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Current Opinion in Neurobiology

Shaping dendrites with machinery borrowed from epithelia

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The ciliated receptive endings of sensory cells and the dendrites of other neurons are shaped by adhesive interactions, many of which depend on machinery also present in epithelia. Sensory cells are shaped by interactions with support cells through adhesion junctions via the Crumbs complex, tight junction components such as claudins, as well as interactions with apical extracellular matrix composed of zona pellucida domain proteins. Neuronal dendrites are shaped by adhesion machinery that includes cadherins, catenins, afadin, L1CAM, CHL1, Sidekicks, Contactin and Caspr, many of which are shared with epithelia. This review highlights this shared machinery, and suggests that mechanisms of epithelial morphogenesis may thus provide a guide to understanding dendrite morphogenesis.

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Current Opinion in Neurobiology 2013, **23**:1005–1010

This review comes from a themed issue on **Development of neurons and glia**

Edited by **Samuel Pfaff** and **Shai Shaham**

For a complete overview see the Issue and the Editorial

Available online 18th July 2013

0959-4388/$ – see front matter, Published by Elsevier Ltd.

http://dx.doi.org/10.1016/j.conb.2013.06.011

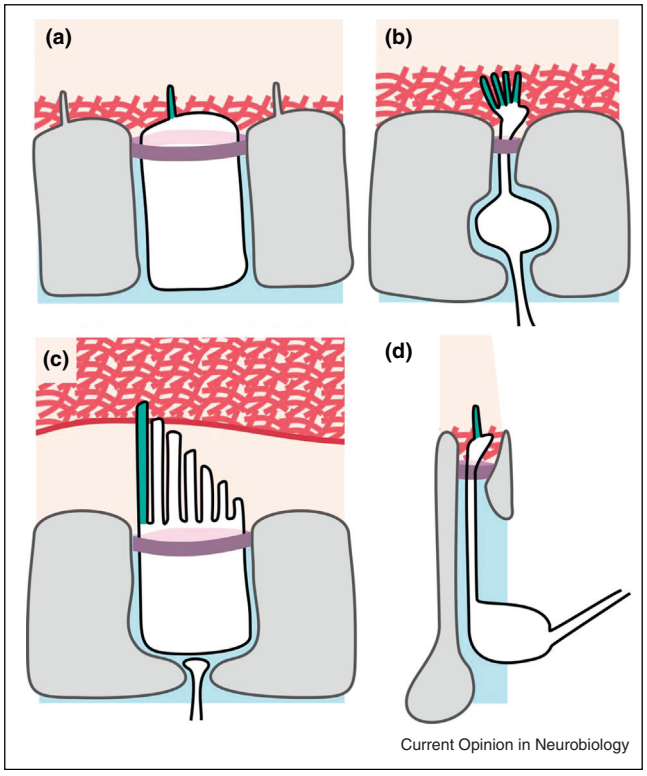
Epithelia are among the most ancient organizational units of multicellular life, possibly pre-dating the evolutionary divergence of animals, fungi and amoebae [1]. Thus, many of the mechanisms that coordinate cell morphogenesis in other cell types, including neurons, may have arisen first in epithelia. These sheets of cells line every surface of our bodies, and provide a barrier that separates an outward-facing apical compartment from an inward-facing basolateral compartment. The basal surface is marked by a well-characterized basement membrane, or basal lamina, composed of collagens, laminins, and nidogens; the apical surface is often decorated with sensory cilia that are used to monitor environmental conditions, and is coated with a specialized apical extracellular matrix (aECM), about which little is known. Apical-basal compartmentalization is accomplished by two large protein machines: adherens junctions, often composed of cadherins, which bind the cells together into a sheet; and tight junctions, often composed of claudins and occludins, which serve as a diffusion barrier between the two compartments. These complexes are coupled to intracellular regulators of cell polarity, notably the MAGUK family of proteins.

The vertebrate nervous system begins as a specialized epithelium, termed a neuroepithelium, that invaginates to form the neural tube, creating an apical lumen that will ultimately fill with cerebrospinal fluid (CSF). In the mature brain, this neuroepithelium lines the CSF-filled ventricles, and is the site from which most neurons arise. For these reasons, it has been said that 'phylogenetically and developmentally, the brain is an epithelium' [2]. This is a powerful idea, because it implies that neuronal development can be understood in terms of established mechanisms of epithelial development. Indeed, proteins that are trafficked to the apical or basal surfaces of epithelia are trafficked to axons or dendrites, respectively, when expressed in neurons [3]. However, while some neurons inherit their polarity from their neuroepithelial precursors, others do not [4], and it has proven difficult to assign a purely apical or basal cell biological identity to axons or dendrites [5]. Here, we will set aside the question of polarity, and focus instead on parallels between adhesion machines found in epithelia and those that shape dendrites.

