molecular diversity that likely contributes to dendritic arbor development and function.

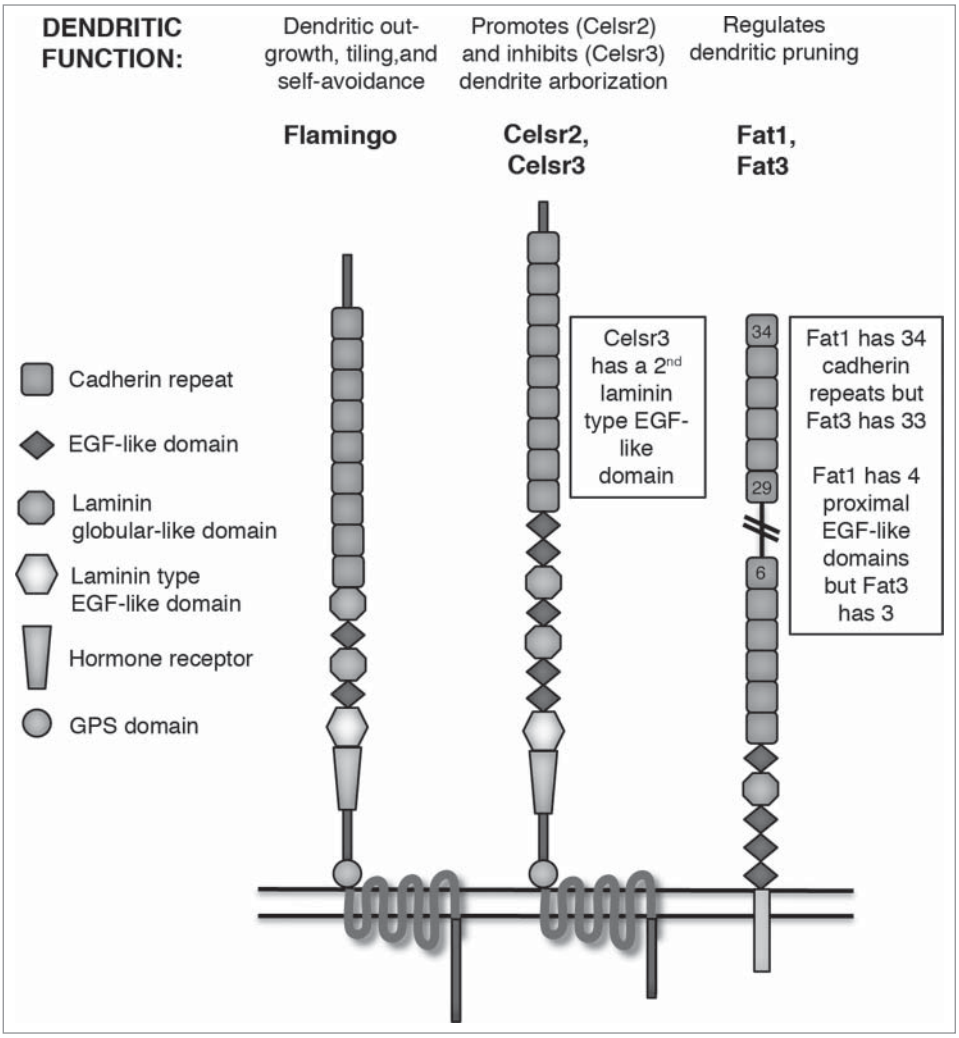

Figure 2. Atypical Cadherins. Schematic domain structures of Flamingo, Celsr, and Fat atypical cadherins. Domains as indicated by legend; double horizontal line represents the plasma membrane. A summary of known dendritic functions appears above each schematic. Because Fat proteins have too many cadherin repeats to easily depict in a reasonably-sized figure, the double-diagonal lines indicate continuation of cadherin repeats between the 6th and 29th.

The Pcdha genes were the first to be analyzed in the nervous system, with the initial characterization of 8 genes isolated as "CNRs" (Cadherin Related Neuronal Receptors).[49] Kohmura et al.[49] demonstrated that these α-Pcdh proteins are localized to cortical dendrites and synapses, using fluorescent and immunogold antibody staining, and concentrated in the post-synaptic density (PSD) fraction using biochemistry, though they are clearly also present in some axons.[50-52] A similar localization pattern has been observed across several studies of the γ-Pcdhs in forebrain, cerebellar, retinal and spinal cord neurons: These proteins are concentrated in synaptosomes and PSD fractions,[53-56] localized at some, but far from all, synapses,[53,55-58] and, while also present in axons, observed prominently in dendrites.[55,56,58-61] Though the β-Pcdhs have been studied far less than their clustered brethren and no functional analysis has yet been published, it was shown that β16 and β22 demonstrate a similar preferential localization to dendritic and PSD compartments in retinal and cerebellar neurons.[62,63]

