Neurobiology of Disease 105 (2017) 273–282

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Regulation of motor proteins, axonal transport deficits and adult-onset neurodegenerative diseases

Scott T. Brady *, Gerardo A. Morfini **

Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL, USA
Marine Biological Laboratory, Woods Hole, MA 02543, USA

ARTICLE INFO

Article history:
Received 17 January 2017
Revised 17 March 2017
Accepted 10 April 2017
Available online 11 April 2017

Keywords:
Axonal transport
Kinesin
Dynen
Kinases
Signaling
Neurodegeneration
Alzheimer's disease
Huntington's disease
Amyotrophic lateral sclerosis
Parkinson's disease

ABSTRACT

Neurons affected in a wide variety of unrelated adult-onset neurodegenerative diseases (AONDs) typically exhibit a "dying back" pattern of degeneration, which is characterized by early deficits in synaptic function and neuritic pathology long before neuronal cell death. Consistent with this observation, multiple unrelated AONDs including Alzheimer's disease, Parkinson's disease, Huntington's disease, and several motor neuron diseases feature early alterations in kinase-based signaling pathways associated with deficits in axonal transport (AT), a complex cellular process involving multiple intracellular trafficking events powered by microtubule-based motor proteins. These pathogenic events have important therapeutic implications, suggesting that a focus on preservation of neuronal connections may be more effective to treat AONDs than addressing neuronal cell death. While the molecular mechanisms underlying AT abnormalities in AONDs are still being analyzed, evidence has accumulated linking those to a well-established pathological hallmark of multiple AONDs: *altered patterns of neuronal protein phosphorylation*. Here, we present a short overview on the biochemical heterogeneity of major motor proteins for AT, their regulation by protein kinases, and evidence revealing cell type-specific AT specializations. When considered together, these findings may help explain how independent pathogenic pathways can affect AT differentially in the context of each AOND.

Contents

* Correspondence to: S. T. Brady, University Of Illinois at Chicago, Dept. of Anatomy and Cell Biology MC512, 808 S Wood St Room 578, Chicago, IL 60612, USA.
** Correspondence to: G. A. Morfini, University of Illinois at Chicago, Dept. of Anatomy and Cell Biology MC512, 909 S Wolcott St. COMRB Room 6051, Chicago, IL 60612, USA.
E-mail addresses: stbrady@uic.edu (S.T. Brady), gmorfini@uic.edu (G.A. Morfini).

Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2017.04.010
0969-9961/

1. Introduction

Adult-onset neurodegenerative diseases (AONDs) represent some of the most difficult human health challenges remaining. AONDs comprise a heterogeneous group of neurological disorders including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), as well as motor neuron diseases such as amyotrophic lateral sclerosis (ALS) and hereditary spastic paraplegias (HSPs). Despite their different etiology, all AONDs feature a sustained decline in the functionality of selected neuronal populations, with the identity of such populations playing a major role on the unique set of clinical symptoms that characterize each disease. As a major risk factor for most AONDs is aging, the longer lifespans in the modern era lead to an increased number of people affected by these diseases, making our need to understand pathogenic mechanisms imperative (Mattson and Magnus, 2006).

Novel insights on AONDs pathogenesis arrived with the identification of gene mutations associated with familial forms of AONDs (Jagmag et al., 2015; McGoldrick et al., 2013; Pouladi et al., 2013; Ribeiro et al., 2013; Wong et al., 1998). While clearly major breakthroughs, these genetic studies left investigators in the neurodegenerative disease research community with more questions than answers. More often than not, specific biological functions for most AOND-associated gene products remain unknown and for those gene products with an established function (i.e.; conversion of free superoxide radicals to peroxide by superoxide dismutase 1; SOD1), pathogenic mutations were found that did not affect such function (Pardo et al., 1995). Remarkably, many AOND-associated mutant gene products are widely expressed, yet only certain neuronal populations exhibit pathology while non-neuronal cells and many other neuronal cell types are spared. For example amyloid precursor protein (APP) and the microtubule-associated protein tau are abundant proteins found in all neurons and both are closely associated with pathology in AD (Rosenberg et al., 2016). However, AD-related mutations in APP preferentially affect neurons in the hippocampus and frontal cortex, while sparing neurons in other brain regions such as motor cortex and cerebellum (Gonzalez-Dominguez et al., 2014). On the other hand, mutations in tau protein are not implicated in AD, but are instead associated with a variety of different tauopathies and some forms of frontotemporal dementia; corticobasal degeneration; progressive supranuclear palsy; and Pick's disease among others that exhibit degeneration in different neuronal populations (Gonzalez-Dominguez et al., 2014). Alterations in the pattern of tau phosphorylation have also been reported in other unrelated AONDs, such as HD (Gratuze et al., 2016). However, the large number of phosphorylation sites in tau make it difficult to determine their specific contribution to pathogenesis in those diseases (Zerr and Bahr, 2016). Similarly, mutations in the highly abundant and ubiquitously expressed SOD1 cause familial forms of ALS, which primarily features dying back degeneration of upper and lower motor neurons (Ozdinler et al., 2011), leaving other neuronal populations largely spared (Fischer et al., 2004; Wong et al., 2002). Complicating matters further, idiopathic AONDs in patients with no family history cannot easily be distinguished from familial forms and mutations in multiple, structurally unrelated gene products may result in phenotypically indistinguishable forms of AONDs (Fink, 2013; Wong et al., 2002).

