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The role of the cofilin-actin rod stress response in neurodegenerative diseases uncovers potential new drug targets

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The cofilin-actin rod stress response is an actin cytoskeletal dynamic arrest that occurs in cells under a variety of stress conditions. Upon stress, the rapidly activated cofilin saturates actin filaments causing them to bundle into rod structures in either the nucleus or cytoplasm, halting actin polymerization and thus freeing ATP. Importantly, these rods dissociate quickly following relief of the transient stress. The rods form inappropriately in neurons involved in the progression of Alzheimer disease (AD) and we have linked dysfunctional dynamics of the nuclear rod response to Huntington disease (HD). Cofilin levels are also perturbed in Parkinson disease (PD), and profilin, an actin binding protein with opposite action to cofilin, is mutated in Amyotrophic Lateral Sclerosis (ALS). The persistence of the rods post-stress suggests that critical molecular switches to turn this response both on and off are being affected in neurodegeneration. We have recently shown that the cofilin protein is regulated by highly conserved nuclear import and export signals and that these signals are required to be functional for appropriate rod formation during stress. The ability of cofilin to form rods is required in a cell culture model for cells to be resistant to apoptosis under stress conditions, indicating that a normal cofilin-actin rod response is likely integral to proper cell health in higher order organisms. Here we hypothesize on the potential physiological function of nuclear cofilin-actin rods and why the dysregulation of this response could lead to the selective vulnerability of the most susceptible populations of cells in HD. We further suggest that learning more about this cytoskeletal cell stress response will open up new avenues for drug target discovery in neurodegenerative disorders.

Keywords: cytoskeleton, cofilin, profilin, actin, cofilin rods, nuclear transport signals, Huntington disease

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There is a unique and understudied cell stress response that occurs involving the dynamic actin cytoskeleton. Under different stress conditions, the actin binding protein, cofilin, becomes hyper-dephosphorylated by activated phosphatases and saturates actin filaments causing them to bundle into cofilin-actin rod structures in either the nucleus or cytoplasm.[1-3] Post stress, LIM kinase is activated and cofilin is de-activated upon phosphorylation, allowing the restoration of actin polymerization and ATP. The presence of rods have now been seen in both Alzheimer disease (AD) when they form in the cytoplasm (neurites),[4,5] Huntington's disease models (HD) when they form in the nucleus as well as perturbations of cofilin and LIM kinase in familial Parkinson disease (PD).[6] Intriguingly, profilin1 mutations have now been identified in familial Amyotrophic Lateral Sclerosis (ALS).[7] Thus, the actin cytoskeleton and the actin rod stress response are now seen as perturbed in an increasing number and variety of neurodegenerative diseases.

We recently reported and defined conserved nuclear import (NLS) and export signals (NES) on the cofilin protein that affect the ability of cofilin to form rods. Cofilin is a small 26 kDa protein, yet uses active transport signals to interact with the karyopherin/importin families of proteins to rapidly enter and exit the nucleus across the nuclear pores by facilitated

diffusion. We show that these nuclear transport signals are critical for the proper formation of cofilin-actin rods. This suggests that during the stress response, some soluble cofilin is actively communicating between the nuclear and cytoplasmic compartments by active protein shuttling. Mutations to the cofilin NLS have been described that allowed cofilin to bind actin and presumably perform its steady-state functions, but inhibited rod forming ability.[8] Little is known about the biology of cofilin-actin rod formation. It has been shown that when rods form in the cytoplasm, one function may be the alleviation of ATP normally involved in actin treadmilling activities.[9] This freed ATP could be used by the protein folding machinery to deal with stresses such as the unfolded protein response (UPR), which is also chronically activated in neurodegenerative diseases and impacts the regulation of autophagy.[10]

Nuclear cofilin-actin rods may have additional functions. Cofilin-dependent stress fibers (which are not cofilin-actin rods) are known to respond to mechanical stress of cell tension and act as tension sensors.[11] The consequences of inhibiting or modulating the cofilin-actin rod stress response is additionally unknown, making it impossible to determine if altering the rod forming ability of cofilin-actin may be a new target for drug discovery in neurodegeneration. By coupling endogenous cofilin knockdown and re-expressing cofilin NLS mutants in our model system, we found that the ability of cofilin to form cofilin-actin rods is imperative to cell health during cell stress, implying that normal cofilin rod formation is essential for cell survival during stress.[8] A significant body of work has gone into the potential involvement of cytoplasmic cofilin-actin rods in AD,[4,5,12,13] and cofilin levels in PD,[6] and we were additionally able to establish a role of nuclear rods in HD.[8,14] Further exploration of the function of nuclear cofilin-actin rods may indicate how they could be contributing to disease, specifically in the differentially affected neuronal population in HD and will indicate if and how we can target this response. Here, we will hypothesize on the function of nuclear cofilin-actin rods and how a malfunction in this response could lead to the differential susceptibility of medium-sized spiny neurons (MSNs) and other projection neurons in HD.[15]

