Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

RNA metabolism in the pathogenesis of Parkinson's disease

*Bingwei Lu**, *Stephan Gehrke*, *Zhihao Wu*

Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305, United States

ARTICLE INFO

Article history:
Accepted 7 March 2014
Available online 13 March 2014

Keywords:
Parkinson's disease
mRNA metabolism
Translation initiation
MicroRNAs
Oxidative stress
Mitochondria
mTOR signaling

ABSTRACT

Neurodegenerative diseases such as Parkinson's disease are progressive disorders of the nervous system that affect the function and maintenance of specific neuronal populations. While most disease cases are sporadic with no known cause, a small percentage of disease cases are caused by inherited genetic mutations. The identification of genes associated with the familial forms of the diseases and subsequent studies of proteins encoded by the disease genes in cellular or animal models have offered much-needed insights into the molecular and cellular mechanisms underlying disease pathogenesis. Recent studies of the familial Parkinson's disease genes have emphasized the importance of RNA metabolism, particularly mRNA translation, in the disease process. It is anticipated that continued studies on the role of RNA metabolism in Parkinson's disease will offer unifying mechanisms for understanding the cause of neuronal dysfunction and degeneration and facilitate the development of novel and rational strategies for treating this debilitating disease.

This article is part of a Special Issue entitled RNA Metabolism 2013.

1. Introduction

Parkinson's disease (PD) is the most common movement disorder and the second most common neurodegenerative disease. Aging remains one of the most significant risk factors for the disease. Approximately 1% of the population is affected at 65 years of age. This is increased to 4–5% in 85 years and older individuals (Lang and Lozano, 1998a, b). Disease is characterized clinically by motor dysfunction that manifests as resting tremor, bradykinesia, rigidity and postural instability. The movement abnormality in PD is largely attributable to the deficiency of brain dopamine content caused by dysfunction and degeneration of dopaminergic neurons in the substantia nigra. Neurons in other brain areas are also affected, which may contribute to the non-motor symptoms of the disease such as depression, dementia, anxiety, and sleeping disturbance. A pathological hallmark of the disease is the formation of Lewy bodies, intracytoplasmic inclusions that are composed mainly of α-synuclein (α-Syn) and ubiquitin, although Lewy body pathology is absent in some disease cases. The most common forms of PD are sporadic with no known cause. Nevertheless, postmortem studies of sporadic cases have revealed protein aggregation, defective mitochondrial respiratory chain function, and oxidative damage of nigrostriatal dopaminergic neurons as shared features of the disease (Dawson and

*Corresponding author.
E-mail address: bingwei@stanford.edu (B. Lu).

http://dx.doi.org/10.1016/j.brainres.2014.03.003
0006-8993/

Dawson, 2003; Dexter et al., 1994; Dunnett and Bjorklund, 1999; Schapira and Jenner, 2011).

It is now well established that genetic factors make significant contributions to PD pathogenesis. Through linkage analysis, genome sequencing and genetic association, many genes have been linked to PD (Dawson et al., 2010; Trinh and Farrer, 2013). Understanding the genetic and biochemical relationships among the disease genes and elucidating the signaling pathways underlying disease pathogenesis remain major challenges of the field. In this respect, genetic studies in animal models of PD, or RNAi-based genome-wide screens for modifiers of PD-relevant cellular phenotypes in human cell culture models have the potential to unravel the molecular mechanisms underlying disease pathogenesis and offer novel and rational therapeutic strategies. Although the implied molecular functions of the disease-associated genes are diverse and the cellular processes they are involved in are still poorly understood, recent studies have emphasized the importance of RNA metabolism, especially translational regulation, in either mediating or regulating the function of several disease-causing gene products.

In this review, we will summarize studies linking PD-related genes to the regulation of mRNA translation and the reciprocal role of RNA metabolism in regulating the function of PD-causing genes. We will discuss how altered mRNA translation may contribute to PD pathogenesis and suggest future directions for further investigation.

