The ubiquitin E3 ligase Human Homolog of Drosophila Ariadne-1 (HHARI) is a structural and functional homolog of Parkin and is required for myogenesis

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Abstract

Several genes implicated in Parkinson's disease (PD) encode components of the ubiquitin-proteasome pathway. In a specific form of PD (human Autosomal Recessive Juvenile Parkinsonism, AR-JP), loss of functional Parkin (ubiquitin E3 ligase) results in a selective loss of midbrain dopaminergic neurons and a absence of Lewy bodies (LB) from the surviving dopaminergic neurons. Since cells in patients with AR-JP do not express functional Parkin, it is unclear why most neuronal and non-neuronal populations remain unaffected. One possible explanation is that most cells express a redundant ubiquitin E3 ligase(s) that is absent from dopaminergic neurons. Such candidate(s) redundant E3-ligase would be expected to fulfill several criteria: (1) bind similar E2 Ubiquitin conjugating enzymes; (2) interact with the same cellular substrates; (3) facilitate the formation of aggresome/lewy bodies with similar properties of those induced by Parkin; (4) be expressed in the nervous system but presumably absent (or largely absent) from dopaminergic neurons. ^ In this thesis I have demonstrated that the Human Homolog of Drosophila Ariadne-1 (HHARI) is a candidate for such a redundant E3 ligase. In addition I have shown that even though HHARI induces the formation of LB like aggresomes in cell culture with properties similar to those produced by Parkin, these aggresomes differ in their detergent solubility properties. ^ Using mouse C_2C_{12} primary skeletal muscle cells with altered expressions of Ariadne-1 or Parkin, I determined if HHARI and Parkin may serve redundant protective roles. Using cell viability assays I have shown that HHARI does not confer protection to cells treated with toxic insults like those implicated in PD. On the contrary, using RNA silencing, I have shown that reduced Ariadne-1 expression appears to confer some benefit. ^ Finally, based on phenotypes reported for Ariadne-1$^{-/-}$ escaper and Parkin$^{-/-}$ flies as well as our protein interaction data, I investigated the roles of Parkin and HHARI during myogenesis. Using engineered C_2C_{12} cells I have shown that Ariadne-1 levels are tightly regulated in proliferating and differentiating C_2C_{12} cells and that increased cellular abundance of Ariadne-1 affects muscle terminal differentiation downstream of myogenin, strongly highlighting the importance of Ariadne-1 and perhaps the Ubiquitin Proteasome Pathway in myogenesis.^

Subject Area

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