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Is modulating translation a therapeutic option for Huntington's disease?

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Despite great advances in the understanding of pathogenic mechanisms underlying Huntington's disease in recent years, no treatments have been identified that halt progression or onset of this devastating neurodegenerative disorder. Huntington's disease is caused by mutations that lengthen a stretch of glutamines in the huntingtin protein [1]. This polyglutamine expansion causes improper folding and aggregation of huntingtin [2], leading to toxic cellular consequences and, ultimately, degeneration of a specific subset of neurons in the striatum of Huntington's disease patients [3]. These cellular disturbances include transcriptional dysregulation, impairment of the ubiquitin–proteasome system, defects in vesicle trafficking and mitochondrial dysfunction [4–6]. In addition to these 'gain-of-toxic-function' effects, it is likely that loss of normal huntingtin function also contributes to pathology in patients [6]. The median age of onset is approximately 50 years, followed by death 10–15 years later [7]. Although length of the polyglutamine expansion is the main determinant of onset age, there is great variation in this parameter even when controlling for expansion length. Approximately 40% of this variation is caused by genetic modifiers [8], suggesting that many therapeutic targets may be available for this disease.

Translation, the process by which a cell produces proteins from mRNA, is an exquisitely controlled and regulated system. Cellular insults that perturb this process can have severe downstream consequences for the health of a cell; for example, many antibiotics function by targeting translation in bacteria. We recently performed a functional genomics survey in yeast, which suggested that translational dysfunction may be a critical aspect of mutant huntingtin toxicity [9]. The baker's yeast *Saccharomyces cerevisiae* has been used for over a decade to model aspects of Huntington's disease, from the mechanisms underlying protein misfolding to transcriptional dysregulation to dysfunction of several cellular processes [10]. Importantly, this simple model has been used to identify several promising candidate therapeutic targets for Huntington's disease, including kynurenine 3-monooxygenase [11]. We recently identified genes (~470) whose expression is perturbed in yeast containing mutant huntingtin protein and found downregulation of many genes involved in ribosome biogenesis and processing of rRNAs, suggesting dysfunction in these cellular processes. Ribosomes are the molecular machinery that perform translation, manufacturing proteins from amino acids by decoding the genetic information present in mRNA. rRNAs are the RNA component of the ribosome, and are critical for this decoding. To test whether these genes have functional consequences in yeast expressing mutant huntingtin, we systematically interrogated the vast majority of these genes by deletion or overexpression,

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and identified 14 genes that can modulate toxicity. Strikingly, we found that six of these genes are involved in the processing of rRNAs. In all cases these six genes were strongly downregulated in yeast expressing mutant huntingtin and overexpression of the individual genes was sufficient to suppress cellular death in this model. Furthermore, four of these genes have clear human orthologs, suggesting that this work may have relevance to humans. Further computational analysis of the differentially expressed genes determined a complex network of interactions in the cell that modulate mutant huntingtin toxicity, which again showed a strong enrichment in genes involved in rRNA processing and ribosome biogenesis, and highlights the central nature of this observation in yeast. These data suggest that mutant huntingtin can perturb ribosome function, and consequently translation, and that by supplementing key proteins involved in these processes dysfunction can be alleviated.

Our observations resonate with recent research on aging and parkinsonian disorders [12,13]. Work exploiting *Drosophila melanogaster* (fruit fly) models of Parkinson's disease found that modulation of eIF4E-dependent translation may present an important therapeutic strategy in this disorder [13]. eIF4E plays a central role in regulating translation by mediating the binding of the translation initiation complex to the 7-methylguanosine cap structure at the 5' end of eukaryotic mRNAs [14]. eIF4E-binding proteins (4E-BPs) serve as translational switches under stress conditions by blocking the action of eIF4E and thereby promoting 5' cap-independent translation, which favors translation of pro-survival factors [14]. Using fruit flies with *PINK1* and *parkin* mutations (genes linked to recessive familial Parkinson's disease) the authors found that expression of 4E-BP strongly suppressed all disease-relevant phenotypes, including neurodegeneration [13]. Pharmacological activation of 4E-BP also suppressed these phenotypes, highlighting the promise of this area for therapeutics. Further studies have noted that *LRRK2* mutations, the predominant genetic cause of Parkinson's disease, may perturb regulation of 4E-BP [15-17]. In total these studies suggest a functional convergence of several familial parkinsonian genes, and a central role for translation regulation in potential treatments for neurodegenerative disease processes.

Although scarce, some other evidence from the literature supports a role for translational perturbations in Huntington's disease. Early work in this area found altered expression of the ribosomal protein Rrs1 prior to onset of symptoms in critical brain regions of both patients and a mouse model of Huntington's disease [18]. Gene profiling in mammalian cell and rodent models of Huntington's disease found enrichment in genes encoding ribosomal proteins [19-22], supporting a role for translational dysfunction in pathology. The therapeutic potential for regulation of translation is underscored by two recent studies. First, it was observed that pharmacological inhibition of cap-dependent translation in mammalian cells reduces aggregation of mutant huntingtin [23]. More recently, a genetic screen in *Drosophila* cells found that genes involved in translation modulated aggregation of mutant huntingtin [24]. It has also been observed that huntingtin may normally function to modulate translation of certain mRNAs during neuronal transport [25], raising the possibility that this process may be disrupted in disease.

So will modulation of translation prove to be a viable therapeutic strategy for Huntington's disease? At this stage, it is much too early to predict. While promising, these observations need to be fully interrogated in more physiologically relevant models of Huntington's disease – studies that are currently underway. Nonetheless, these studies highlight the importance of teasing apart these mechanism(s) in pathology. Future work will need to clarify the nature of the translational dysfunction observed, and whether regulation of translation has a place at the therapeutic table for Huntington's disease.

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