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Exogenous delivery of chaperonin subunit fragment ApiCCT1 modulates mutant Huntingtin cellular phenotypes.

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Abstract

Aggregation of misfolded proteins is characteristic of a number of neurodegenerative diseases, including Huntington disease (HD). The CCT/TRiC (chaperonin containing TCP-1/TCP-1 ring) chaperonin complex can inhibit aggregation and cellular toxicity induced by expanded repeat Huntingtin (mHtt) fragments. The substrate-binding apical domain of CCT/TRiC subunit CCT1, ApiCCT1, is sufficient to inhibit aggregation of expanded repeat mHtt fragments in vitro, providing therapeutic promise for HD. However, a key hurdle in considering ApiCCT1 as a potential treatment is in delivery. Because ApiCCT1 has a region of similarity to the HIV Tat protein cell-transduction domain, we tested whether recombinant ApiCCT1 (ApiCCT1(r)) protein could enter cells following exogenous delivery and modulate an established panel of mHtt-mediated cell-based phenotypes. Cell fractionation studies demonstrate that exogenous ApiCCT1(r) can penetrate cell membranes and can localize to the nucleus, consistent with a strategy that can target both cytosolic and nuclear pathogenic events in HD. ApiCCT1(r) application does indeed modulate HD cellular phenotypes by decreasing formation of visible inclusions, fibrillar oligomers, and insoluble mHtt derived from expression of a truncated mHtt exon 1 fragment. ApiCCT1(r) also delays the onset of inclusion body formation as visualized via live imaging. ApiCCT1(r) reduces mHtt-mediated toxicity in immortalized striatal cells derived from full-length knock-in HD mice, suggesting that therapeutic benefit may extend beyond effects on aggregation. These studies provide the basis for a potentially robust and unique therapeutic strategy to target mHtt-mediated protein pathogenesis.

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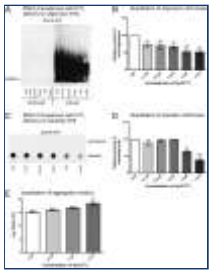

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