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Title: The cellular basis of dendrite pathology in neurodegenerative diseases

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ABSTRACT

One of the characteristics of the neurons that distinguish them from other cells is their complex and polarized structure consisting of dendrites, cell body, and axon. The complexity and diversity of dendrites have been particularly well recognized, and accumulating evidences suggest that the alterations in the dendrite structure are associated with many neurodegenerative diseases. Given the importance of the proper dendritic structures for neuronal functions, the dendrite pathology appears to have crucial contribution to the pathogenesis of the neurodegenerative diseases. Nonetheless, the cellular and molecular basis of dendritic changes in the neurodegenerative diseases remains largely elusive. The previous studies in normal condition have discovered that several cellular components such as local cytoskeletal structures and organelles located locally in dendrites play crucial roles in dendrite growth. By reviewing what has been unveiled to date regarding dendrite growth in terms of these local cellular components, we will provide an insight to categorize the potential cellular basis that can be applied to the dendrite pathology manifested in many neurodegenerative diseases.

INTRODUCTION

Neurodegenerative diseases include a range of neuronal disabilities such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Lou Gehrig's disease/Amyotrophic lateral sclerosis (ALS) (1). Although the manifested symptoms and the progress of these diseases look quite different from each other, there exist certain features, which are common to many diseases. One of the common features is the accumulation of toxic proteins (1). The other common feature is the massive neuronal loss in the brain of the late-onset patients, which renders their name, "neurodegenerative diseases"(2), although the affected brain regions vary depending on the types of the diseases. Notably, this massive neuronal cell death is known to be associated primarily with the late stages of the diseases. Thus it may not account for the disease symptoms beginning at the early stages of the diseases. For example, the brains of polyglutamine (polyQ) disease patients typically show eventual neuronal loss 10~20 years after onset of symptoms (3). Consistent with this, it has been observed that the animal models of neurodegenerative diseases such as HD (4) and PD (5, 6) displayed behavioral symptoms even without severe neuronal loss. In other words, these findings indicate that certain neuronal alterations in function and/or morphology preceding cell death should contribute crucially to the initiation of symptoms at the early stages of neurodegenerative diseases.

As a plausible candidate of these neuronal alterations preceding cell death, dendrite pathology in AD (7), PD (8), polyQ diseases (9, 10), and ALS (11) have been well recognized in both animal models and human patients. However, the exact nature of this dendrite pathology in these neurodegenerative diseases still remains largely elusive. From

extensive studies done so far, we are now aware that the different diseases are associated with the different patterns of dendritic spine and dendrite destabilization (12). It is of note that this dendrite pathology at the early stages of the diseases is phenotypically distinguishable from the dendrite degeneration of dying neurons. Dying neurons display dendrite blebbing/beading followed by extensive cleavages of dendrites involving rapid disruption of dendritic cytoskeletons shortly after the turning-on of the death signal [e.g. under hypoxic condition, (13)]. On the other hand, the dendrites affected by neurodegenerative diseases at the early stage tend to undergo relatively slow and progressive alterations or maintain the changed shape for a while [e.g. polyQ diseases, (9)].

The molecular control of dendrite growth seems very complex and involves a large number of regulator molecules performing quite diverse molecular functions such as transcriptional control, RNA metabolism, signal transduction, and so on (14). Given numerous molecules either directly or indirectly associated with the pathogenesis of neurodegenerative diseases, there may exist a huge number of combinations of these molecules regulating dendrite growth, when we consider a possible molecular mechanism underlying each case of dendrite defects in various neurodegenerative diseases. On the other hand, there are only a small number of cellular components that are closely associated with dendrite growth. These cellular components such as cytoskeletal structures are supposed to serve as a final effector of dendrite growth at the downstream of complex signaling from aforementioned numerous molecules associated with the dendrite growth. Importantly, emerging evidence suggests that local cellular components located within dendrites play very crucial roles in the control of dendrite growth (14). These local cellular