Though the initial analyses of *Pcdhg* mutant mice by our lab and others focused on roles for these proteins in regulation of neuronal apoptosis and synaptogenesis,[53,57,58,64-68] a major role for the γ-Pcdhs in dendrite arborization has recently emerged (**Table 1**). Using cortically-restricted *Pcdhg* mutant mice, we found that the γ-Pcdhs are essential for the formation of properly complex dendritic arbors in cortical pyramidal neurons.[69] The *Pcdhg* mutant cortex appears to develop normally in terms of neurogenesis, neuronal migration, and establishment of major axonal tracts, but reduced arborization of pyramidal neurons leads to a thinner cortex, primarily due to loss of the cell-sparse, apical dendritic tuft-rich layer I. This is accompanied by

Table 1. Clustered Protocadherin Dendritic Roles

Gene Symbol	Name	Reported Dendritic Role	References
PCDHA	α-Protocadherins	PCDHA knockout results in decreased dendrite arborization and spine loss in hippocampal neurons, *in vivo* and *in vitro*. This arborization defect was dependent on PYK2/Rho/Rac pathway as PYK2 knockdown and constitutively active Rac1 rescued the phenotype while PYK2 overexpression reduced arbors.	Suo, et al., 2012
PCDHB	β-Protocadherins	β16 and β22 localizes postsynaptically in retinal and cerebellar neurons. As of yet, no functional data published.	Junghans, et al., 2008; Puller and Haverkamp, 2010
PCDHG	γ-Protocadherins	γ-Pcdhs are found at dendro-dendritic and axo-dendritic appositions, with significant portions retained intracellularly in compartments rich in COPII and ERGIC vesicles. γ-Pcdh staining colocalizes with both calnexin (ER protein) and COPII puncta, and is found in tubulovesicular structures in dendrites.	Fernandez-Monreal et al., 2009, 2010
		γ-Pcdh knockout reduces dendritic arborization in apical and basal dendrites of cortical layer V pyramidal neurons. γ-Pcdh inhibition of a FAK/PKC/MARCKS pathway allows for normal arborization, as γ-Pcdh loss results in aberrant upregulation of this pathway.	Garrett et al., 2012
		γ-Pcdh knockout in retinal starburst amacrine cells (SACs) and cerebellar Purkinje cells leads to aberrant self-crossing of dendrites isoneuronally. Single γ-Pcdh isoform expression rescues this self-avoidance defect, but leads to aberrant heteroneuronal avoidance of SAC dendrites.	Lefebvre, et al., 2012
		γ-Pcdh knockdown of hippocampal neurons in vitro results in reduced dendritic arborization as well as activation of PYK2 and FAK and increased Rho inhibition. Constitutively active Rac1 rescues this phenotype.	Suo et al., 2012
		γ-Pcdh knockout in individual subventricular zone progenitor cells causes a reduction in dendritic arborization and loss of dendritic spines in olfactory bulb granule cells derived from these cells.	Ledderose et al., 2013
		γ-Pcdh-mediated Purkinje cell self-avoidance was shown to be genetically independent of similar slit/robo-mediated self-avoidance.	Gibson, et al., 2014
PCDHA, B, and G	All clustered Protocadherins (and/or possibly other genes affected by manipulation)	Dnmt3b methylation of PCDHA and selected PcdhB/G promoters determines expression frequency of α-Pcdhs within Purkinje neurons. Cell specific knockout of Dnmt3b decreases methylation and increases frequency of expression leading to self-avoidance defects in Purkinje cell dendritic arbors. May be due to non-Pcdh gene disruption as well.	Toyoda, et al., 2014
		CTCF knockout cortex exhibited decreased PCDHA, PCDHB, and PCDHG expression, as well as a reduction of arborization of both apical and basal dendrites. Dendritic spines were also reduced in these neurons, and hippocampal neurons also had reduced dendritic arbors. May be due to non-Pcdh gene disruption as well.	Hirayama, et al., 2012

aberrantly high activity in a signaling pathway leading from FAK, which is known to be inhibited through binding to the γ-Pcdh constant cytoplasmic domain,[70] to PKC and its phosphorylation target MARCKS.[69] In *Pcdhg* cortical mutants, FAK and MARCKS are hyper-phosphorylated and PKC enzymatic activity is increased, all of which is consistent with prior studies of the roles played by these proteins in dendrite arborization.[71-76] Confirming that this aberrant signaling pathway is the cause of

reduced dendrite arborization, *Pcdhg* mutant neurons can be rescued by pharmacological inhibition of FAK or PKC, or by transfection with a non-phosphorylatable MARCKS mutant.[69]

