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Involvement of Actin Pathology in Alzheimer's Disease

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Overview

The best pathologic correlate of cognitive impairment in Alzheimer's disease (AD) is loss of synapses, and a growing body of evidence suggests that abnormalities of the actin cytoskeleton may play a critical role in synaptic degeneration in AD. Hirano bodies, rod shaped structures found in CA1 neurons from AD patients, contain filamentous actin (F-actin) and ADF/cofilin (AC), a family of actin-binding proteins [1,2]. Recent studies demonstrate that abnormal actin-AC rods form in response to energy depletion, oxidative stress and excitotoxicity [3]. Moreover, actin-AC rods affect APP transport in neuronal processes and synaptic stability and activity [4-6]. However, the mechanisms underlying actin-AC rod formation in AD are unclear. The consequences of these rod-like structures in neurodegeneration are also needed to be determined.

Biology of Actin and ADF/Cofilin (AC)

The actin cytoskeleton is highly dynamic and an important player in growth cone motility, spine development, and synapse formation and activity. Actin dynamics are modulated by actin-associated proteins, such as the highly conserved family consisting of actin-depolymerizing factor (ADF), cofilin-1, and cofilin-2. These proteins function similarly and are considered as a single entity (AC) [6,7]. AC is known to be a major regulator of actin dynamics, filament turnover, and directed cell migration [8-10]. AC increases dissociation of ADP-actin from the minus end of actin filaments, promoting depolymerization [11] and severing filaments into small fragments [2]. Recent studies indicate that AC severing of actin filaments could generate new filament ends, promoting nucleation and polymerization of actin filaments, which is the force driving membrane protrusion and cell migration [12,13].

Both the amount and the activity of AC may be important in determining actin dynamics. Disassembly is favored when AC is at low concentrations, but it nucleates actin filaments at high concentrations [6]. Degenerative stressors may also affect actin dynamics via the actin-AC interaction. The pool of intracellular ADP-actin monomers is dramatically increased when cells are under stress or ATP levels fall, and activated AC has higher affinity with ADP-actin than ATP-actin [6].

Regulation of AC Expression

AC protein levels are increased in Tg19959 mouse brain, but mRNA levels are unchanged, indicating post-transcriptional regulation [14]. Post-transcriptional regulation of gene expression by microRNA (mirRNA) has recently attracted great interest in neurodegeneration research [15]. Mature mirRNAs are short noncoding RNAs, the first 6 nucleotides of which interact with the 3'-untranslated region (UTR) of target mRNAs, an interaction that generally represses translation. A recent study showed that a mirRNA important in dopamine neuron maturation and function is deficient in Parkinson's disease [16]. Several mirRNAs that target APP and BACE-1 are also deficient in AD, associated with increased levels of these proteins [17-19].

We investigate the mechanisms underlying the formation of cofilin rods. We show that miR-103 and miR-107 bind to the 3'UTR of cofilin mRNA as predicted, and repress translation of cofilin. Decreasing miR-107 elevates cofilin protein levels, and overexpression of active cofilin induces formation of cofilin-actin rods. Finally, we show in a transgenic APP mouse model that brain levels of miR-103 and miR-107 are decreased, with corresponding increases in brain cofilin protein levels, and formation of cofilin-actin rods or aggregates in primary neurons and brain sections. Since overexpression of inactive cofilin does not induce rod formation, the increased cofilin protein levels seen with decreased miR-103/107 in AD must be followed by activation of the cofilin, in order to lead to rod formation [14].

Regulation of AC Activity

AC activity is regulated by LIM kinases (LIMK) and Slingshot (SSH) phosphatases at serine 3 [20]. Phosphorylation of Ser3 by LIMK deactivates AC. LIMK is regulated by Rho GTPase pathways (Figure 1), and is activated by phosphorylation at Thr508/505 [21-23]. Dephosphorylation of Ser3 by SSH activates AC [21,22]. SSH is in turn regulated by calcineurin and PI3 kinase [24,25]. Furthermore, SSH also deactivates LIMK to regulate AC [26].