components include dendritic cytoskeletal structures consisting of F-actin and microtubules, Golgi outposts (GOPs, local Golgi apparatus in dendrites), and dendritic Mitochondria (Fig. 1). To our knowledge, the dendrite defects appear to be the outcome of combinatorial alterations in these local cellular components. Although the defects in the same type of cellular components (e.g. defects in dendritic F-actin) can result in variable dendrite phenotypes (e.g. dendrite branching defect harboring much less number of branches or terminal dendrite shortening), it doesn't seem to be a very difficult task to deduce the altered cellular component from these known or predictable phenotypic variations in dendrites. Here in this article, by reviewing how local cellular players affect dendrite growth in both normal and pathological conditions, we hope to establish clear criteria for categorizing types of dendrite pathology manifested in a number of neurodegenerative diseases. In the following section, we will focus on three local cellular components [dendritic cytoskeleton as a structural backbone, GOPs as a local supplier of plasma membrane (PM), and dendritic Mitochondria as a local supplier of Ca^{2+} and ATP] closely associated with dendrite growth.

Disturbance of local cellular components to be responsible for the dendrite pathology in neurodegenerative diseases

Dendritic changes resulted from cytoskeletal alterations in dendrites

There are two major cytoskeletal components within cells. They are filamentous actin (F-actin) and microtubules (15). To perform diverse biological activities, cells constantly undergo dynamic assembly and disassembly of these cytoskeletons under tight control of upstream regulators. The cytoskeletons serve as a backbone of cells that primarily supports the cellular structures and are also involved in the transport of intracellular cargoes. In highly polarized neuron cells, the relative composition of these two components in dendrites is supposed to be one crucial factor determining dendrite shapes (12). In general, main dendrite branches are known to be supported primarily by a packed network of microtubules whereas terminal dendrites such as spines and filopodia are supported mainly by F-actin structures (12). It is intriguing that a previous study proposed the exception to this general rule that microtubules are also present in spines and may play important role in the control of spine development (16). After full establishment of dendritic field, main dendrite branch supported primarily by microtubules remains relatively static at some homeostatic ‘set point’ in dendrite size (12), while the terminal dendrite mainly consisting of F-actin continuously undergoes dynamic changes (17-20).

Given the role of dendritic cytoskeletons as a structural backbone of highly polarized neurons, it is easy to conceive that alterations in these dendritic cytoskeleton result in dendritic changes. The best example of microtubule-mediated dendritic changes

during normal development comes from the studies on the dendrite remodeling using a *Drosophila* sensory neuronal system (21). These studies have successfully identified severing of microtubule structures by local caspases as a key step in the remodeling process of dendrites known as dendrite pruning (21, 22) .There is another example that potentially links microtubules to dendrite growth in normal condition; a recent study reported that the microtubule array near a dendritic branch site serves as a docking site for a GOP, another crucial regulator of dendrite growth, which potentially links microtubule organization to the regulation of dendrite growth (23). Then, is there any evidence linking alterations in microtubules to dendrite pathology in neurodegenerative diseases? Firstly, the changes in microtubule dynamics have been reported in many neurodegenerative diseases (24). A representative example is the changes in the phosphorylation status of tau, a microtubule-binding protein, leading to the formation of neurofibrillary tangle in AD (25). In addition, microtubule depolymerization has been proposed to be crucial for PD pathogenesis (26). There are more direct evidences linking microtubules to dendrite pathology. For example, LRRK2/Park8 mutation is known to induce dendrite degeneration involving microtubule fragmentation together with tau (27). Moreover, the alterations in dendritic microtubule dynamics have been reported to be linked to the dendrite pathology of polyQ diseases (28).

As for F-actin, several key players in the actin regulatory machinery such as Rac1, RhoA, and their associated signaling pathways have been extensively studied for their roles in dynamic control of terminal dendrite growth (29). For tight control of F-actin formation, numerous regulator molecules of F-actin act on multiple processes related to F-actin such

