Ataxin-3 phosphorylation decreases neuronal defects in spinocerebellar ataxia type 3 models

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Different neurodegenerative diseases are caused by aberrant elongation of repeated glutamine sequences normally found in particular human proteins. Although the proteins involved are ubiquitously distributed in human tissues, toxicity targets only defined neuronal populations. Changes caused by an expanded polyglutamine protein are possibly influenced by endogenous cellular mechanisms, which may be harnessed in order to produce neuroprotection. Here, we show that ataxin-3, the protein involved in Spinocerebellar ataxia type 3, also known as Machado-Joseph disease, causes dendritic and synapse loss in cultured neurons when expanded. We report that S12 of ataxin-3 is phosphorylated in neurons and that mutating this residue so as to mimic a constitutive phosphorylated state counters the neuromorphologic defects observed. In rats stereotaxically injected with expanded ataxin-3-encoding lentiviral vectors, mutation of serine 12 reduces aggregation, neuronal and synapse loss. Our results suggest that S12 plays a role in the pathogenic pathways mediated by polyglutamine-expanded ataxin-3 and that phosphorylation of this residue protects against toxicity.