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Deregulation of protein translation control, a potential game-changing hypothesis for Parkinson's disease pathogenesis

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Protein translation is one of the most fundamental and exquisitely controlled processes in biology, and is energetically demanding. The deregulation of this process is deleterious to cells, as demonstrated by several diseases caused by mutations in protein translation machinery. Emerging evidence now points to a role for protein translation in the pathogenesis of Parkinson's disease (PD); a debilitating neurodegenerative movement disorder. In this paper, we propose a hypothesis that protein translation machinery, PD-associated proteins and PD pathology are connected in a functional network linking cell survival to protein translation control. This hypothesis is a potential game changer in the field of the molecular pathogenesis of PD, with implications for the development of PD diagnostics and disease-modifying therapies.

Molecular pathogenesis of PD

Research on molecular disease pathogenesis is a complex endeavor involving the identification of disease factors in patients then investigating in depth how these factors affect cellular functions. By confirming the relevance of affected processes in disease models it is ultimately possible to exploit these findings to develop novel diagnostics and therapeutics for patients. In the past 15 years, a wealth of genetic studies has identified several disease factors for PD; a debilitating and incurable neurodegenerative disease. Scientists in the PD field agree that the cause of neurodegeneration lies in a chronic deregulation of cellular processes causing accumulations of subtle cytotoxic effects ultimately leading to premature dopaminergic neuron death. Several cellular processes have been extensively studied in this regard; the most notable of which are protein folding, mitochondrial physiology, membrane physiology, vesicular transport, gene transcription, protein degradation and autophagy. Here, we discuss the hypothesis that protein translation problems are an integral part of PD pathogenesis and that further detailed investigation of protein translation in PD is warranted.

Protein translation

Protein translation, one of the most fundamental and exquisitely controlled processes in biology, has received little attention in PD. Protein translation is the overall process whereby proteins are synthesized from the genetic

Glossary

5′ cap: The chemical modification at the 5′ end of mRNAs, often in the form of a modified guanine nucleotide, which stabilizes the mRNA. The 5′ cap is required for efficient nuclear export as well as for the recruitment of translation initiation complexes in cap-dependent protein translation.
Cap-dependent translation: protein translation that involves recruitment of a translation initiation complex to the 5′ cap structure of the mRNA to be translated.
Cap-independent translation: protein translation that involves recruitment of a translation initiation complex to a structure of the mRNA to be translated other than the 5′ cap structure.
Cap-independent translation element (CITE): a sequence in mRNA that mediates translation initiation without requiring the 5′ cap.
Eukaryotic elongation factor (eEF): protein that is in complex with ribosomal proteins and the mRNA being translated, which contributes to the synthesis of the polypeptide chain.
Eukaryotic initiation factor (eIF): protein which acts in complex with ribosomal proteins and other eIFs during the protein translation initiation phase, which includes recruitment of ribosomes to mRNA to be translated and scanning for the start codon.
Genetic linkage study: study of the co-segregation of a trait (such as disease) and an allele (such as mutation of a gene) in families. Linked genes are dominant when a single copy of the allele confers disease or recessive when disease occurs only when alleles are present on both chromosomes.
Genome-wide association study (GWAS): study searching across the entire genome for SNPs that vary between populations (such as of a population of PD patients compared to a matched control population). Polymorphisms enriched in disease populations point to candidate risk factors for that disease.
Internal ribosomal entry site (IRES): a nucleotide sequence in mRNA that allows translation initiation to occur in the middle of the mRNA, as opposed to at the 5′ cap.
Mitochondrial translation: protein translation occurring in mitochondria or on mitochondrial membranes. A limited number of proteins are translated in mitochondria; mostly proteins that are components of the oxidative phosphorylation pathway. Mitochondrial translation is distinct from protein translation occurring in the cytoplasm and across the membrane of the ER, where the majority of cellular proteins are translated.
Ribosome: ribonucleoprotein complexes that serve as the protein synthesis machinery, linking amino acids together in polypeptide chains dictated by successive codon triplets of messenger RNA. Ribosomes act in conjunction with protein translation factors to fulfill the different steps of protein synthesis.

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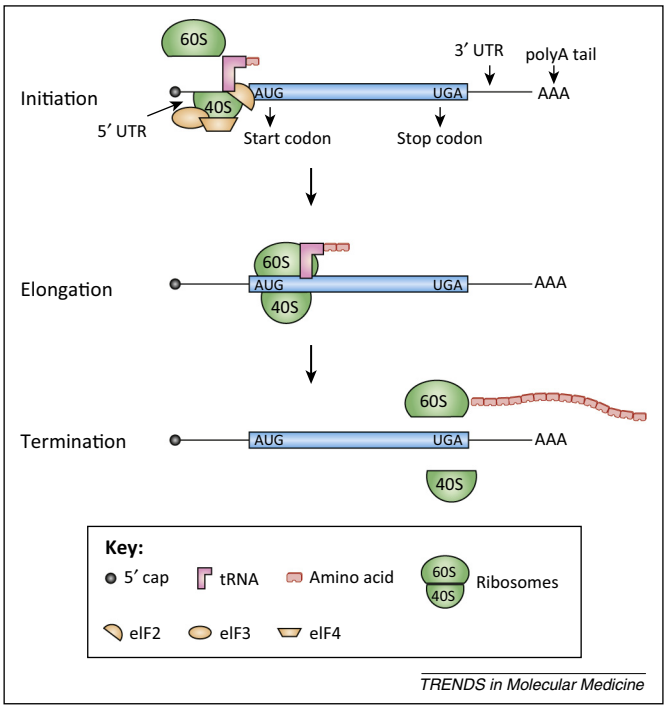