as capping, severing, nucleation, and crosslinking/bundling, and so on (30). According to the previous studies, over 80% of dendritic F-actin undergoes turn-over every minute, whereas 75% of dendritic microtubules undergo turn-over within tens of minutes (12). This means that F-actin is more dynamically controlled than microtubules, and thus neurons may be more sensitive to temporal or chronic changes in the regulator activity of F-actin in shaping terminal dendrites after the full establishment of dendritic arbors. In line with this, the pathological implication of F-actin defect has been investigated in the context of many neurodegenerative diseases including a subset of polyQ diseases, PD, and AD. Our previous study has characterized that the toxicity from a subset of nuclear polyQ proteins such as pathogenic forms of SCA3/MJD1 and SCA1 causes almost complete ablation of F-actin structures in dendrites in *Drosophila* sensory neurons (9). Interestingly, these F-actin alterations led to cell type-specific terminal dendritic defects due to different compositions of cytoskeletal make-ups of dendrites in these different types of neurons. In addition, the LRRK2/Park8 function has been linked to the regulation of actin dynamics (31). Moreover, abnormal bundling and accumulation of F-actin were reported in the tau-induced AD model (32). In AD brain, aggregates of ADF/Cofilin have been also described in association with both amyloid plaques and neurofibrillary tangles (33, 34). Despite of these extensive studies, further studies are demanded to clearly link F-actin defects to specific dendrite pathology in neurodegenerative diseases.

Dendritic changes derived from alterations of GOPs

Neurons have tremendous PM area because of their complex structure. For

example, it has been estimated that neurites may have about 30 times bigger surface area than the surface area of a soma in cultured hippocampal neurons (35). This implies that highly polarized neurons should have a very active machinery performing PM supply and recycling compared to other cells. Especially, terminal structures of neurons such as dendrite terminals are supposed to need constant and very active membrane supply due to their nature of undergoing dynamic changes in morphology (36). Indeed, neurons are known to have their unique local systems for membrane supply and recycling to fulfill this local need (37).

In general, Golgi apparatus that receives materials from ER is known to play a key role in the secretory pathway that sends vesicles intra-cellularly and supplies PM through exocytosis regardless of cell types. In neurons, a specialized local Golgi structure, named GOP, is present in dendrite (38, 39). According to a recent study, GOP ablation inhibits dendritic growth (40). Despite of these seminal works, still details about GOPs remain largely elusive. For example, we don't know the exact differences in their nature between somatic Golgi and GOPs. Also, a source of GOPs remain controversial whether somatic Golgi fragment is transported to distal dendrites to form GOPs or local ER elements generate GOPs (42).

To date, GOPs have been implicated with a few neurodegenerative diseases. Interestingly, a recent study showed that Lrrk2 mutation associated with PD is able to induce GOP-mediated dendrite reduction (43). In addition, TDP43 mutation associated with ALS is known to induce fragmentation of somatic Golgi (44), but the impact of somatic Golgi fragmentation on Golgi outposts is unidentified. However, a lot of unsolved

questions still exist such as how GOPs are affected by these disease conditions.

Alteration in mitochondrial physiology affecting dendrites

Mitochondria play critical roles for supplying cellular energy and buffering Ca^{2+}. In neuronal system, these functions of Mitochondria seem to be more crucial than other cells because of the following reasons. First, neurons have elongated and complex structures, therefore making the simple diffusion of ATP produced from somatic Mitochondria to be difficult and not sufficient to fulfill local need (45). Second, neuronal firing is accompanied by massive influx of Ca^{2+}, so the ability of Mitochondria to buffer Ca^{2+} is particularly important in neurons (46).

These functions of Mitochondria are supposed to be crucial for dendrite growth. For example, adequate supply of ATP by Mitochondria is very essential for F-actin elongation associated with dendrite growth (47). In addition, Ca^{2+} signaling has been implicated with the regulation of dendritic development (48). Moreover, high amount of Ca^{2+} is well known to result in excitotoxicity inducing dendritic degeneration (49). Notably, there are a couple of papers regarding changes in mitochondrial physiology linked to dendrite phenotypes: mitochondrial fusion/fission status has been linked to dendrite phenotypes (50), and a mutation in a specific mitochondrial protein, preli-like, is known to induce dendritic changes (51). However, the exact mechanism of how mitochondria affect dendrite morphology still remains unknown.

Notably, mitochondrial dysfunction has been reported in many neurodegenerative diseases (52). The changes in mitochondrial quality control system has been proposed to be

a key pathogenic mechanisms of familial cases of PD (53). Thus, it will be interesting to see whether these mitochondrial changes are indeed linked to the dendrite pathology in these diseases.