True epithelia: shaping the receptive endings of sensory cells

Because epithelia form the interface between an organism and its environment, it is not surprising that they have been modified to generate most sense organs. Sensory cells such as photoreceptors, auditory hair cells, gustatory cells, olfactory receptor neurons, and skin receptors, as well as invertebrate sense organs, are all within true epithelia (Figure 1). In these tissues, junctional complexes between sensory and supporting cells generate a continuous sheet. As in other epithelia, the apical surfaces of sensory cells are decorated with modified cilia, such as the rods and cones of photoreceptors. Hair cells in the inner ear and gustatory cells in the tongue have a morphology similar to that of a traditional epithelial cell, while olfactory sensory neurons have a bipolar morphology with a well-defined dendrite and an axon that extends into the brain, and are thus considered 'true neurons' [6]. Yet, they are no less epithelial: ultrastructural analysis and immunolabeling of the olfactory epithelium reveals conventional tight and adherens junctions between olfactory sensory neurons and their supporting cells [7] (Figure 1b). The supporting cells, such as sustentacular cells in the olfactory epithelium and

Figure 1



Schematics of **(a)** canonical epithelium, **(b)** olfactory sensory neuron, **(c)** hair cell of the inner ear, and **(d)** amphid chemosensory neuron of *C. elegans*. In each case, an outward-facing apical compartment (pink) is separated from an inward-facing basal compartment (blue) by cell junctions (purple). The apical surface is decorated with a non-motile primary cilium (green) and lined by apical extracellular matrix (aECM, red).

Deiters' cells of the inner ear, are sometimes referred to as glia and share properties with astrocytes [8]. Thus, sensory cells and support cells can be viewed as an epithelium composed of neurons and glia.

Consistent with this idea, the machinery of epithelial morphogenesis is repurposed by sensory cells to shape their receptive surfaces, which can be dendrites, cilia, or some combination. For example, the Crumbs complex was first identified as an apical polarity cue required for the organization of epithelial cells [9] and was later shown to be required for *Drosophila* photoreceptor morphogenesis due to its crucial role in forming the light-sensitive apical membrane domain [10,11]. Remarkably, overexpression of the cytoplasmic portion of Crumbs is sufficient to induce the formation of ectopic light-sensitive domains, showing it actively shapes this receptive surface [12•]. As in other epithelia, it normally acts through adhesion: Crumbs and its binding partner Stardust act in different photoreceptor subtypes to regulate adherens junction formation in *Drosophila* [13•] and the extracellular domain of Crumbs mediates adhesion between photoreceptors and Müller glia in zebrafish [14•]. Photoreceptor cells also borrow epithelial machinery for secretory trafficking [15], actin-microtubule cross-linking [16], the distribution of cell adhesion molecules [17], and other aspects of polarization (reviewed in [18]).

Mechanisms first identified in epithelia affect the development and function of other sense organs as well. For example, the planar cell polarity machinery was identified in epithelia such as the *Drosophila* wing, and was later shown to pattern hair cells in the inner ear [19]. The tight junction machinery that maintains diffusion barriers in epithelia also acts in hair cells to maintain distinct ionic environments in the apical and basolateral compartments, with mice defective in the tight junction component claudin becoming deaf due to toxic leakage of potassium ions [20]. Loud noises can rupture this epithelial permeability barrier, and its loss may therefore play a role in noise-induced deafness [21]. Importantly, interactions with epithelial neighbors provide more than structural roles: the glial-like supporting cells of the inner ear regulate synapse formation by secreting BDNF [22] and eliminate dying hair cells by excision and phagocytosis [23], possibly similar to remodeling mechanisms found in other epithelia.

Finally, we and others have shown that the receptive endings of many sense organs are coated in a specialized aECM composed of proteins with a zona pellucida (ZP) domain. ZP domain proteins were first identified in the mammalian egg coat, but have since been found at the apical surfaces of nearly all animal epithelia examined. Despite their prevalence, they have no known shared function. Structurally, the ZP domain is a polymerization module that self-assembles into a filamentous matrix [24]. Intriguingly, almost all sense organs express a ZP domain protein: α-tectorin and β-tectorin in the inner ear [25], olfactorin in the olfactory epithelium [26], vomeroglandin in the pheromone-responsive vomeronasal organ [27], and ebnerin in taste buds [28]. We showed that the ZP domain proteins DYF-7 [29] and FBN-1 (unpublished) are required to shape dendrites in the major *Caenorhabditis elegans* sense organ, the amphid.