Complementary concurrent work from Qiang Wu's laboratory confirms the importance of γ-Pcdhs in dendrite arborization, and strongly implicates the α-Pcdhs as well.[77] Analyzing *Pcdha* mutant hippocampal neurons both *in vivo* and *in vitro*, Suo et al.[77] show that mutants exhibit simplified dendritic arbors as well as significant loss of dendritic spine density; the effects, interestingly, are somewhat less severe than those obtained by using RNAi to knockdown γ-Pcdh levels in cultured neurons. As observed previously for *Pcdhg,*[69,70] deletion of the *Pcdha* cluster leads to aberrantly active (i.e., tyrosine-phosphorylated) FAK and the homologous kinase PYK2/FAK2 in the brain. Dendritic arbor and spine defects similar to those observed in *Pcdha* mutant neurons are found in wild-type neurons overexpressing PYK2, and mutant neuron defects can be rescued by knocking down PYK2 using RNAi. Using pharmacological inhibitors and constitutively active protein mutants, Suo et al.[77] go on to show that the Rho GTPase Rac1 is a positive downstream regulator of dendrite development that is normally inhibited by PYK2. Additionally, lentiviral-mediated Cre-driven *Pcdhg* mutation in progenitor neurons of the subventricular zone, as reported in Ledderose et al.,[78] led to a reduction in dendritic arborization and in dendritic spine density in the olfactory bulb neurons derived from these progenitors. Together with the results of Garrett et al.,[69] these data provide strong support for the importance of clustered Pcdhs to the elaboration of complex dendrite arbors and the proper density of postsynaptic spines.[70,77,78] This work, building on the initial observation by Chen et al.[70] that the α- and γ-Pcdh constant domains bind to, and inhibit, FAK and PYK2, also confirms the importance of this kinase family in linking cell adhesion molecules at the membrane to regulation of multiple downstream signaling pathways that influence cytoskeletal rearrangements necessary for the formation of complex neuronal morphologies.

Though studies using heterologous cell *in vitro* assays indicate that the γ-Pcdhs can mediate homophilic cell adhesion,[44,48] it should be noted that many initially adhesive events at the cell surface of neurons can lead to subsequent repulsion in the proper signaling context. This occurs, for example, in the action of the immunoglobulin superfamily molecule DSCAM, which interacts homophilically to signal repulsion of contacting axon and dendrite branches, mediating a process called self-avoidance that is critical for the function of many neurons whose arbors must spread out to cover an appropriate receptive field.[79-82] Mutation of *Dscam* genes in both *Drosophila* and mice leads to aberrant self-crossing and fasciculation of dendrites and clumping of cell bodies.[83-87] Intriguingly, Lefebvre et al.[88] have demonstrated that in at least 2 neuronal subtypes, retinal starburst amacrine cells (SACs) and cerebellar Purkinje cells, loss of the γ-Pcdh proteins leads to an aberrant self-crossing phenotype similar to that observed in *Dscam* mutants.

Turning on a Cre-inducible transgene expressing a single γ-Pcdh isoform can cell-autonomously restore proper self-avoidance in a mutant SAC, but when 2 SACs expressing only this single isoform meet, they aberrantly avoid each other.[88] This suggests that, at least in neurons with planar dendritic arbors such as SACs and Purkinje cells, the γ-Pcdhs mediate repulsive interactions in a manner similar to Dscam1 in *Drosophila*. Recent work from the lab of Le Ma indicates that γ-Pcdh-mediated self-avoidance in mouse Purkinje cell dendrites is genetically independent of a similar self-avoidance role played by Slit/Robo signaling.[90] It should be noted that no obvious self-avoidance phenotypes are observed in the non-planar, bushy dendritic arbors of cortical neurons in the absence of the γ-Pcdhs,[69] nor are they immediately apparent in other, non-SAC retinal neurons.[58] However, the aberrantly clumped axon terminals we previously observed in *Pcdhg* mutant Ia afferent sensory neurons in the spinal cord[89] could be consistent with disrupted self-avoidance, a possibility that remains to be addressed. In any case, it appears that *Pcdhg* mutant dendrite phenotypes vary among distinct neuronal subtypes. A key question going forward will be to directly assess whether homophilic γ-Pcdh interactions can result in both adhesion or repulsion, as appears to be the case. If so, it is likely that distinct *cis*-membrane or cytoplasmic signaling partners can modulate the outcome of γ-Pcdh *trans*-interactions, and these remain to be identified.

