

Editorial

Neuronal Polarity and Neurological Disorders

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EDITORIAL

Neuronal cell function is largely dependent on polarity. Studies in the past decades indicate that the neuronal polarity machinery is one of the major targets of neurological disorders. Planar cell polarity (PCP) and apicobasal (AB) polarity modules were shown to be crucial for the establishment of neuronal polarity. Accordingly, neural tube defects (NTDs) have been associated with mutations in several polarity genes [1]. Similarly, genetic screening has identified several mutated genes that are associated with dysfunction of cytoskeletal components in Alzheimer's disease (AD) and Parkinson's disease (PD). Downstream of the polarity pathways, aggregations of misregulated cytoskeletal products are frequently observed in hereditary familial diseases such as AD and PD. Nonetheless, disruption of neuronal polarity-related cell functions including protein transportation and synaptic connections constitutes the main cause for the abnormal neural development and/or neuronal loss. As such, restoration of neuronal polarity in neurodegenerative diseases would potentially slow down or prevent neuronal degeneration over time.

An overview of neuronal polarity

In neuronal morphology, dendrites and axons are uniquely polarized to operate in opposing directions from the cell body. Dendrites collect incoming signals, while axons integrate and sending out responses. At the end of an axon is the synaptic terminal, where neurotransmitters are released and received by dendrites of a neighboring neuron it synapses with. It is through such polarized configurations that environmental stimuli are relayed to different locations throughout the nervous system and processed as sensory perceptions. Adapting to different tissue contexts, this neuronal blueprint could be significantly modified to meet specific requirements. For example, the hippocampal pyramidal neurons develop both basal and apical dendritic trees which receive distinct synaptic inputs [2]. Cellular compartments are also polarized along axons and dendrites with asymmetrically regionalized membrane proteins such as receptors and ion channels [3]. Compared to other cell types, the unique neuronal polarity endows a neuron with functional capacity to transfer information across long distances with high fidelity.

The establishment of neuronal polarity

To develop from a rounded precursor cell to a fully polarized neuron, the cytoskeleton and lipid membrane are actively

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rearranged and intracellular trafficking concurrently establishes cellular compartments. These processes are orchestrated through communications between extracellular signals and intracellular polarity machinery. Extracellular signals include growth factors such as NGF, BDNF, WNT, NETRIN and so forth [4]. Upon binding to their receptors, these secreted molecules trigger signaling cascades eventually leading to reorganization of membrane and cytoskeletal components, through which neuron shape is established.

Neuronal polarity modules share significant similarities with those of epithelial cells. Epithelial cells possess two-dimensional polarities, namely apicobasal (AB) and planar cell polarity (PCP). It is well recognized that epithelial AB polarity modules such as PAR3/PAR6/aPKC and PI3K/PIP2/AKT are essential for axon versus dendrite differentiation [5,6]. Small GTPases such as Cdc42 and RhoA are also involved in regulation of epithelial AB and neuronal polarity.

Planar cell polarity (PCP) modules have also been shown to be critical for neuronal polarity, especially for steering growth cone polarization, and hence pathfinding [7]. Two functionally overlapping yet distinct PCP modules have been characterized in mammals. The 'Core PCP' module first identified in the fly consists of six proteins (Frizzled/Van Gogh/Dishevelled / Flamingo/Prickle/Diego) [8]. Core PCP proteins provide vectorial guidance for polarization of epithelial cells orthogonal to the apicobasal axis. Mutations in *Fz3* and *Celsr* (homologues of *Frizzled* and *Flamingo*, respectively) in mouse led to cortical-thalamic tract defects. By in vitro assays, *Dvl* (mouse homologue of *Dishevelled*) and *Celsr* have been shown to be involved in dendritic arborization [9,10], and mouse *Prickle1* is crucial for axon-dendritic outgrowth as well [11]. Another PCP module, namely the 'Wnt/PCP' module, functions in directed cell migration through regulation some of the 'Core PCP' components. As such, Wnt5a treatment or overexpression of *Dvl* induces multiple axons in cultured neurons [12]. PCP also interacts with AB in variety of developmental processes to refine neuronal polarity during maturation.