Nuclear actin has been shown to be involved in multiple steps of transcription through binding of all three RNA polymerases, recruiting chromatin remodelling complexes, as well as in the export of mRNA.[16-19] In addition to these functions, nuclear actin and its associated motor protein myosin have been implicated in the actual movement of gene loci in response to transcription activation.[20] Experiments in epithelial cells show that a decreased pool of nuclear actin is required for cells to obtain a quiescent state,[21] while increased levels of nuclear actin are required for macrophage differentiation.[22] This indicates that nuclear actin dynamics are closely linked to cell state which may be specifically important to post-mitotic neurons. With the recent influx of knowledge with respect to active actin remodeling in the nucleus and actin as a master regulator of transcription,[23] it is attractive to hypothesize that intranuclear rod formation during stress may have some bearings on transcriptional control during stress. Huntingtin is observed associated with nuclear cofilin rods, and huntingtin has a normal role in the nucleus as a scaffolding protein involved with the epigenetic modifying polycomb repressive complex 2 or PRC2.[24] Overexpression of wildtype huntingtin is protective against apoptotic stimuli in tissue culture cells[25] and conditional knockout of huntingtin in the brain leads to neurodegeneration in mice,[26] both of which suggest a pro-survival function. Huntingtin itself is transcriptionally regulated by a p53-responsive element in the huntingtin promoter,[27] which implies that p53 responses to damage or stress may explain why mutant huntingtin neurons are pro-apoptotic.[28] Outside of neurons, this pro-apoptotic state of all cells may explain the reduced incidence of cancer among individuals that carry the mutation in HD.[29]

Cofilin has now been shown to be required for the nuclear translocation of actin and has been shown to have specific activity with respect to transcription in the nucleus, likely through mediating the polymerization state of actin.[30] The large influx of cofilin and actin into the nucleus during stress and the formation of cofilin-actin rods will likely impact the transcriptional functions of actin and cofilin. It is well documented that cell stress induces a large shift in transcriptional activities, leading to decreased transcription of most steady-state proteins and increased transcription and translation of chaperones and other stress related proteins.[31] During stress, actin may act directly on DNA or indirectly through altered chromatin modification or movement of chromosomes within the nucleus. If transcriptional changes coupled with ATP alleviation are the important functions of these nuclear rods, then inappropriate execution of the nuclear rod stress response could lead to many of the defects in HD. Single gene studies as well as microarray technology have shown that there are a large number of genes dysregulated in multiple HD systems from in vitro to actual patient samples.[32] A defect in this response could further be tied to cell stress and energetics failure widely noted in HD,[33-35] and other forms of neurodegeneration, and may correlate to some of the nuclear functions of huntingtin during stress.[14,36] Changes in actin related transcription during stress should be looked at as a target or as a read out for neurodegeneration in general and looking at transcriptional alterations caused by nuclear cofilin rods will indicate if this is a normal function of the rods and if this could be contributing to the disease pathology.

We have demonstrated a dysfunctional cell stress response via the actin cytoskeleton in the presence of the mutant huntingtin protein.[8,14] In HD patient blood cells, this manifests as a covalent cross-link between cofilin and actin mediated by stress-induced hyperactivity of the transglutaminase 2 enzyme.[14] Transglutaminase 2 is a calcium-dependent, stress-dependent, transamidating acyltransferase that can act as a G protein and regulates the cytoskeleton.[37] We propose that this function is a good target for drug discovery since it seems to be directly affected by mutant huntingtin and may tie into the energetic defects, transcriptional defects and problems with cell stress and aging hypothesized to

cause neurodegeneration, and therefore is a good pathway to experimentally test for rescue. An altered cell stress response would likely be cell autonomous but we propose that a stress response involving both ATP alleviation and the actin cytoskeleton would conceivably differentially affect projection neurons, the population of neurons that are most sensitive to the insult of mutant huntingtin. We propose a mechanism that would lead to the increased susceptibility of these neurons based on an impairment of the cofilin-actin rod stress response. Due to unique morphological aspects of neurons such as long axons that traffic vesicles and highly plastic spines, dendrites and synapses, neurons have a high energy consumption rate and are responsible for most of the energy consumption in the brain.[38] As the brain is the single largest site of ATP storage and usage in the body, this may explain why defects in this general stress response in all cells manifest as neurologic diseases.

