Neurodegeneration in humans and mice: lessons from a polyglutamine disease

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Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant, polyglutamine-induced neurodegenerative disorder that includes progressive motor dysfunction due to the loss of cerebellar Purkinje cells. Polyglutamine-induced neurodegeneration in transgenic mice carrying the spinocerebellar ataxia type 1 (SCA1) gene is modulated by subcellular distribution of ataxin-1 and by components of the protein folding/degradation machinery. Since phosphorylation is a prominent mechanism by which these processes are regulated, we examined phosphorylation of ataxin-1 and found that serine 776 (S776) was phosphorylated. The importance of S776 for polyglutamine-induced pathogenesis was examined by generating ataxin-1[82Q]-A776 transgenic mice. These mice expressed ataxin-1[82Q]-A776 within Purkinje cell nuclei, yet the ability of ataxin-1[82Q]-A776 to induce disease was substantially reduced. These studies demonstrate that polyglutamine tract expansion and localization of ataxin-1 to the nucleus of Purkinje cells are not sufficient to induce disease. Recently, we have developed a conditional SCA1 mouse model to examine whether stopping the expression of mutant ataxin-1 alters the disease phenotype. At all stages of disease analyzed mutant ataxin-1, including protein in intranuclear inclusions, was cleared from Purkinje cells within a week. Upon cessation of SCA1 transgene expression, mutant ataxin-1, including that in nuclear inclusions was cleared rapidly from Purkinje cells. At an early stage of disease, Purkinje cell pathology and motor dysfunction were completely reversible. Upon halting SCA1 expression at a later stage of disease, only a partial recovery was seen. These results show that the progression of SCA1 pathogenesis is dependent on the continuous expression of mutant ataxin-1.