In wild-type *C. elegans*, amphid sensory neurons extend unbranched dendrites to the nose tip, where their ciliated endings form junctions on a glial cell called the sheath (Figure 1d). The sheath, in turn, forms junctions on a second glial cell called the socket. We found that amphid dendrites normally arise by a process we call retrograde extension, in which the neuron is born at the nose tip, adheres there, and then the cell body migrates away, stretching out a dendrite behind it [29]. In the absence of DYF-7, the presumptive dendrite is dragged behind the migrating cell body, resulting in severely shortened dendrites that fail to extend to the nose tip [29]. These

shortened dendrites maintain their junctions with the sheath, but the dendrites and sheath together are dissociated from the socket, suggesting that the aECM may be required to prevent rupture of glial cell junctions that normally maintain the integrity of this sense organ during morphogenesis (Williams and Heiman, unpublished). Consistent with this notion, aECM prevents rupture of cell junctions in other epithelia as well [30••].

The machinery of epithelial adhesion also shapes neuronal dendrites

Unlike sensory cells, most mature neurons (or their precursors) detach from their parent neuroepithelium, in a process called delamination. Delamination depends on downregulating N-cadherin: neurons that fail to downregulate N-cadherin maintain inappropriate apical attachments to the neuroepithelium, while experimentally inactivating N-cadherin causes precocious loss of apical attachments [31•]. Paradoxically, although loss of cadherin is a key step in neuronal maturation, recent work has shown that mature neurons continue to use cadherin and other epithelial adhesion machinery to shape their dendrites.

For example, the atypical cadherin Fat3 mediates adhesion among amacrine cell dendrites in the retina to regulate dendrite number and targeting [32•], while a large family of cadherin-related proteins, the protocadherins, act in dendrite tiling (reviewed elsewhere in this issue). N-cadherin itself is used to restrict the dendrites of each *Drosophila* olfactory projection neuron to a single glomerulus [33], and is also required in the mammalian hippocampus for normal dendrite arborization [34]. In cultured hippocampal neurons, dendrites grow in response to depolarization, and this growth requires N-cadherin, correlates with increased cadherin/catenin complexes, and is dependent on cell–cell contact [35], suggesting that N-cadherin is acting in its canonical role as part of an epithelial-like adhesion machine.

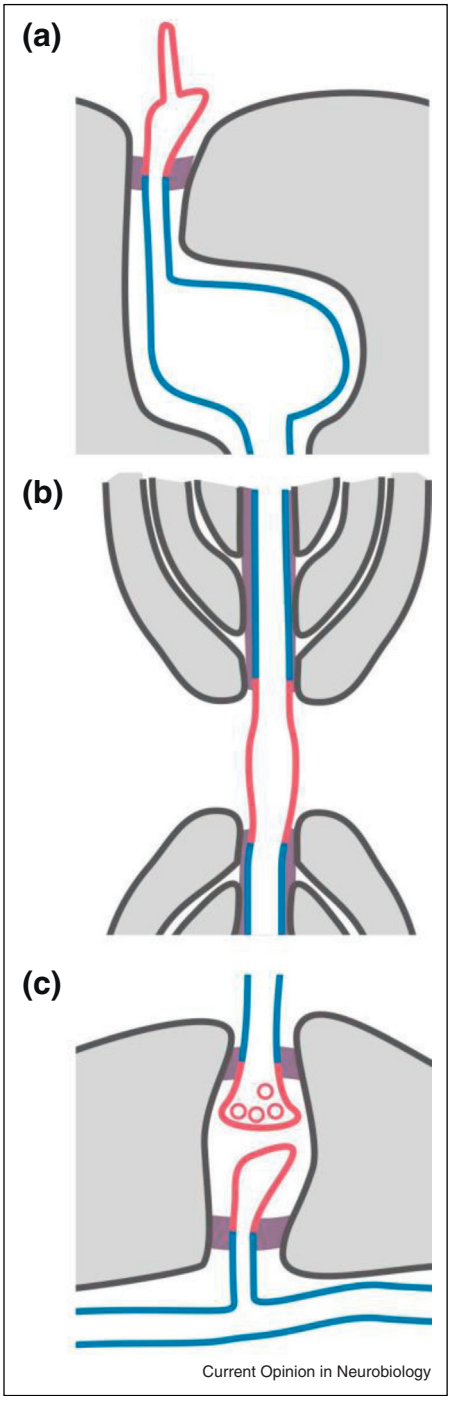
Indeed, additional components of the canonical epithelial adhesion machinery are implicated in dendrite morphogenesis. The maintenance of cortical dendrites and spines requires δ-catenin, which interacts with cadherins at epithelial adherens junctions [36]. Similarly, afadin, a scaffolding protein that directly associates with epithelial cadherin/catenin complexes, is required to maintain dendritic fields [37]. Members of the cadherin–catenin pathway are also involved in regulating the morphology of dendritic spines [38–40]. An important question is whether these examples involve the formation of bona fide epithelial-like adherens junctions in neurons, or if individual components of the adhesion machinery are repurposed in novel contexts.