More revealing was the observation that most pathogenic gene mutations in familial AONDs are inherited in an autosomal dominant manner, and knocking out these genes failed to replicate AOND symptoms [see for example (Reaume et al., 1996; Zeitlin et al., 1995)]. Collectively, observations derived from genetic findings appear consistent with a scenario where multiple independent pathogenic pathways, typically involving a toxic gain of function, affect cellular processes critical for neuronal function. Identification of these processes and the cellular factors contributing to differential vulnerability of specific neuronal populations in each AOND will prove invaluable for the development of effective therapeutic strategies. As discussed below, an analysis of early pathogenic events common to AONDs provide hints on the identity of such processes.

1.1. Neurons affected in AONDs undergo a progressive loss of synaptic and neuritic connectivity

For decades, the significant neuronal loss observed in post-mortem brains of patients affected by AONDs at advanced disease stages focused primary research efforts on understanding of cell death-related mechanisms (Martin, 2001). To that end, identification of mutant genes associated with familial forms of AONDs allowed the development of animal models, which recapitulated major clinical hallmarks observed in human AONDs. These models provided researchers with an unprecedented opportunity to reveal early, presymptomatic pathogenic events in the context of specific AONDs. Remarkably, analysis of multiple unrelated AOND models revealed consistent alterations in *neuronal connectivity* that were concurrent or even preceded the manifestation of clinical symptoms (Adalbert and Coleman, 2013; Vickers et al., 2009). Phenotypically, such deficits manifested as behavioral and motor abnormalities in the absence of significant neuronal cell death, suggesting that clinical symptoms of AONDs result from neuronal dysfunction or disconnection, rather than loss of neurons (Brady and Morfini, 2010; Coleman, 2011). A significant body of pathological evidence provided a cellular basis for these functional abnormalities, documenting synaptic dysfunction (Henstridge et al., 2016; Wishart et al., 2006) and neuritic atrophy (Bellucci et al., 2016; Fischer and Glass, 2007; Gatto et al., 2015; Kanaan et al., 2013) in animal models of multiple unrelated AONDs. In some familial forms of AONDs, brain imaging-based studies highlighted the relevance of these findings, documenting microstructural alterations in white matter, axon-rich brain areas of living presymptomatic patients (Poudel et al., 2014; Rosas et al., 2010).

Collectively, the available data indicates that neurons affected in AONDs undergo a gradual loss of synaptic and neuritic connectivity, early pathogenic events that appear responsible for the disease-specific neurological symptoms. Accordingly, therapeutic strategies that successfully prevented neuronal cell death in various animal models of AONDs failed to prevent the progression of clinical symptoms (Djaldetti et al., 2003; Gould et al., 2006; Waldmeier et al., 2006) and targeting prevention of neuronal cell death in humans have been similarly ineffective (Waldmeier et al., 2006). Instead, the degeneration pattern of neurons affected in AONDs suggests that maintenance of neuronal connectivity may be a better target for therapeutic intervention than prevention of cell death (Cheng et al., 2010; Lingor et al., 2012). However, such strategies require knowledge of mechanisms underlying loss of connectivity in the context of each AOND (Conforti et al., 2007; Gerdts et al., 2016; Luo and O'Leary, 2005). Unfortunately, the study of mechanisms has been hampered in part due to the scarcity of experimental systems designed to study axon and synapse-specific molecular events in isolation (Grant et al., 2006; Leopold et al., 1994; Llinas et al., 1992).

1.2. Pathological hallmarks common to unrelated AONDs: commonalities amid diversity

As a group, AONDs share a number of common features (see Table 1). A major one includes the increased vulnerability of certain populations of *projection neurons*, which typically extend axons to anatomically distant targets. In contrast, interneurons that bear short axons usually confined to the boundaries of specific brain structures are commonly spared or affected very late in the course of AONDs. Along with other cellular factors, such morphological differences appear to contribute to the differential vulnerability of specific neuronal populations observed in each disease (Han et al., 2010; Mattson and Magnus, 2006; Parent and Parent, 2006; Prensa et al., 2009).

At the cellular level, early pathological events common to neurons affected in all AONDs include synaptic dysfunction and neurite atrophy,