Figure 1. Schematic depiction of the three main steps of protein translation: initiation, elongation, and termination. Shown is an mRNA molecule including a coding sequence (in blue, including the AUG start and UGA stop codons), flanked by a 5′ UTR with cap and polyadenylated 3′ UTR. Ribosomal proteins, tRNAs, and translation factors are recruited to the mRNA to mediate the different steps of the protein synthesis process, shown here for cap-dependent translation. At translation initiation, eIF2 recruits tRNAs to the 40S ribosomal subunit. eIF3 and eIF4 initiation factors are also recruited to the 40S and this complex binds to the 5′ cap structure of mRNAs and scans the 5′ UTR to find the start codon, at which point the 60S ribosomal subunit is recruited and initiation factors are released. During the elongation phase, elongation factors (not depicted) are recruited to the ribosome and polypeptide chain synthesis occurs via the cycle of positioning the appropriate tRNA to the ribosome, forming the new peptide bond and shifting the ribosome complex by 1 codon on the mRNA chain. When the translation complex reaches the stop codon, elongation stops and the ribosome is released from the mRNA with the help of release factors (not depicted). Abbreviations: eIF, eukaryotic initiation factor; UTR, untranslated region.

information of RNA transcripts (Figure 1). This process is divided into three phases: initiation, elongation and termination. Initiation involves the concerted action of multiple translation initiation factors (eIFs; see Glossary). When loaded with GTP, eIF2 recruits tRNAs to the 40S ribosomal subunit. eIF3 and eIF4 initiation factors are also recruited to the 40S ribosomal subunit and this complex of 40S with tRNA and eIFs, called the pre-initiation complex, can then bind to the 5′ cap structure of mRNAs. The pre-inititation complex scans the 5′ untranslated region (UTR) to find the start codon, at which point the 60S ribosomal subunit is recruited and initiation factors are released. It should be noted that there is also a cap-independent translation initiation mechanism where ribosomes are not recruited to the 5′ cap but rather to a region of the mRNA presenting a sequence capable of recruiting ribosomes and/or translation initiation factors such as an internal ribosomal entry site (IRES) [1] or cap-independent translation element (CITE) [2]. During the elongation phase, elongation factors are recruited to the ribosome and a sequence of events is repeated for the addition of each new amino acid to the polypeptide chain: positioning the appropriate tRNA to the ribosome acceptor site (A site), forming the new peptide bond and shifting the ribosome complex by one codon on the mRNA chain. The elongation process is subject to ribosome pausing, for instance in the case of cotranslational folding of the nascent protein. When the translation complex reaches the stop codon, elongation stops and the ribosome is released from the mRNA with the help of release factors. While the majority of mRNAs are translated in the cytosol or across endoplasmic reticulum (ER) membranes, some are also translated in mitochondria or on mitochondrial surfaces [3].

Several inherited diseases are caused by mutations in genes involved in the protein translation process. For instance, mutations in the ribosomal protein RPS19 are known to be a cause of diamond–blackfan anemia [4]. Mutated protein translation proteins are also the cause of brain disorders, such as autistic spectrum disorder [5], neurodegenerative disorders such as Charcot–Marie–Tooth disease (where mutations in tRNA synthetases are reported) [6], and forms of cerebellar ataxia (where mutations are reported in translation initiation factor eIF2B) [7]. Other evidence for the role for protein translation in ataxia comes from the ataxin-2 gene (*ATXN2*) that is linked to spinocerebellar ataxia 2 (SCA2). Ataxin-2 protein binds ribosomes [8] as well as the polyA binding protein cytoplasmic 1 (PABPC1) protein [9] that interacts with eIF4G, thereby favoring transcript circularization and translation initiation [10]. Ataxin-2 is also reported to interact with GW182 and Argonaute 1 (Ago1), two proteins involved in the biogenesis of miRNAs [11], and is also located in cellular compartments where protein translation occurs, such as P bodies [12] and rough endoplasmic reticulum [13]. Interestingly, some mutations in *ATXN2* are associated with a PD phenotype, suggesting that disturbances in protein translation may contribute to PD pathogenesis.

Genetic links between PD and protein translation

Although the etiology of PD is not fully understood, genetic studies in patients have identified several mendelian and susceptibility genes involved in the disease. A first series of disease genes were identified as causative factors of rare monogenic forms of PD. These include autosomal dominant genes such as the gene encoding the α-synuclein protein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*) and *EIF4G1*, or recessive genes such as the parkin gene (*PRKN*), Pten-induced kinase 1 (*PINK1*) or *DJ-1*. More recently, genome-wide association studies (GWASs), have identified genomic loci where single nucleotide polymorphisms are associated with increased risk for PD. Meta analysis has confirmed at least 22 candidate risk loci [14], including at the *SNCA*, microtubule associated protein τ (*MAPT*), *LRRK2* and glucosidase β acid (*GBA*) genes.

Recent reports have shown that several proteins implicated in PD intervene in protein translation processes. The most obvious example is EIF4G1, which linked to both PD [15] and Lewy body dementia [16]. EIF4G1 is a translation initiation factor, and is known to play a role as a scaffold in the eIF4F translation initiation complex that recruits ribosomes and tRNAs to the 5′ cap structure of mRNA [17]. Several mutations in EIF4G1 have been identified in PD patients, including p.A502 V and p.R1205H [15],