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THE ROLE OF P62 IN THE DEGRADATION OF THE MUTANT HUNTINGTIN PROTEIN

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ABSTRACT

Huntington's disease is a fatal, incurable neurodegenerative disease characterized by protein aggregates in the brain. These aggregates result from an accumulation of the mutant form of the Huntingtin protein (mHTT). Initially, the mHTT exists in the form of small, soluble species, but eventually, it forms large aggregates. Surprisingly, the soluble species are thought to be more toxic for the cells than the large aggregates. The cells have pathways to degrade the mHTT, but they are overwhelmed in the disease state. The degradation of the large aggregates is well characterized, but the alternative pathway by which the small, more toxic species are degraded is not well understood. I found that protein P62 is involved in the degradation of the soluble mutant Huntingtin. My working model is that P62 functions to degrade proteins through an interaction with TRAF6, an E3 ubiquitin ligase. My data show that TRAF6 affects ubiquitination of ER stress-induced aggregates, which are degraded by the same pathway as the mHTT. Current and future work will aim at further investigating the P62-TRAF6 role in the degradation of the mutant Huntingtin protein. By improving our understanding of the degradation pathway of the toxic mHTT species, we may be able to enhance the pathway as a therapeutic to combat Huntington's disease. Clarifying the role of P62 will give us a better understanding of the pathway as well as potential target for therapy.