Recent studies of mouse mutants in 2 gene regulatory proteins have also indirectly implicated the clustered Pcdhs in dendrite development. Binding sites for the zinc finger transcription factor/insulator protein CTCF are found at many sites within the 3 *Pcdh* gene clusters, and CTCF positively regulates the expression of these genes in a variety of cell lines.[36,91-93] Hirayama et al.[94] analyzed a forebrain-restricted conditional CTCF knockout mouse and found reduced cortical and hippocampal neuron dendrite arborization similar to that observed by Garrett et al.[69] and Suo et al.,[77] as well as disrupted barrel formation in somatosensory cortex. Microarray analysis showed significant downregulation of nearly all *Pcdha, Pcdhb,* and *Pcdhg* genes, which is consistent with the demonstrated roles for these proteins in dendrites; it should be noted, however, that 390 genes were significantly altered in the CTCF mutant forebrain, so it is possible that disruption of other genes also contributed to the observed phenotypes.[94] In a separate study, it was found that embryos lacking the DNA methyltransferase Dnmt3b exhibit hypomethylation of the clustered Pcdh genes.[95] Loss of Dnmt3b cell-autonomously leads to aberrantly constitutive expression of many normally stochastically-expressed Pcdh genes, and disrupted dendrite arborization, including reduced branch number and length as well as increased self-crossing, in Purkinje cells.[95] Though, again, it is likely that expression of many other genes are aberrant in the absence of Dnmt3b, these results are consistent with a major role for the clustered Pcdhs in the formation of proper dendritic arbors.

Non-clustered δ-Protocadherins

The largest group of non-clustered Pcdhs is made up of the δ1 (7 EC domains) and δ2 (6 EC domains) families, which are distantly related but exhibit short conserved motifs in their

cytoplasmic domains (**Fig. 1**).[96,97] One of the first Pcdhs to be identified 20 y ago was a δ1, Pcdh1 (initially termed Pc42);[26] subsequently the δ1 family was expanded to include Pcdh7, Pcdh9, and Pcdh11, while the δ2 family encompasses Pcdh8, Pcdh10, Pcdh17, Pcdh18, and Pcdh19.[15] All of the δ-Pcdhs are expressed in the nervous system, with some (e.g., Pcdh10, also known as OL-Pcdh) marking particular subsets of regions and circuits (reviewed in ref. 12). Though several δ-Pcdhs have been reported to exhibit homophilic adhesion (e.g., Pcdh10,[98] Pcdh8,[99] Pcdh17,[100] and Pcdh19[101]), like the clustered Pcdhs this is generally considered to be modest in comparison to the classical cadherins.[12] Several δ-Pcdhs partner in *cis* with classical cadherins to regulate adhesion: Pcdh8 (also known as paraxial protocadherin in *Xenopus* and Arcadlin in mammals) antagonizes adhesion by C-cadherin[102] and induces the internalization of N-cadherin at synapses in response to increased electrical activity,[103] while Pcdh19 can mediate homophilic adhesion only when in a *cis*-complex with N-cadherin, and this interaction actually precludes homophilic adhesion through N-cadherin itself.[104,105] While several of the δ-Pcdhs play interesting roles in axon guidance, and/or have been implicated in various cancers (reviewed in ref. 15), only a few studies have demonstrated roles in dendrite development and/or dendritic spine function thus far (**Table 2**).

Pcdh7 is a δ1-Pcdh also known as NF-protocadherin in *Xenopus*, where it is expressed in retinal ganglion cells (RGCs) and their targets in the optic tectum. Expression of a dominant negative Pcdh7 lacking the extracellular domain in the retina led to significantly reduced RGC dendrite arborization, though it should be noted that the disruption of axonogenesis was far more severe.[106] Expression of a dominant-negative template-activating factor (TAF1), which despite being predominantly known as a nuclear protein is also found at the cell membrane where it binds to the C-terminus of Pcdh7, produced an exact phenocopy, suggesting that Pcdh7 acts through TAF1 to promote axonogenesis and dendrite arborization in RGCs.[106] Intriguingly, a meta-analysis of genome-wide association studies for human epilepsies recently implicated Pcdh7 as a potential risk factor for these disorders.[107]