Several recent studies support the idea that alterations in AC activity contribute to actin pathology in neurodegeneration. Treating

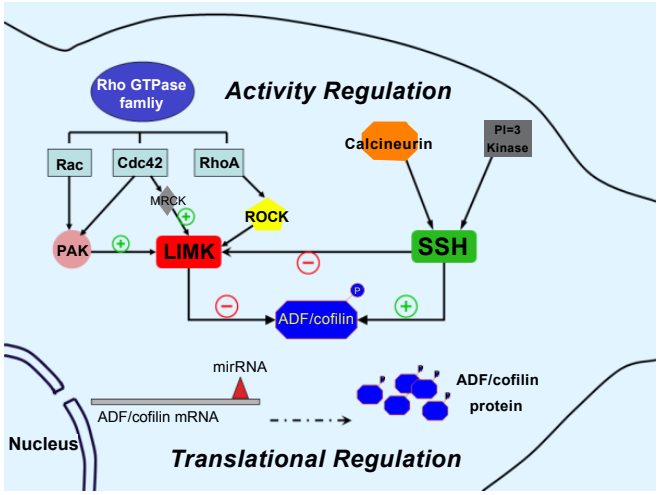

Figure 1: Regulation of ADF/cofilin expression and activity.

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neurons with azide, H_2O_2, or glutamate resulted in dephosphorylation and activation of AC and formation of actin-AC rods [3]. αβ oligomers reduce PAK activity, and PAK defects in AD induce cofilin pathology [27], consistent with decreased LIMK and increased AC activities (Figure 1). On the other hand, fibrillar αβ increased LIMK and decreased AC activities, and this also resulted in abnormal actin remodeling [28]. Thus, the situation regarding regulation of AC activity in AD is complex, with evidence for both increases and decreases, both producing actin cytoskeletal pathology.

Consequences of Actin Cytoskeletal Pathology for Transport and Mitochondrial and Synaptic Morphology

Defects in axonal transport occur early and play critical roles in AD [29-31]. Recent studies show that actin cytoskeletal pathology may be an early cause of transport defects [5,6,32]. Actin-AC rods directly damage microtubule bundles and interfere with axonal transport [6,33]. The inability to transport important cargos between cell bodies and distal processes could then be responsible for neurite degeneration. Mitochondria in particular are critical in morphogenesis and plasticity of spines and synapses [34]. Transport of mitochondria likely depends on interaction between kinesins and dyneins along microtubules and myosins along the actin cytoskeleton [35,36] and anchoring of mitochondria at synapses is actin-dependent [37]. Moreover, mitochondrial morphology is dependent on F-actin, which facilitates mitochondrial recruitment of dynamin-related protein 1, a protein critical for normal mitochondrial fission [38].

Alzheimer disease is the most common form of dementia. There is no cure and the disease gets worsen as the age advances. This disease was first described by Germen psychiatrist, Alois Alzheimer in 1906 and then named after him. Early symptoms include difficulty in remembering events. As the disease progresses, it manifests itself into various forms such as confusion, irritability, personality change and memory loss. Amyloid plaques and neurofibrillary tangles are classic hallmarks of AD.

Aggregates of cofilin and actin occur in human AD brains [1,2,14], but are less well appreciated than amyloid plaques or neurofibrillary tangles. Rod-like structures containing cofilin and actin also form in cell [3] and animal [5,39] models of AD. Several lines of evidence suggest that such cofilin-actin rods are pathophysiologically important. They form under pathologic conditions, such as energy depletion, excitotoxicity, oxidative stress, and Aβ exposure **[3,6,40]**. They have functional consequences. We showed that increased cofilin level seen with decreased miR-103/107 leads to cofilin rods formation in a AD mouse model [14]. Feaney and colleagues showed that neurodegeneration in *Drosophila* and mouse models of tauopathy was associated with formation of actin-rich rod-like structures, and neurodegeneration could be markedly attenuated by genetic manipulations to reduce actin accumulation [5]. Formation of cofilin-actin rods may also be important in recruitment of phosphorylated tau into neuropil threads [39]. Furthermore, disrupted actin structure interferes with mitochondrial dynamics as a direct mechanism of tau toxicity in neurons [33].

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