Projection neurons are large cells with long axons, many dendrites and many spines. The cytoskeleton is required for structure and trafficking along these axons and active actin remodelling through cofilin activities is required at spines for plasticity through changes in spine morphology.[39] Recently, cofilin activity has been found to be critical in response to activities of N-Methyl-D-aspartate (NMDA) as well as 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptors for motility of synapses, controlling spine morphology and post-synaptic potentiation and depression.[40,41] Cofilin gene knockout is embryonic lethal in mouse, therefore selective knockout of cofilin from postnatal neurons in the forebrain has been performed to specifically probe cofilin function at synapses using a flanked by LoxP, or "floxed" system. This system reveals that cofilin is essential in controlling the turnover of F-actin at synapses. The consequence of an overload of F-actin at synapses results in problems with post synaptic physiology including spine morphoplogy, number of synapses and decreased receptor mobility leading to impaired associative learning.[41] Interestingly, actin depolymerizing factor (ADF) gets upregulated when cofilin is depleted in this model,[41] ADF can sometimes compensate for cofilin knockdown in other actin related functions,[42] however, it cannot fully compensate for the loss of cofilin in neurons with respect to spine morphology.[41] Additionally it has been shown that upon NMDA receptor activation and associated calcium level increases, activated calcineurin (CaN) causes a dephosphorylation of cofilin through SSH1 activity and cofilin is translocated to dendritic spines for remodeling activities,[40] agreeing with the specific need for active dephosphorylated cofilin in actin remodeling at spines. Therefore the normal regulation of cofilin is intimately and specifically tied to proper neuron function.

Between the large cytoskeleton of neurons and the active remodeling of actin required at synapses it is clear that neurons have a high demand for actin turnover. This high demand for active actin turnover is energetically costly. It has been found that inhibiting treadmilling of actin after stopping ATP production in neurons alleviated approximately 50 percent of the already produced ATP in the cell, indicating that actin turnover may have been overlooked as a major energy drain for neurons.[43] An additional large pool of ATP is required in neurons for electrical activity and restoring transmembrane ionic gradients,[44] and ATP is important in synaptic signaling and co-signaling. Overall, projection neurons in particular, including MSN and pyramidal neurons, have high energy demands associated with maintaining the ionic gradient and high levels of actin turnover in spines, and are unique from other neuronal cell types in this way. The cofilin-actin rod stress response is currently shown to be involved in alleviating a pool of ATP that is normally used for active actin processes, so it can be used elsewhere in the cell during times of stress.[9] Since neurons are already utilizing a large portion of ATP under normal conditions, dysregulation of the cofilin-actin rod stress response may have additional negative effects in neurons compared with other cell types if ATP is not being relieved.

Based on this, we propose two scenarios connected to our analysis of the cofilin rod stress response in the presence of mutant huntingtin that would lead to the differential neuronal vulnerability in HD. If ATP is not being alleviated appropriately then these energy hungry cells would likely be the first cell types to be affected by the dysfunctional cofilin-actin rod response. Alternatively or in concert, the misregulation of the cofilin protein, including inappropriate phosphorylation or cofilin being stuck in persistent rods, may have dire consequences on spine morphology and synaptic activities which may lead to the early dysfunction in neurodegenerative processes.

The exact role of huntingtin on the cofilin rods is not known, but a well-described interactor of huntingtin at a proline-rich region just adjacent to the expanded polyglutamine tract in huntingtin is profilin1. Profilin1 is an actin binding protein with opposite action to cofilin in that profilin acts to stimulate actin polymerization and we hypothesize that profilin may be required for the dissociation of cofilin rods. Profilin1 has been very recently shown to be mutated in familial ALS.[7] Profilin1 is known to interact more tightly with polyglutamine-expanded huntingtin seen in HD.[45] Phosphorylation of profilin by ROCK1 kinase can affect the ability of mutant huntingtin to misfold and form aggregates,[46] while in familial ALS, mutations in profilin1 seem to promote aggregates of profilin1 itself.[7] Those aggregates of profilin1 in ALS may contain huntingtin protein.

The next question is how to test if altering cofilin and the cofilin-actin rod stress response is a therapeutic avenue for drug discovery in HD. The requirement of cells to form rods has never been looked at and we found a correlation between cell survival during stress and the ability of cofilin to form rods.[8] Therefore we hypothesize that inhibiting rod formation may not be the way to target this, although this needs to be tested in higher order model organisms, as suggested by others.[12] The active shuttling of cofilin through nuclear import and export signals seems to be intimately tied to the ability of cofilin to respond to stress and form rods, and as such, finding compounds that alter the shuttling ability of cofilin may answer some of these questions, or be therapeutic.

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