The rat ortholog of the δ2-family member Pcdh8 was initially identified as Arcadlin in a screen for mRNAs rapidly induced in hippocampus following seizures.[99] The protein is found in cortical and hippocampal dendrites and co-localizes with the excitatory postsynaptic marker PSD-95 as well as with N-cadherin, but is also detected in axons and growth cones.[99,103] Pcdh8 can be co-immunoprecipitated with N-cadherin and blocks its homophilic adhesion in an *in vitro* assay. Homophilic interaction of Pcdh8 activates the kinase TAO2β, which in turn phosphorylates and activates p38 MAPK via another kinase, MEK3; this leads to the internalization of the Pcdh8/N-cadherin *cis*-complex, which limits dendritic spine density in hippocampal neurons. Consistent with this, Pcdh8 knockout neurons exhibit significantly increased spine density, but only in the presence of N-cadherin.[103] Though effects on dendrite arborization were not reported, these data demonstrate a role for Pcdh8 in the regulation of dendritic spine density and synaptogenesis, and demonstrate an important neuronal function for the observed *cis*-interactions between δ2-Pcdhs and classical cadherins.

Similarly, a prominent role at dendritic spines has been reported recently for the δ2 protein Pcdh10, also known as OL-Pcdh.[108] The activity-regulated transcription factor MEF2 (myocyte enhancer factor 2) had previously been shown to promote synapse elimination through a mechanism involving the translation-regulating RNA binding protein FMRP (fragile X mental retardation protein), encoded by a gene disrupted in the most common inherited cause of intellectual disability and autism, fragile X syndrome. Comparison of the known MEF2 target genes with the known FMRP-binding mRNAs identified Pcdh10, deletion of which has also been associated with autism.[109] Using cultured cortical neurons, Tsai et al.[108] found that shRNA knockdown of Pcdh10 prevented synapse elimination induced by introduction of constitutively-active MEF2. Active MEF2 leads to the ubiquitination (by the E3 ligase murine double minute 2) and proteosomal degradation of the spine protein PSD-95, and this mechanism depends on Pcdh10, which could be co-immunoprecipitated with both ubiquitinated PSD-95 and proteosomal components.[108] Together with the results of Yasuda et al.,[103] Tsai et al.[108] suggests that multiple δ2-Pcdhs

Table 2. Nonclustered Protocadherin Dendritic Roles

Gene Symbol	Name	Reported Dendritic Role	References
	δ1 (Delta 1) family		
PCDH7 (NFPC)	Protocadherin 7, NF-protocadherin (*Xenopus)*	Promotes retinal ganglion cell dendrite arborization, possibly through TAF1.	Piper, et al., 2008
	δ2 (Delta 2) family		
PCDH8	Protocadherin 8, Arcadlin (mammals), paraxial protocadherin (*Xenopus*)	Pcdh8 causes a decrease in spine number by activation of a MAPK pathway resulting in Pcdh8/N-cadherin endocytosis. Consequently, neurons cultured from Pcdh8 knockout mice have increased dendritic spines, but only when in the presence of N-cadherin.	Yasuda, et al., 2007
PCDH10	Protocadherin 10, OL-protocadherin	Pcdh10 knockdown prevented MEF2-induced synapse elimination. Pcdh10 is necessary for ubiquitination and proteosomal degradation of PSD-95, leading to spine loss.	Tsai, et al., 2012

can regulate synapse density and dendritic spine number, likely through promoting synapse elimination.

Fat and Dachsous Atypical Cadherins

The Fat and Dachsous (Ds) atypical cadherins were initially described in *Drosophila*, where they interact heterophilically to play important roles in tissue growth and patterning through the Hippo pathway, and in planar cell polarity (PCP), the process by which cells are directionally organized along the plane of a cell sheet, perpendicular to each cell's apical-basal axis; mammals have 4 homologous Fat genes (*fat1–4*; *fat4* is considered to be the ortholog of *Drosophila fat*) and 2 Dachsous genes (*Ds1* and *2*).[16] These genes encode very large type I transmembrane proteins, with Fat1–4 having 34 cadherin repeats and Ds1–2 having 27; Fat proteins also exhibit varying numbers of EGF-like and laminin-like domains (**Fig. 2**). Relatively little is known about the roles of Fat and Ds proteins in nervous system development, outside of the fact that the genes are expressed there (**Table 3**). The intracellular domain of Fat1 interacts with Homer scaffolding proteins, suggesting a possible synaptic role.[110] This possibility has yet to be addressed due to the perinatal lethality of *fat1* mutant mice, which present with kidney defects and partially-penetrant holoprosencephaly and anophthalmia;[111] *fat1/fat4* double mutants also exhibit a high incidence of exencephaly.[112] Fat2 is expressed by cerebellar Purkinje cells,[113] while Fat3 protein localizes to both axons and dendrites throughout the nervous system.[114]