Drugs that have potential for amelioration of dendrite pathology

In this section, we discuss the possible therapeutic strategies targeting cytoskeleton in neurodegenerative diseases and future targets. Microtubule-stabilizing compounds have been investigated and used as cancer therapeutics. Brain penetrant epothilone D (EpoD), which stabilizes microtubule similar to taxol, has been demonstrated to rescue microtubule organization, cognitive defect, and tau pathology in a couple of mouse models (54, 55). Based on these results, a phase I clinical trial by Bristol-Myers Squibb was carried out from 2012 to 2013, but the results were not announced yet (ClinicalTrials.gov identifier NCT01492374). In addition, EpoD rescued microtubule defects in PD mice model (56). Given that the balance of microtubule dynamics is important to maintain dendrite and axon integrity, blood-brain barrier (BBB)-permeable agents that can stabilize microtubule dynamics will remain as a promising therapeutics for neurodegenerative diseases.

Microtubule dynamics is mainly regulated by microtubule-associated proteins (MAPs). Tau and collapsin response mediator protein 2 (CRMP2), which belong to MAPs, are hyperphosphorylated in AD. GSK3β and CDK5 are the kinases responsible for these hyperphosphorylation (57, 58). The phosphorylation of tau and CRMP2 by CDK5 is a prerequisite for the subsequent phosphorylation by GSK3β, which is called ‘priming’. Both kinases have been known to be involved in neurodegenerative disorders (58, 59). Various

compounds that block the activity of GSK3β have been investigated in neurodegeneration mice model and clinical trials. Tideglusib, a selective GSK3β inhibitor, showed not only decreased tau phosphorylation and improved behavioral functions, but also decreased Aβ pathology and neuronal death in AD models (60, 61). However, a phase II trial using Tideglusib in AD patients showed the drug safety in 26 weeks without clinical benefit (62). A recent work published in this year demonstrated that DYRK1, a kinase overexpressed in Down syndrome patients, can phosphorylate tubulin per se and inhibit their polymerization, leading to the defect in dendrite patterning (63). It would be of much intriguing to see whether selective DYRK1 inhibitors modulate the disease symptoms of AD, PD, and ALS.

RhoA/ROCK pathway regulates the polymerization of actin cytoskeleton and has been implicated in AD, PD, HD and ALS (64). Although it is not clear whether the inhibition of this signaling is beneficial for the treatment of neurodegeneration, there are several lines of evidences that ROCK inhibitors may have potential to cure the diseases. For example, knockdown of ROCK2 (an isoform strongly expressed in the brain) reduced the loss of dopaminergic neurons and improved motor behavior in 6-OHDA mice model (65). Several compounds selective for ROCK2 have been recently developed to treat autoimmune diseases. It would be of much interest to test the compounds in the neurodegeneration mouse models. There is, however, a concern to use ROCK inhibitor as a therapeutic for the neurodegenerative diseases. Recent work unveiled that RhoA/ROCK pathway is required for GOP formation (66), so careful interpretation of the inhibitor study should be performed.

Besides studying the specific targets for the diseases, there have been efforts to

screen compounds that restore the ability of dendritic spine formation in neurons. One of the efforts led to the discovery of benzothiazole amphiphiles, which promote the formation of dendritic spines (67). These chemicals may facilitate spinogenesis through the activation of Ras pathway, though they are a bit toxic to the cells at their active concentration.

The drugs intervening cytoskeleton functions seem to have a huge potential to improve the symptoms in neurodegenerative diseases in mice models, but many obstacles still remain to be overcome. Target-related toxicity due to non-specific inhibition of cytoskeleton or kinases will be a great concern. In addition, the delivery of compounds to central nervous system is always a tough question in drug discovery. Despite of these circumstances, it is very demanding to make an effort to seek more selective and brain-penetrant therapeutics.

CONCLUSION

In this article, we reviewed alterations in local structural supports by dendritic cytoskeletons, local supply of PM components by GOPs, and local supply of Ca^{2+} and ATP by dendritic Mitochondria to be potentially associated with dendrite pathology in neurodegenerative diseases. As reviewed here, we begin to recognize key players for decoding the mystery of the dendrite pathology, but many questions still remain to be addressed. We don’t even know yet the exact contribution of the dendrite pathology to the pathogenesis of the diseases and to the disease symptoms. Also, in particular, not much is known about the nature of GOPs. Thus, further studies are highly demanded to clearly address these questions. With the tremendous efforts of the related research fields, we hope

to fully understand the cellular basis of the dendrite pathology manifested in many neurodegenerative diseases someday in the future, which will be of great help to develop effective treatment specifically targeting early stages of the diseases.