Polarity machinery and neurological disorders

Gene mutations in a few of core PCP components including *VANGL1*, *VANGL2* and *PRICKLE1* have been found in patients with neural tube defects (NTDs). Mutations in *FUZZY* and *DACT1*,

two PCP-related genes have also been identified in sporadic NTDs (OMIM: <http://omim.org/entry/182940>). Interestingly, *Prickle1* has recently been associated with the neurological disorder myoclonic epilepsy [13]. Considering *Prickle1* function in axon and dendrite outgrowth [11], it is likely that neuronal polarity is compromised in *Prickle1* mutant neurons, which can lead to a number of consequences including aberrant synaptic connections.

Cytoskeleton and neurodegenerative diseases

The downstream effectors of polarity modules (both for AB and PCP polarity), is the rearrangement of the cytoskeletons, which are the building blocks of neuronal polarity. In contrast to the above-mentioned developmental defects such as NTDs, mutations in genes associated with dysfunction of microtubules/actins seem closely related to neurodegenerative diseases. Microtubule associated proteins (MAPs) are important for polymerization and stabilization of microtubules. One such protein, tau, has attracted great attention for its misregulation in several neurodegenerative diseases such as Alzheimer's disease (AD) and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [14]. In these diseases, tau proteins are hyperphosphorylated, which destabilizes microtubules and forms neurofibrillary tangles (NFT), and consequently results in a 'tauopathy'. The consequences of tau hyperphosphorylation include the disruption of neuronal structures such as axons and local tissue lesions, which lead to neuronal death [15,16]. Polyglutamine diseases such as Huntington's disease are also closely tied to cytoskeletal disruption. Huntington's protein has been shown to interact with cytoskeleton-associated proteins such as HIP1 [17], tubulin [18] and motor protein dynactin [19].

Additionally, tau modifiers have gained further attention in the search for deciphering the underlying mechanisms of tauopathies and potential therapeutic targets. Among those, Gsk3b, an mediator of Wnt/b-catenin signaling, is critical for the establishment of neuronal polarity. GSK3b phosphorylates CREM2, a protein which binds to tubulin heterodimers involved in microtubule assembly [20]. Interestingly, like tau, recent studies indicate that phosphorylated CREM2 is also present in neurofibrillary tangles [21] of AD brain. GSK3b could directly or indirectly phosphorylates tau at several serine/threonine sites, therefore regulating tau microtubule binding affinity. Another tau kinase is the microtubule-affinity regulating kinases (MARK) [22]. This kinase is also present in NFT on AD brain section [23]. It is worth mentioning that GSK3b and MARK2 activities are regulated by polarity complex/modules PAR3/PAR6/aPKC and PI3K/PIP2/AKT, respectively [4].

The cure of neurological disorders

Neurological disorders can be described from different perspectives from histopathology to behavioral anomaly. On a molecular level, if we can prevent neuronal loss and restore neuronal polarity, we may reestablish neuronal functions and neural circuitry. Could neuronal survival, plasticity and function all be related to neuronal polarity? If yes, we can strategize our treatment of neurodegenerative diseases by focusing on protection of neuronal polarity. We have accumulated much knowledge about the establishment of neuronal polarity, which

offers us opportunities to look for therapeutic targets. Although not all polarity components have been associated neuronal disorders, they may still be associated with disease pathogenesis and so may be useful therapeutic targets. For example, as both GSK3b and MARK2 are regulated by polarity modules, we can therefore modify their activities through manipulation of upstream regulators, such as PAR3, PAR6, or aPKC. Eventually, a tight control of tau phosphorylation may be achieved to reduce the toxicity from the tauopathy.

Another avenue for treatment of neurological disorders is cell-based therapy, which requires reprogramming neuronal cell fate. In this aspect, two issues are important: plasticity and survival. One hypothesis is that neuronal polarity may play a critical role in neuronal plasticity and survival. If this proves correct, modulation of the polarity of a neuron may alter its plasticity and survival potentially facilitating the reprogramming process. Both way, understanding neuronal polarity is the key to cure neurological diseases and there is still a long way to go in dissecting disease pathogenesis.

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