One study has provided evidence that Fat3 is critical for the formation of dendritic arbors by amacrine cells of the retina.[115] Mature amacrine cells, situated in the inner nuclear layer or ganglion cell layer of the retina, exhibit a unipolar morphology, with a dendritic arbor projecting to distinct sublaminae within the synaptic inner plexiform layer. During development, however, their arbors are initially multipolar, with neurites pruned as the amacrine cells migrate into the inner nuclear layer. Deans et al.[115] show that in *fat3* mutant retina, this pruning process is defective, and some amacrine cells form 2 dendritic arbors: a

Table 3. Atypical Cadherin Dendritic Roles

Gene Symbol	Name	Reported Dendritic Role	References
FAT3	Fat3	In retinal amacrine cells, Fat3 regulates dendritic pruning. Fat3 knockout mice have defective pruning and exhibit a second, aberrant dendritic arbor projecting to an inappropriate layer.	Deans, et al., 2011
Fmi	Flamingo, starry night	*Fmi* is required for the extension of dorsal dendrites and the repulsion between dendrites of homologous multiple dendrite (md) sensory neurons.	Gao, et al., 1999,2000; Grueber et al., 2002; Sweeney, et al., 2002; Kimura, et al., 2006
		Fmi does not act through frizzled to regulate dendritic tiling. *Fmi* mutants showed overextension into adjacent dendrites potentially mixing their dendritic fields.	
		Fmi controls the timing and extent of dendrite arborization of md neurons.	
		Fmi has a dual molecular function that intially controls dendrite extension followed by avoidance between dendritiC-terminals.	
		Dendrites of the drosophila mushroom body neurons (CNS) show overextension phenotypes similar to that of md neurons (PNS).	Reuter, et al., 2003
		Fmi overexpression enhances the negative regulation of dendrite outgrowth mediated by Gogo.	Hakeda-Suzuki, et al., 2011, 2013
		Dendritic self-avoidance of Drosophila sensory neurons requires *fmi* and Espinas.	Matsubara, et al., 2011
Celsr2	Cadherin EGF LAG 7-pass G-type receptor (Celsr) 2	RNAi knockdown of Celsr2 leads to reduced complexity of dendritic arbors of cortical pyramidal neurons and cerebellar Purkinje neurons.	Shima, et al., 2004
		RNAi knockdown indicates that Celsr2 normally functions to enhance neurite outgrowth. In vitro gene silencing and coculture assays showed reduced neurite outgrowth and dendrite arborization.	Shima, et al., 2007
Celsr3	Cadherin EGF LAG 7-pass G-type receptor (Celsr) 3	RNAi knockdown indicates that Celsr3 normally functions to suppress neurite growth. In vitro gene silencing and coculture assays showed increased neurite outgrowth and dendrite arborization. The opposite effects of Celsr 2 and 3 are controlled by a single amino acid difference in a cytoplasmic loop.	Shima, et al., 2007

proper one within the inner plexiform layer, and an aberrant one facing the opposite direction within the inner nuclear layer, forming a supernumerary plexiform layer. Though it is not known whether Fat3 interaction with Ds1 or 2 is important for this role, it was shown that *Fjx1*, the mammalian homolog of *Drosophila 4-jointed*, a Golgi-kinase that can modulate Fat-Ds binding,[16] interacts genetically with *fat3*. *Fat3* heterozygotes that also carry a homozygous mutation in *Fjx1* exhibit a mild phenotype, consistent with the fact that *Drosophila* Fj typically promotes Fat signaling.[115] Consistent with this is the prior demonstration that *Fjx1* can negatively regulate dendrite extension and branching in hippocampal neurons.[116] This suggests a possible role for *Ft/Ds* signaling in the regulation of dendrite arborization in a variety of neuronal types, which remains to be shown directly.

7TM Atypical Cadherins

Along with the clustered Pcdhs, the 7TM atypical cadherins, which include Flamingo in *Drosophila* and its mammalian homologues Celsr1–3 (**Fig. 2**),[17,18] play perhaps the best-characterized roles in axon and dendrite development (**Table 3**). Most of these were first uncovered for *Drosophila flamingo (fmi)*, which like *ft* and *ds* is also known for roles in PCP. Subsequent analyses of rodent *Celsr* genes have shown that many of these functions in neurite development are evolutionarily conserved. The structure of the 7TM cadherins sets them apart from other members of the family: They each contain 7 transmembrane domains similar to G-protein-coupled receptors (GPCRs) of the secretin receptor family, a hormone receptor domain, 2 laminin-G-like domains, varying numbers of EGF-like domains, and 9 cadherin repeats situated at the N-terminus (**Fig. 2**).[18] Cell aggregation assays using *Drosophila* S2 cells indicate that Fmi/Celsr proteins engage in homophilic adhesion that is dependent on the presence of the cadherin repeats.[117-119] While it is unclear whether Fmi or the Celsrs act as true GPCRs, some mutant phenotypes (see below) can be rescued by constructs lacking much of the extracellular region (including the cadherin repeats),[120] and Celsr cadherin repeat binding can trigger intracellular Ca^{2+} release,[121] suggesting that these proteins are capable of mediating signaling as well as adhesion. While we focus here only on dendritic functions, we note that both Fmi and Celsr1–3 have been shown to play critical roles in axon outgrowth and guidance in a number of studies of multiple neuronal types (e.g. in refs. 122–126; reviewed in ref. 18).