1.1. *Translational regulation*

Regulated mRNA translation offers one important mechanism of cell growth and survival control. By regulating translation, an organism is able to generate quick responses to physiological or environmental cues by directing the expression of proteins from existing cellular mRNAs. Translational control plays a critical role during early development of most metazoans, because zygotic transcription does not occur during the first few hours of life and cells rely solely on maternal RNAs and proteins (Wilhelm and Smibert, 2005). Under stress conditions in adult animals, translational regulation promotes survival by upregulating the expression of a subset of protective proteins and down-regulating non-essential proteins to conserve energy resources (Holcik and Sonenberg, 2005). Although translation rates can be regulated at each of three steps: initiation, elongation, and termination, control of translation initiation has emerged as a major regulatory mechanism under various pathophysiological conditions.

Increased protein synthesis correlates with enhanced formation of the eIF4F initiation complex, which binds to the 5′ cap of eukaryotic mRNAs containing the m^7GpppX structure (Gingras et al., 1999). eIF4F mediates the binding of mRNAs to the 43S pre-initiation complex to form the 48S initiation complex. eIF4F is a multi-protein complex, with eIF4G, eIF4A, and eIF4E being its known subunits. eIF4G is a scaffolding protein that binds to eIF4E and eIF4A and also interacts with proteins in the 43S pre-initiation complex (Gradi et al., 1998). eIF4A is an ATP-dependent helicase that unwinds secondary structures present in the 5′ untranslated regions (UTRs) of certain mRNAs (Ray et al., 1985). The 5′ cap-binding activity of the complex is conferred by the eIF4E subunit (Sonenberg et al., 1979), which appears to be the rate-limiting factor in the formation of eIF4F, and whose activity is tightly regulated under cell growth conditions. The activity of eIF4E is regulated by the binding of eIF4E by 4E-BP, which precludes the binding of eIF4E by eIF4G and eIF4A, thus preventing the formation of the eIF4F complex (Gingras et al., 1999; Richter and Sonenberg, 2005). 4E-BP has been established as a major downstream effector of the target of rapamycin (TOR) signalling pathway, which tightly couples nutrient availability, growth factors, and energy status to cell growth (Wullschleger et al., 2006). TOR forms at least two protein complexes, TORC1 and TORC2 (Zoncu et al., 2011). TORC1 has been shown to phosphorylate 4E-BP, weakening its binding to eIF4E and promoting cap-dependent mRNA translation. In addition, TORC1 stimulates protein synthesis by positively regulating the activity of ribosomal protein S6 kinase (S6K) through direct phosphorylation (Zoncu et al., 2011). Various stress signals have been shown to influence mRNA translation and metabolism by impinging on the TOR pathway (Wullschleger et al., 2006). Intriguingly, several proteins encoded by PD-associated genes have recently been shown to interact with components of the translation initiation complex or signaling pathways that regulation mRNA translation (Fig. 1).

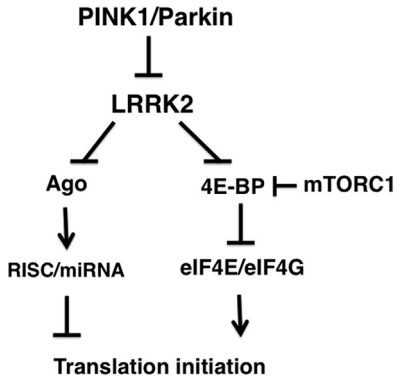

Fig. 1 – A diagram of a signaling network regulating translation initiation that has been linked to PD-pathogenesis caused by mutations in LRRK2 or PINK1/Parkin. LRRK2 has been shown to negative regulate the stability of Ago, a component of the Risc/miRNA repressor complex that inhibits translation initiation. LRRK2 has also been shown to phosphorylate 4E-BP, releasing the repression of eIF4E/eIF4G-mediated translation initiation by 4E-BP, similar to the regulation of 4E-BP by mTORC1. The relationship between PINK1/Parkin and LRRK2 is based on the results of genetic epistasis studies carried out in *Drosophila* and *C. elegans*, although the precise biochemical mechanism underlying the genetic interactions remains to be established.

1.2. *Leucine rich repeat kinase 2 (LRRK2) (OMIM #609007)*

LRRK2 encodes a large protein that contains a leucine rich repeat (LRR) domain, a kinase domain, a RAS-like GTPase