Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

How Parkinson's disease meets nucleolar stress ☆

Rosanna Parlato [a,b,c,*], Birgit Liss [a]

[a] Institute of Applied Physiology, University of Ulm, Ulm, Germany
[b] Institute of Anatomy and Cell Biology, Department of Medical Biology, University of Heidelberg, Heidelberg, Germany
[c] Dept. of Molecular Biology of the Cell I, DKFZ-ZMBH Alliance, German Cancer Research Center, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 13 December 2013
Accepted 31 December 2013
Available online xxxx

Keywords:
Nucleolus
Neurodegeneration
Stress response
Dopaminergic neuron
p53
mTOR

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Although the causes of PD are still not understood, aging is a predisposing factor and metabolic stress seems to be a common trigger. Interestingly, the response to stress conditions and quality control mechanisms is impaired in PD, as well as in other neurodegenerative disorders. Downregulation of rRNA transcription is one major strategy to maintain cellular homeostasis under stress conditions, as it limits energy consumption in disadvantageous circumstances. Altered rRNA transcription and disruption of nucleolar integrity are associated with neurodegenerative disorders, and with aging. Nucleolar stress can be triggered by genetic and epigenetic factors, and by specific signaling mechanisms, that are altered in neurodegenerative disorders. The consequences of neuronal nucleolar stress seem to depend on p53 function, the mammalian target of rapamycin (mTOR) activity and deregulation of protein translation. In this review, we will summarize findings identifying an emerging role of nucleolar stress for the onset and progression of in particular PD. Emphasis is given to similarities in molecular causes and consequences of nucleolar stress in other neurodegenerative disorders. The mechanisms by which nucleolar stress participates in PD could help identify novel risk factors, and develop new therapeutic strategies to slow down the progressive loss of neurons in neurodegenerative diseases. This article is part of a Special Issue entitled: Role of the Nucleolus in Human Disease.

1. Introduction

Neurodegenerative disorders are chronic diseases, characterized by the progressive loss of specific neurons in the central or peripheral nervous system. This definition is however an oversimplification of complex diseases for which up to now there is still no cure and therapies are mostly symptomatic [1]. While distinct populations of neurons seem to be primarily lost in distinct diseases, various symptoms, neurodegenerative triggers and pathways may overlap. For example, Alzheimer's disease (AD), which causes dementia, is characterized by degeneration of cortical and hippocampal neurons [2]. Major movement-related symptoms of Parkinson's disease (PD) are associated with the loss of a particular subpopulation of dopaminergic (DA) midbrain neurons [3]; nevertheless other neurons are also affected in PD and a subpopulation of PD patients (ca. 30%) shows additional dementia symptoms [3–5]. Familial forms leading to Mendelian inheritance of disease are described for both PD and AD, and certain genetic loci have been identified that increase the risk for idiopathic AD or PD [5]. Furthermore, converging disease mechanisms are evident downstream of the causes or trigger factors that primarily initiate or increase the risk of each disease [6]. In addition even in clearly inherited monogenic neurodegenerative diseases, such as Huntington's disease (HD), unknown predisposing and environmental factors modify onset and progression of the selective loss of striatal neurons, implying the existence of additional risk or trigger factors (genetic and not) [7]. This is also true for the selective degeneration of distinct motor-neuron populations in amyotrophic lateral sclerosis (ALS) or spinal muscle atrophy (SMA), where idiopathic as well as inherited forms are described [8,9]. These aspects should be taken into account to fully understand distinct and common disease mechanisms and to design effective neuroprotective treatments.

Ideally one would like to identify *the individual disease cause* as well as its molecular pathomechanism and utilize this as a target for a causal therapy of a neurodegenerative disease. However this strategy has not been too successful in neurodegenerative research so far. Most likely because the situation is much more complex — rather a neurodegenerative disease is caused by a complex interplay of variable genetic and

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DA, dopaminergic; ER, endoplasmic reticulum; 4E-BP1, eukaryotic initiation factor 4E (eIF4E)-binding protein; HD, Huntington's disease; LRRK2, leucine-rich repeat kinase 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSNs, medium spiny neurons; mTOR, mammalian/mechanistic target of rapamycin; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PINK1, PTEN-induced kinase 1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; RPs, ribosomal proteins; SMA, spinal muscle atrophy; SMN, survival motor neuron; SN, Substantia nigra; TIF-IA, transcription initiation factor-IA; TRAF, TNF receptor-associated factor; TTRAP, TRAF and TNF receptor-associated protein; VTA, ventral tegmental area

☆ This article is part of a Special Issue entitled: Role of the Nucleolus in Human Disease.

