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## What is gained or “lost in translation” in Huntington’s disease

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Robert Frost, the famous American poet (1874–1963), defined poetry as what is “lost in translation”. But there is also complexity, and indeed poetry, in the process of “translation” in biology. Translation, through its subprocesses of initiation, elongation and termination, allows a cell to read the genetic code to synthesize proteins. Even in healthy cells, approximately 30% of newly synthesized polypeptides are lost during translation as a result of mistakes (defective ribosomal products – DriPs). This suggests that translation is tightly controlled and that failure rates are likely to be even higher in diseased cells (Alvarez-Castelao et al., 2012). In neurons, most proteins are produced in the rough endoplasmic reticulum and the soma. However, translation also occurs in the dendrites and the axon to allow neurons to swiftly adapt to changes in demand or in local energy requirements. It is thus conceivable that defects in translation may contribute to neurodegeneration, as has recently been shown for genetic forms of Parkinson’s disease associated with *LRRK2* mutations (Martin et al., 2014). In this issue of *Brain*, Creus-Muncunill and co-workers present data suggesting that disruption of translation may also contribute to pathology in Huntington’s disease (Creus-Muncunill et al., 2019).

Huntington’s disease is an inherited neurodegenerative disorder caused by mutation of the *huntingtin* gene. Expansion of a triplet CAG repeat leads to expansion of a polyglutamine tract in the huntingtin protein (HTT). This leads to early loss of striatal projection neurons. Mutant huntingtin (mHTT) is neurotoxic to neurons and astrocytes, through gain- and loss-of-function mechanisms affecting many cellular functions (Saudou & Humbert, 2016). Creus-Muncunill *et al.* discovered that levels of 4E-BP1, a protein that inhibits translation, are reduced in a mouse model of Huntington’s disease. 4E-BP1 is also hyper-phosphorylated, which prevents it from interacting with the regulatory protein eIF4E. This suggests that translation may be activated inappropriately in Huntington’s disease, and indeed, Creus-Muncunill *et al.* found an increase in translation in the brain of patients *post mortem*. The group, led by Esther Pérez-Navarro, also used mass spectrometry to obtain a global view of several hundred proteins with altered expression in Huntington’s disease mice. While levels of proteins related to

ribosomal function and energy production were increased, there was decreased translation of proteins related to neuronal function. Pharmacological blockade of translation using 4EGI-1, a selective inhibitor of 4E-BP1, restored ribosomal and mitochondrial proteins to control levels in Huntington's disease mice. Furthermore, injecting 4EGI-1 into the brain improved motor signs in the mice.

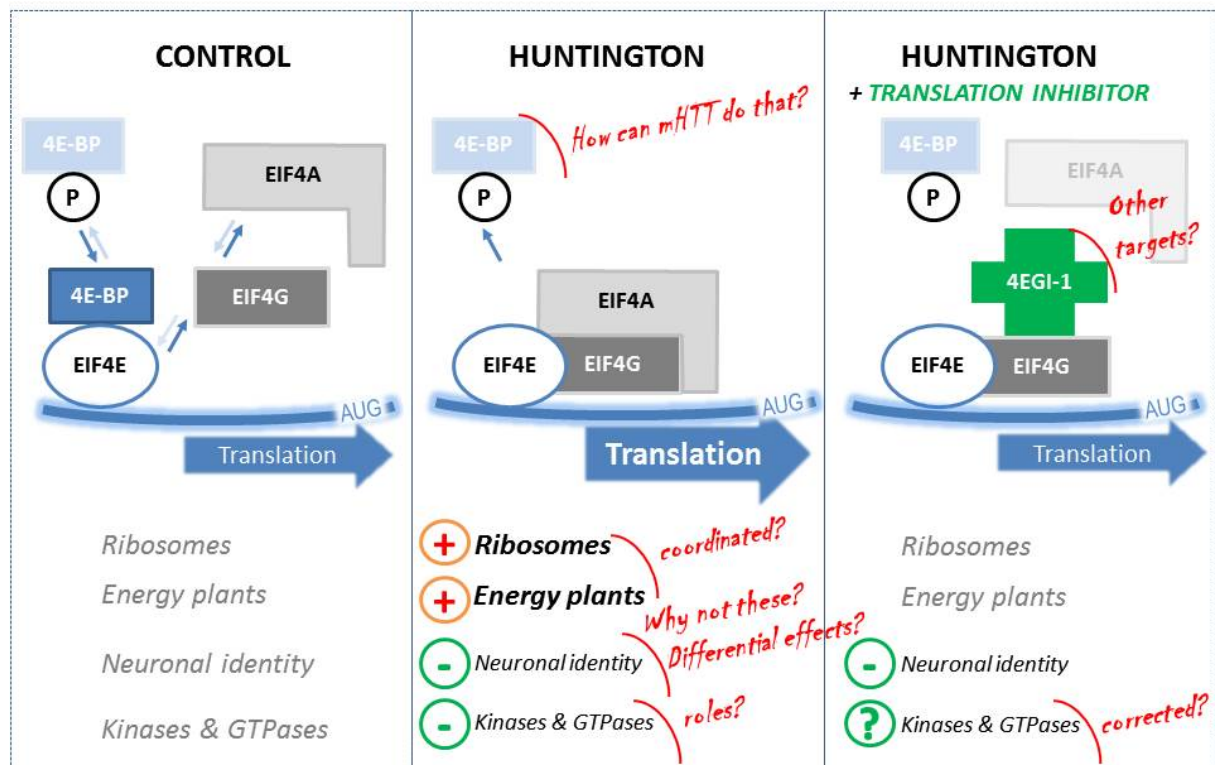
But as with many discoveries, these findings raise more questions than they provide definitive answers. Is an increase in translation “logical” in neurodegeneration? At first sight, it might appear to be a sensible reaction of cells that are under stress. And indeed, the proteins that show increased translation in Huntington's disease are linked to regulation of translation and energy metabolism. Thus, increasing their levels could in principle make cells healthier. But this is not the case, as blocking translation with 4EGI-1 is neuroprotective. Transcriptomic data related to Huntington's disease have not shown major dysregulation of genes controlling translation (Seredenina et al., 2012). Increased translation seems to be linked to increased phosphorylation of 4E-BP1. This may result from increased activity of a kinase and/or a decreased activity of a phosphatase both of which remains to be identified. Moreover, the increase in translation does not affect all striatal proteins indiscriminately. Levels of proteins preferentially expressed by striatal projection neurons (e.g. DARPP32) are down-regulated in Huntington's disease, and do not recover under 4EGI-1 treatment. This is consistent with known reductions in mRNA levels of striatal identity genes (Seredenina et al., 2012). For these genes, transcription and translation are both reduced. Another intriguing question is how can mHTT have different effects on translation depending on a gene's function? One possibility is that specific molecular machinery might control the translation of different types of genes, with mutant HTT having differential effects on these machineries. This issue remains to be resolved.