Fmi (a.k.a. *starry night*) was initially cloned by Chae et al.[118] and Usui et al.,[117] in studies that identified a role in PCP of the wing in collaboration with *frizzled*, the receptor for Wg/Wnts. Concurrently, it was isolated in a mutagenesis screen for genes affecting dendritic patterning in md (multiple dendrite) sensory neurons, in which *fmi* mutant neurons exhibited excessive growth of dorsal dendritic arbors.[127] A follow-up study[128] showed that both loss and gain of function of *fmi* leads to overextension of dorsal md dendrites and an aberrant lack of repulsion between 2 md dendritic fields when they meet at the midline. In contrast to its role in PCP, *fmi* appears to act independently of *frizzled*[128] to regulate the proper timing and extent of dorsal dendrite arborization in md neurons,[129] though. Grueber et al.[130] showed that the da (dendritic arborization) subset of md neurons exhibits a phenomenon called "tiling," the complete coverage of a receptive area by dendritic branches without any overlap of branches from adjacent neurons of the same class. It was shown that *fmi* mutant da dendrites occasionally disrupted tiling by extending into neighboring territories. A screen for defects in mushroom body neurons also identified a dendritic over-reach phenotype in *fmi* mutants, extending the role of this gene to CNS neurons.[131]

Through what mechanisms does *fmi* regulate dendrite extension and branching in *Drosophila* neurons? Kimura et al.[120] performed a structure-function analysis and found that the overgrowth of da neuron dendrites seen in *fmi* mutants could be partially rescued by an *fmi* transgene lacking the N-terminal cadherin repeats and EGF domains, but not by one lacking the C-terminal cytoplasmic tail. The aberrant dorsal *overlap* of adjacent dendrites, however, was not rescued by either construct, suggesting that the cadherin repeats, required for adhesion, are also required for subsequent heteroneuronal avoidance.[120] In some of its functions, *fmi* collaborates with Golden Goal (Gogo), a single-pass transmembrane protein that interacts with Flamingo in *cis*. In addition to conferring laminar synaptic specificity of R8 photoreceptor axons,[132] *gogo* regulates dendrite arborization in md-da neurons in collaboration with *fmi*. Hakeda and Suzuki[133] recently presented evidence that Gogo can negatively regulate dendrite outgrowth, possibly by responding to an inhibitory cue from the midline, and this can be enhanced by overexpression of *fmi*. Tiling involves repulsive self-avoidance of isoneuronal dendritic branches, which allows for the proper spread of a neuron's dendritic field. Matsubara et al.[134] show that class IV da neurons lacking *fmi* exhibit defective self-avoidance, manifested as increased self-crossing of dendritic branches. The LIM domain protein Espinas binds to an intracellular juxtamembrane domain of Flamingo, and this interaction is required for proper isoneuronal dendritic branch repulsion.[134]

While Flamingo is generally a negative regulator of dendritic growth in *Drosophila* neurons, the different mammalian Celsr proteins have diverged in function. Shima et al.[119,121] have revealed opposing roles for Celsr2 and Celsr3 in the regulation of dendrite arborization by using RNAi knockdown in organotypic brain slice cultures. Knockdown of Celsr2 leads to greatly reduced dendrite arborization in both cortical pyramidal neurons and cerebellar Purkinje cells. This knockdown phenotype could be rescued by re-expression of a Celsr2 construct lacking the EGF and hormone receptor domains, but not by constructs lacking the cadherin repeats or the Celsr2B splice variant lacking a portion of the C-terminal cytoplasmic domain.[119] In contrast, knockdown of Celsr3 had the opposite effect: dendrite arborization was increased, with more basal dendrites and greater branching complexity.[121] These experiments, as well as those co-culturing neurons with non-neuronal cells expressing individual Celsr proteins, indicate that Celsr2 promotes, while Celsr3 inhibits, dendrite growth and arborization. Through elegant use of chimeric Celsr2/3 molecules, Shima et al.[121] surprisingly show

