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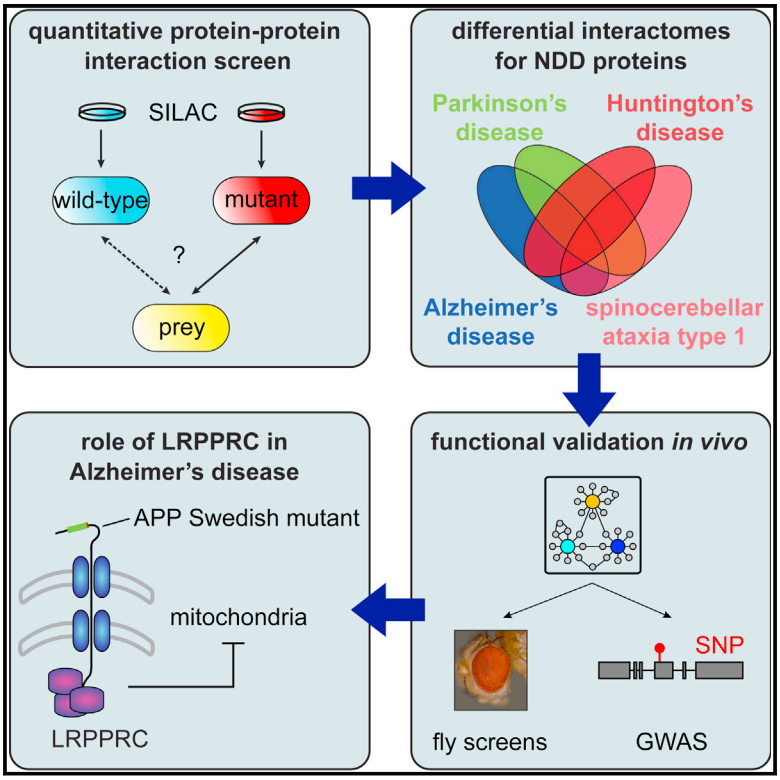
Quantitative Interaction Proteomics of Neurodegenerative Disease Proteins

Graphical Abstract



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In Brief

Hosp et al. show that quantitative interaction proteomics of neurodegenerative disease proteins captures interactions relevant to pathogenesis. Differential interactome mapping reveals preferential binding of the mitochondrial protein LRPPRC with an early-onset Alzheimer's disease (AD) variant of APP, potentially contributing to mitochondrial dysfunction observed in AD.

Highlights

- Quantitative interactomics of proteins involved in four neurodegenerative diseases
- Differential interaction mapping of wild-type and disease-associated proteins
- Interaction partners are significantly linked to disease phenotypes in vivo
- Interaction of APP and LRPPRC appears to induce mitochondrial dysfunction in AD

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Quantitative Interaction Proteomics of Neurodegenerative Disease Proteins

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SUMMARY

Several proteins have been linked to neurodegenerative disorders (NDDs), but their molecular function is not completely understood. Here, we used quantitative interaction proteomics to identify binding partners of Amyloid beta precursor protein (APP) and Presenilin-1 (PSEN1) for Alzheimer's disease (AD), Huntingtin (HTT) for Huntington's disease, Parkin (PARK2) for Parkinson's disease, and Ataxin-1 (ATXN1) for spinocerebellar ataxia type 1. Our network reveals common signatures of protein degradation and misfolding and recapitulates known biology. Toxicity modifier screens and comparison to genome-wide association studies show that interaction partners are significantly linked to disease phenotypes in vivo. Direct comparison of wild-type proteins and disease-associated variants identified binders involved in pathogenesis, highlighting the value of differential interactome mapping. Finally, we show that the mitochondrial protein LRPPRC interacts preferentially with an early-onset AD variant of APP. This interaction appears to induce mitochondrial dysfunction, which is an early phenotype of AD.

INTRODUCTION

The functional characterization of disease-associated proteins is a major challenge in the post-genomic era. Since proteins typically exert their function by binding other proteins, systematic mapping of protein-protein interactions (PPIs) can help with the understanding of protein function. The yeast two-hybrid (Y2H) system generated large-scale human PPI networks (Rual et al., 2005; Stelzl et al., 2005). Similarly, affinity purification and mass spectrometry (AP-MS) has been employed to create interactome maps for model organisms and humans (Ewing et al., 2007; Gingras et al., 2007; Guruharsha et al., 2011; Malovannaya et al., 2011). Although such interaction networks are still incomplete, they are beginning to provide valuable functional insights for human diseases (Barabási et al., 2011; Ideker and Sharan, 2008; Vidal et al., 2011).

Since mutations might alter PPIs, comparing the interactions of wild-type proteins and their disease-linked variants might be particularly informative (Schuster-Böckler and Bateman, 2008; Zhong et al., 2009). This information cannot be extracted from most available interaction datasets. The Y2H assay is at best semiquantitative and unable to detect small alterations in the affinity of PPIs (Estojak et al., 1995; Zhong et al., 2009). Similarly, most AP-MS studies only used semiquantitative methods like spectral counting or were performed entirely without quantification. Spectral counting yields unreliable data, especially when the interaction partner is of low abundance and/or the number of samples is small (Gingras and Raught, 2012; Rinner et al., 2007).

To overcome these problems, we sought to investigate PPIs of disease-associated proteins in a quantitative manner. Quantitative affinity purification and mass spectrometry (qAP-MS) can accurately distinguish between specific interaction partners and non-specific contaminants and quantify changes in PPIs upon perturbation (Paul et al., 2011; Vermeulen et al., 2008; Wepf et al., 2009). We reasoned that qAP-MS should be particularly well suited to identify interaction partners of disease-associated proteins. Therefore, we employed this technology to assess interaction partners of proteins involved in neurodegenerative diseases (NDDs). We focused on five well-known disease proteins involved in Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and spinocerebellar ataxia type 1 (SCA1). These four NDDs are characterized by the accumulation of protein aggregates in the brain and the progressive loss of neurons (Ross and Poirier, 2004). HD and SCA1 are caused by expansion of CAG repeats in the huntingtin and ataxin-1 genes, respectively, which gives rise to proteins with abnormally long polyglutamine (polyQ) tracts (Chung et al., 1993; Rubinsztein et al., 1996). Although many risk factors