Cellular power sources (i.e. mitochondria and glycolysis) and translation machinery have evolved simultaneously and are remarkably conserved in eukaryotes, likely because the energy cost of translation is extremely high (Alvarez-Castelao et al., 2012). Are translation and energy metabolism “in tune” in Huntington's disease? Increased translation should increase cellular demand for ATP, and Creus-Muncunill *et al.* identified a consistent increase in translation of proteins related to energy metabolism. But why is this increase in translation detrimental? Energy metabolism and production of reactive oxygen species are abnormal in Huntington's disease (Liot et al., 2017). Thus it is conceivable that increased expression of proteins related to energy production may augment oxidative stress in unhealthy cells.

The mechanisms underlying the improvement in motor function in Huntington's disease mice treated with 4EGI-1 remain to be fully elucidated. 4EGI-1 does not change the number of mHTT-containing

aggregates, indicating no direct effect on mHTT aggregation. 4EGI-1 may act through unexpected targets, as shown for cycloheximide which blocks apoptosis by mechanisms other than just translation inhibition (Chow et al., 1995). The improved motor function of Huntington's disease mice receiving 4EGI-1 could also result from changes in cell signalling. In the data from Creus-Muncunill *et al.*, it is quite remarkable to see that 20% of the down-regulated proteins in R6/1 mice are kinases (20%) while 10% are GTPases, including Rab proteins. Restoring expression of these proteins with 4EGI-1 may also be protective, improving cell signalling and trafficking of vesicles.

The results with 4EGI-1 provide a convincing proof-of-concept of the potential value of targeting translation. Inhibition of translation is also being explored in cancer therapy (Blagden & Willis, 2011). For Huntington's disease, a selective molecular tool that restores expression of ribosomal and energy-related proteins could be a good option. Creus-Muncunill *et al.* illustrate perfectly how basic research feeds into medicine by laying the foundations for *translational* research. The value of basic research is too often neglected by local and governmental funding agencies that exclusively favour applied approaches. The origins of research into translation can be traced back to the beginning of the 20<sup>th</sup> century. Since that time, many basic scientists, including more than 20 Nobel prize winners, have contributed to our knowledge of translation. Thanks to this work, "translational" research on translation in Huntington's disease can finally begin.



**Figure 1** The discovery that mRNA translation is inappropriately increased in Huntington's disease raises several questions. In the healthy brain (control), translation regulation involves an equilibrium in the formation of the molecular complex (comprising 4E-BP, EIF4E, EIF4G and EIF4A) that initiates translation. While 4E-BP tends to inhibit translation through binding to EIF4E, its phosphorylated form (P-4E-BP) has a low affinity for EIF4E, losing its inhibitory effect. Creus-Muncunill et al. show that elevated phosphorylation of 4E-BP in Huntington's disease could produce a disinhibition of translation leading to increased levels of proteins involved in ribosomal function and energy metabolism. Intracerebral injection of the inhibitor of translation 4EGI-1 in a mouse model of Huntington's disease, restores ribosomal and energy production proteins to normal levels and improves motor performance. This indicates that increased translation in Huntington's disease is detrimental, and as such represents an interesting target or new therapeutic strategies. Questions remaining to be answered are shown in red (see main text for details).

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