The arrow of history has also pointed the other way, with classical neuronal adhesion molecules later becoming appreciated as components of the epithelial adhesion machinery. The immunoglobulin superfamily (IgSF) protein L1CAM, in particular, was initially identified as a neuronal adhesion molecule [41]. The *Drosophila* L1CAM homolog, neuroglian, promotes branching of sensory dendrites in the larval body wall [42], and region-specific endocytosis of neuroglian appears to be a mechanism by which dendrite branching patterns are dynamically altered [43•]. In mammals, the L1 family member CHL1 is expressed in neurons, astrocytes, and oligodendrocytes in areas including cortex, hippocampus, and cerebellum [44]. It is required in the cortex for the orientation and branching of the dendrites of pyramidal neurons [45–47] and in the cerebellum for interaction between Purkinje neurons and Bergmann glia, which promotes proper dendritic targeting [48]. Interestingly, L1CAM was later found to be widely expressed in epithelia, including skin, lung, intestine and kidney, as well as sensory epithelia [49,50]. Likewise, the *C. elegans* homolog SAX-7 was identified for a neuronal role in axon guidance [51], but is also expressed in epithelia where it acts at sites of cell contact to maintain tissue attachment [52,53]. Recent work has shown that SAX-7 acts in concert with the MAGUK family protein MAGI-1 and the cadherin–catenin complex to maintain epithelial apical junctions in the skin during embryonic enclosure [54••]. These results lead to the speculation that L1CAMs and cadherin-containing complexes might act cooperatively in dendrites, as they do in epithelia.

There are hints that other IgSF adhesion molecules important in dendrite morphogenesis may also play parallel roles in epithelial adhesion. Dscam and Sidekick control dendrite targeting of retinal ganglion cells in the inner plexiform layer of the retina [55]. Similar to L1CAM, Sidekick-2 interacts with MAGUK family proteins, and this interaction is necessary for dendrite targeting [56]. Sidekick proteins exhibit widespread expression that includes epithelial tissues; in particular, Sidekicks are upregulated in kidney diseases and are associated with defects in renal morphology [57]. Recent work has also implicated another class of IgSF adhesion molecules, the contactins, in retinal dendrite targeting [58], and contactins are expressed in epithelial tissues such as lung and kidney [59]. Likewise, Casprs are neurexin family members that bind contactins, are associated with autism spectrum disorders and are required for normal dendritic arborization and spine development in pyramidal neurons [60•]; they are also expressed along with contactins in epithelia [61].

These studies highlight the extensive overlap between epithelial adhesion machinery and proteins that mediate dendrite morphogenesis. We expect that these proteins act in neurons in their canonical roles known from epithelia, and vice versa — but, of course, there could be surprises. For example, in *C. elegans*, EFF-1 was found as an epithelial protein that mediates cell fusion [62], yet was later shown to regulate dendrite branching [63] in a

Figure 2



Three possible ways in which epithelial-like adhesion machinery could create specialized membrane subdomains in the nervous system: **(a)** support cells forming junctions on the ciliated receptive ending of a sensory cell; **(b)** myelinating glia forming junctions on an axon to create a node of Ranvier; **(c)** astrocytic glia forming junctions on an axon terminal and dendritic spine in a tripartite synapse configuration.

mechanism that does not seem to primarily involve fusion. Thus, a major future direction will be to determine if the adhesion proteins that shape dendrites are indeed acting in their epithelial roles as we predict, or if they are instead repurposed in unexpected ways.

Perspective

Here, we have reviewed evidence that epithelial adhesion molecules shape the receptive endings of sensory cells and the dendrites of other neurons. It would be exciting to extend these ideas to axons. Myelinating Schwann cells and oligodendrocytes have well-defined apical and basal domains [64], and their junctions with axons resemble epithelial cell junctions [65,66]. These ideas may even extend to chemical synapses: many synaptic scaffolding proteins resemble epithelial cell junction components, notably the postsynaptic density protein and MAGUK family member PSD-95 [67], and a glial-ensheathed dendritic spine resembles a sensory cilium [8]. Thus, the problem of assigning apical and basal identities to axons and dendrites might be discarded, and a new model proposed in which both axons and dendrites form specialized membrane domains using adhesion machinery borrowed from epithelia (Figure 2).

Acknowledgements

We thank Norbert Perrimon and Josh Sanes for thoughtful comments on the manuscript. This work is supported by a National Science Foundation predoctoral fellowship (IGM) and a March of Dimes Basil O'Connor Scholar Starter Award (MGH).

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- •• of outstanding interest

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