that this functional reversal is controlled by a single amino acid in the cytoplasmic loop between TM1 and TM2. Flamingo, Celsr1, and Celsr3 share a conserved histidine in this domain, while Celsr2 uniquely has an arginine residue at this position. Neurons expressing Celsr2 exhibit longer neurites than controls when cultured with non-neuronal cells expressing Celsr2, but neurons expressing Celsr2 with the arginine mutated to a histidine exhibit *shorter* neurites than controls. Conversely, neurons expressing Celsr3 exhibit shorter neurites than controls when cultured with non-neuronal cells expressing Celsr3, but neurons expressing Celsr3 with the histidine mutated to an arginine exhibit *longer* neurites than controls.[121] In all cases these effects required homophilic matching between cadherin repeats present either in co-cultured cells or as soluble ectodomain proteins. Shima et al.[121] go on to present evidence that Celsr2 exerts its effect on dendrite growth through CaMKII while Celsr3 acts through calcineurin. Together these data support an evolutionarily conserved role for Flamingo and the Celsrs in the control of dendrite arborization, and uncover a fascinating divergence of function among the Celsrs due to a single amino acid difference that affects downstream signaling.

Concluding Remarks

Though Pcdhs were first identified in 1993, their first *in vivo* functions were not demonstrated until nearly a decade later, and only in the past few years have the molecular mechanisms underlying their *cis* and *trans* interactions and their intracellular signaling begun to be elucidated. As this review of the literature demonstrates, we are in a period of rapid growth in the understanding of this intriguing family of molecules, and, in particular, in the discovery of their important roles in the formation of neuronal circuitry during development, particularly in regulating the arborization of dendrites. Though the sheer diversity of the molecules discussed under the "Pcdh" (and atypical cadherin) banner ensures that many mechanisms will be unique to each family, subfamily, or even individual protein, we note here a few unifying points for future research.

First is the importance of Pcdh/atypical cadherin intracellular signaling, outside of any adhesive role they may have. For instance, the 7TM cadherins can clearly act as signaling receptors, even if not as *bona fide* G-protein coupled receptors (which remains unclear); the clustered Pcdhs can regulate adhesion and cytoskeleton-associated kinase pathways involving FAK, PYK2, and Rac1; some δ-Pcdhs such as Pcdh8 can activate kinases (such as TAO2β) to initiate cascades of intracellular signaling; and other δ-Pcdhs such as Pcdhs 10, 17, and 18b interact with Nap1 and the WAVE complex to regulate actin dynamics.[142-144] It is not clear in many cases whether such signaling is regulated constitutively by Pcdhs, or whether it is initiated upon homophilic *trans*-interactions, a key question that should be addressed in the future. Similarly, though progress has been made as described above, we still know relatively little about the intracellular binding partners and signaling pathways affected by many of the Pcdhs. Screens for Pcdh protein interactors should open up new vistas into the roles of these CAMs in neural development.

Second is the apparent dual adhesive function of the Pcdhs, in which depending on the cell type and situation, they can mediate attractive adhesion between cells, repulsive signaling among processes of the same neuron, or primarily affect the adhesion of other CAMs. This is most striking for the γ-Pcdhs, which can mediate adhesion as well as self-avoidance, but is also true for some of the δ-Pcdhs, which predominantly modulate adhesion of classical cadherins, as well as for Flamingo. It is possible that a switch from a primarily attractive adhesive event, to a repulsive event following initial adhesion, could be mediated by *cis* interactions with different partners at the membrane. In this way, certain Pcdhs could have distinct cellular effects in different neuronal subtypes depending on which interaction partners are present. Again, further identification of Pcdh-interacting proteins, particularly by focusing on distinct brain regions or neuronal cell types, will be helpful in this regard.

Third is the intriguing fact that all of the Pcdh families discussed here have some reported link to signaling by the Wnt family of growth factors. Though Flamingo appears to influence dendrite branching and outgrowth without requiring Wnt pathway interaction in flies, it does collaborate with this pathway in PCP and a recent report in *C. elegans* suggest it may do so in neurite outgrowth as well.[135] Two recent reports indicate that several γ-Pcdhs can inhibit the Wnt pathway in multiple cancer cell types,[136,137] though the mechanisms involved are unknown, and any relevance to neuronal Wnt signaling is not established. Several δ-Pcdhs were isolated in a large screen for proteins interacting with the Wnt receptor RYK, though again, it remains to be confirmed whether any such interactions are meaningful in a neuronal context.[138] Nevertheless, as it is known that Wnt signaling can affect dendrite arborization[139,140] and synaptogenesis,[141] these hints of Pcdh-Wnt pathway interactions are worthy of further analysis in neuronal contexts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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