Mechanisms of disease: Proteolysis of ataxin-3

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Proteolytic cleavage of disease-causing proteins is a widely discussed mechanism in neurodegenerative disorders, which gives rise to toxic fragments and thus may amplify the formation of protein aggregates. This molecular model - known as the *toxic fragment hypothesis* - was also proposed to play a crucial role in Machado Joseph Disease (MJD) and several studies have reported on the proteolysis of polyglutamine-expanded ataxin-3, the causative protein in MJD. Hitherto two classes of enzymes, caspases and calpains, were linked with the proteolytic processing of ataxin-3, triggering neurotoxicity and cell death. Inhibition of protease activity and mutation of caspase or calpain cleavage sites within mutant ataxin-3 was shown to reduce toxicity and neuronal death in cell and animal models of MJD. Our better understanding of proteolytic events in MJD has opened new possibilities to identify therapeutic targets as a treatment for this fatal disorder.