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

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Abstract

Transport defects may arise in various neurodegenerative diseases from failures in molecular motors, microtubule abnormalities, and the chaperone/proteasomal degradation pathway leading to aggresomal-lysosomal accumulations. These defects represent important steps in the neurodegenerative cascade, although in many cases, a clear consensus has yet to be reached regarding their causal relationship to the disease. A growing body of evidence lends support to a link between neurite transport defects in the very early stages of many neurodegenerative diseases and alterations in the organization and dynamics of the actin cytoskeleton initiated by filament dynamizing proteins in the ADF/cofilin family. This article focuses on cofilin, which in neurons under stress, including stress induced by the amyloid-β (Aβ) 1-42 peptide, undergoes dephosphorylation (activation) and forms rod-shaped actin bundles (rods). Rods inhibit transport, are sites of amyloid precursor protein accumulation, and contribute to the pathology of Alzheimer’s disease. Because rods form rapidly in response to anoxia, they could also contribute to synaptic deficits associated with ischemic brain injury (e.g., stroke). Surprisingly, cofilin undergoes phosphorylation (inactivation) in hippocampal neurons treated with Aβ1-40 at high concentrations, and these neurons undergo dystrophic morphological changes, including accumulation of pretangle phosphorylated-τ. Therefore, extremes in phosphoregulation of cofilin by different forms of Aβ may explain much of the Alzheimer’s disease pathology and provide mechanisms for synaptic loss and plaque expansion.

Index Entries: Alzheimer’s disease; Down syndrome; stroke; ADF/cofilin; actin; amyloid-β; inclusions; transport; neurodegeneration.

Received July 17, 2006; Accepted September 5, 2006.
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Introduction

Ischemia, oxidative stress, and excitotoxic insults are key factors driving neurodegeneration. These can arise from stroke, trauma, or mitochondrial dysfunction or may be initiated or enhanced by genetic risk factors (1). With these upstream initiating factors and final stage pathology well-defined, the focus of current research lies in deciphering the biochemical pathways involved in the disease process and to what extent each contributes to it. These investigations are defined partly by the necessity and, in some cases, an inability to connect cellular and biochemical aspects of neurodegeneration with the behavioral consequences observed in the associated human diseases. One example of this disparity is a failure to define the molecular mechanisms responsible for the cognitive decline associated with early stages of Alzheimer’s disease (AD). Lower scores on the mini-mental state examination and other neuropsychological tests directly correlate with reduced synapse number in AD (2,3). During this period of synapse loss, overt neuronal loss is minimal (4,5). Transport defects arising from abnormal regulation of the neuronal cytoskeleton present a promising model not only for explaining early cognitive decline but also for bringing together key features driving progressive neurodegeneration.

The cytoskeleton is a dynamic array of proteins creating a critical framework upon which many cellular functions rely. Abnormal regulation of the neuronal cytoskeleton can lead to improper location of growth cone paths, dendritic spine abnormalities, transport defects, protein aggregation and cell death. Actin aggregates in the form of cofilin-actin rods have been identified in postmortem brains of patients with AD (6). The abnormal regulation of actin and cofilin proteins can be linked to a wide range of human neurodegenerative disorders, including corticobasal degeneration, William’s syndrome, fragile X syndrome, AD, dystonia with dementia, and spinal muscular atrophy. Although these diseases ultimately result from a range of defects, including dendritic spine abnormalities, loss of long-term potentiation (LTP) and long-term depression, and alterations in specific messenger RNA (mRNA) transport and translation, they are all related to processes involving the actin cytoskeleton (7). This article reviews the role and regulation of cofilin in cellular actin dynamics and explains how its abnormal regulation could be at the root of many neurodegenerative diseases.

Amyloidopathies: Down Syndrome and Alzheimer’s Disease

Amyloidopathies are a class of degenerative diseases arising from the accumulation of amyloid-β protein aggregates. Many different proteins or proteolytic fragments of proteins are capable of forming amyloid-β aggregates. Some common neuronal amyloidoses include AD, Down syndrome (DS), spongiform encephalopathies (a.k.a. prion diseases), Parkinson’s disease, and Huntington’s disease. In DS and AD, the major peptide components of the extracellular amyloid aggregates are derived from proteolysis of a large transmembrane protein, the amyloid precursor protein (APP).

APP can be divided into three domains: a large extracellular N-terminal domain, a single transmembrane domain, and a short cytoplasmic C-terminal tail. Multiple isoforms of APP are expressed, ranging in size from 695 to 770 amino acids, with APP695 being the most abundant in brain. The APP gene is found on chromosome 21 in humans and on chromosome 16 in mice. Proteolytic processing of full-length APP occurs via one of two pathways. The nonamyloidogenic pathway, which dominates APP processing in most cell types, begins with cleavage by α-secretase (ref. 8; Fig. 1A). α-Secretase is a protein that resembles the tumor necrosis factor (TNF)-α converting enzyme and belongs to the disintegrin/metalloproteinase family. This cleavage releases the soluble APP N-terminus (sAPPα) extracellularly and leaves the membrane-bound 83-amino acid C-terminal (C83). C83 undergoes subsequent cleavage...