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FIGURE LEGENDS

Figure 1. Localization of dendritic cellular components in *Drosophila melanogaster* dorsal cluster dendritic arborization (da) neurons

Merged images of local cellular components (green, marked by arrowheads) with membrane marker protein, CD4-tdTOM (red). Dendritic distribution of microtubules labeled by Tau-GFP (A), F-actin labeled by GMA (B), GOPs labeled by galT-eGFP (C), and Mitochondria labeled by Mito-GFP (D) was examined in dorsal cluster da neurons by using *109(2)80*-Gal4 driver. Dendrite images of da neurons of *Drosophila* 3rd instar larva located in abdominal segments A2 to A4 were captured using confocal microscopy. Scale bar indicates 50μm

Figure 2. A schematic diagram showing local cellular components crucial for dendrite growth

Microtubules are located mostly in primary branches, and F-actin is located in both primary branches and terminal dendrites (the diagram depicts F-actin at terminal dendrites only). Mitochondria and GOPs are distributed throughout the dendrites.

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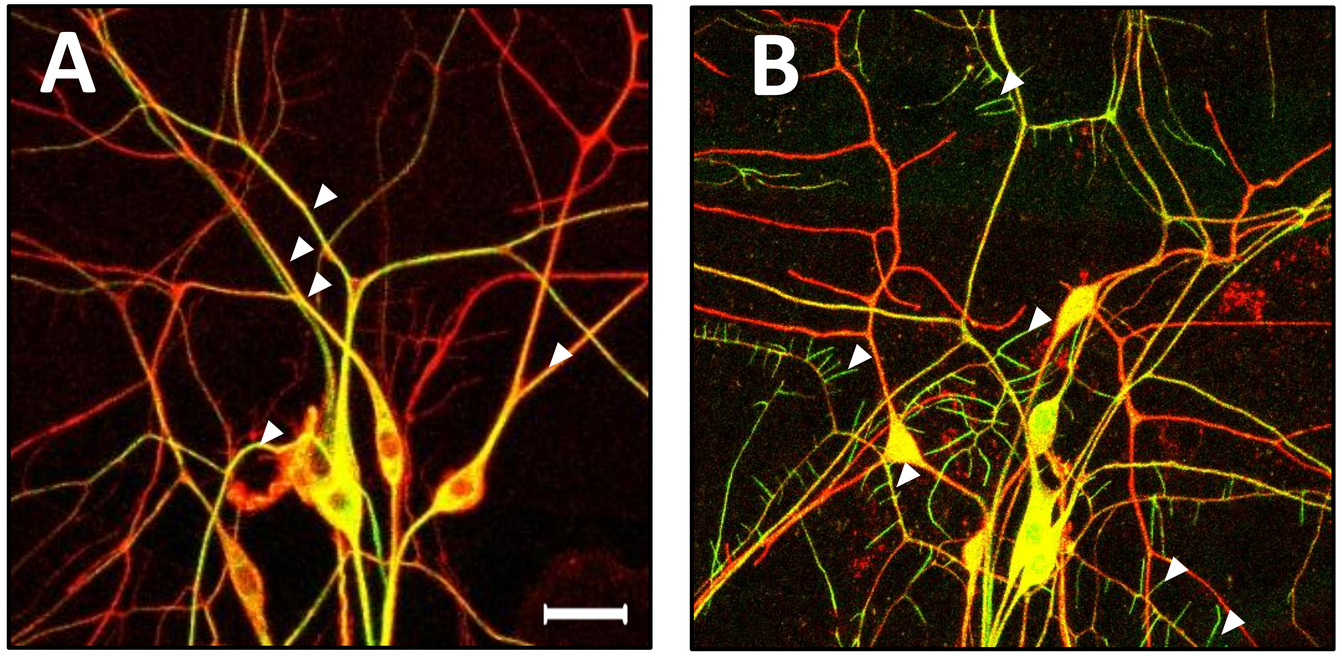

Figure 1

Microtubule

F-actin

Golgi outpost

Mitochondrion

Figure 2