Cofilin-Mediated Neurodegeneration in Alzheimer's Disease and Other Amyloidopathies

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Owing to an editing error, uncorrected versions of Figs. 1, 2, and 4 were printed. The correct versions of these figures are reprinted below.

The online version of the original article with published errors can be found at <http://www.doi.org> using the article DOI 10.1007/BF02700622.

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Fig. 1 Proteolytic process of the amyloid precursor protein (APP). **(a)** Sequential processing of APP by α - and γ -secretases yields a soluble extracellular fragment (sAPP α) and a 99-amino acid transmembrane peptide that is cleaved to yield a soluble P3 fragment and an APP-intracellular domain (AICD), which is targeted to the nucleus. **(b)** Sequential APP processing by β - and γ -secretases occurs mainly in

membrane lipid raft domains and gives rise to a soluble extracellular domain (sAPP β) and a 99-amino acid transmembrane fragment that is cleaved to yield AICD and the amyloidogenic peptides (A β). Variability in the C-terminal cleavage site by γ -secretase gives rise to peptides most commonly either 40 or 42 amino acids in length

Fig. 2 Schematic diagram showing how cofilin enhances actin treadmilling in normal cells and how cofilin-actin rods form in cells under stress. **(a)** Phosphocycling of cofilin by LIM/TES kinases and slingshot or chronophin phosphatases enhances actin filament turnover and treadmilling. The phosphorylated form of cofilin may be sequestered by 14-3-3 family scaffolding proteins. Active cofilin binds along ADP-actin subunits to promote severing and increased rate of subunit loss from filament (-) ends. The dissociated ADP-actin undergoes nucleotide exchange enhanced by Srv2/Cap1 or profilin and the ATP-actin monomer has low affinity for cofilin, allowing it to

recycle back onto the plus end of a growing filament. A rapid hydrolysis of the actin bound ATP to ADP-Pi is followed by the loss of inorganic phosphate. **(b)** When cells are under stress and ATP levels fall, cofilin undergoes enhanced dephosphorylation and actin exchanges bound ATP for ADP. Cofilin has higher affinity for ADP-actin subunits and binds to them and assembles them into cofilin-saturated ADP-actin filaments. These filaments can bundle to form rods, presumably because of the ability of cofilin to neutralize the negative surface charge on F-actin. Within these rods there is little if any turnover of subunits until ATP levels recover

Fig. 4 Hypothetical model showing possible signaling pathways of $fA\beta_{1-40}$ and $sA\beta_{1-42}$ that lead to opposing effects on cofilin activity. APP is cleaved by β - and γ -secretases to produce $A\beta$ within endosomes. Some $A\beta$ assembly may occur before membrane fusion releases soluble species, including monomers, dimers, trimers, and other oligomers into the extracellular space. The binding of $sA\beta$ to as yet unidentified receptors may occur at synaptic locations and leads to increased intracellular Ca^{2+} , presumably from extracellular sources. Elevated Ca^{2+} can lead to a multiplicity of cellular effects including calcineurin activation, which in turn activates slingshot. Active

slingshot can dephosphorylate cofilin, leading to its hyperactivity and, if coupled with ATP reduction, rod formation. Extracellular $A\beta$ also can polymerize into fibrils ($fA\beta$), some of which precipitates to form senile plaques. The activation of integrin receptors by $fA\beta_{1-40}$ causes recruitment of adhesion proteins and can lead to activation of Rho family GTPases, whose downstream kinases activate LIMK, which inactivates cofilin. Enhanced polymerization and bundling of F-actin in the cell body, growth cones and other lamella ensues, possibly leading to neuritic dystrophy