* Corresponding author at: Institute of Anatomy and Cell Biology, Department of Medical Biology, University of Heidelberg, Im Neuenheimer Feld 307, 69120 Heidelberg, Germany.
E-mail address: rosanna.parlato@uni-ulm.de (R. Parlato).

0925-4439/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbadis.2013.12.014

environmental factors [10,11]. Even if there is one specific genetic cause for a disease (e.g. in HD the expanded CAG repeat in the huntingtin gene), the question of *when* and *why* its effects become threatening is still unanswered.

Another approach for developing novel therapeutic treatments is based on the identification of downstream neurodegenerative pathways that are common in distinct neurodegenerative diseases. Indeed, such common neurodegenerative determinants and pathways have been identified in the last years: in particular cellular and metabolic stress, such as oxidative stress, proteasomal stress, and nucleolar stress seem to be common events in neurodegenerative disorders [12–14]. Nucleolar stress is an emerging component of the degenerative process, caused by impaired rRNA transcription and altered nucleolar integrity [15]. rRNA transcription itself strongly depends on cellular stress and it is controlled by a combination of genetic and epigenetic factors [16]. rRNA transcription is epigenetically regulated during aging as well as in neurodegenerative diseases like AD and HD e.g. by hypermethylation of rDNA promoter or post-translational modifications of RNA Polymerase I co-factors [17–20]. Similar findings in PD are still missing, however in light of the emerging role of epigenetics in PD pathogenesis [21,22], it is tempting to hypothesize an association with PD as well.

This review aims at presenting evidence for a role of nucleolar stress in PD and other neurodegenerative diseases. We will summarize in particular, mechanisms by which nucleolar stress could play a role in PD progression. These mechanisms include p53-dependent programs, as well as the mammalian/mechanistic target of rapamycin (mTOR) signaling. P53 is a tumor suppressor gene and transcription factor, controlling cell-cycle, apoptosis and genomic stability [23], while mTOR is a phosphatidylinositol 3-kinase-related kinase regulating cell proliferation, protein and RNA synthesis as well as cell survival [24]. Finally, we will summarize evidence that dysregulation of protein translation may cause neurodegenerative disorders including PD.

2. Parkinson's disease and nucleolar stress

PD is the second most common neurodegenerative disorder; it is known to not only cause abnormal motor function (bradykinesia, resting tremor, rigidity and postural instability), but also impair autonomic functions and cognition [3]. Most motor symptoms of PD are caused by a progressive loss of DA midbrain neurons, in particular within the *Substantia nigra* (SN), while DA neurons within the ventral tegmental area (VTA) remain largely unaffected [25,26]. Approximately 10–20% of PD is ascribed to familial inherited mutations in PARK1–13 genes, but PD is generally considered a sporadic disease influenced by genetic and environmental risk factors [27–30].

PD shares with other neurodegenerative disease deficits in mitochondrial and proteasomal/lysosomal function, mechanisms regulating protein quality control, stress response and cell metabolism [31,32]. Proteasomal and mitochondrial dysfunction is either caused by environmental factors, such as mitochondrial complex I blockers (e.g. rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/MPTP, paraquat), or proteasomal inhibitors (e.g. epoxomycin), or by genetic factors — like mutations or variations in PARK genes [10,27,33,34]. Given the relatively late onset (65–85 years) and slow progression of most idiopathic PD cases, identification of molecular mechanisms responsible for maintaining cellular homeostasis as well as compensatory mechanisms might allow a therapeutic intervention in early disease stages, to slow down or even stop the progressive loss of DA neurons in the course of the disease [35].

Nucleolar activity and integrity are tightly linked to the cellular well-being and metabolic state [16]. The nucleolus hosts several hundreds of proteins that are shuttled between different cellular compartments [36]. Crucial regulatory functions can be altered by nucleolar disruption and the release of nucleolar proteins to the nucleoplasm [36]. The dynamic retention/release of nucleolar proteins provides a control of cellular functions, including stress response [37]. For example, the nucleoplasmic release of ribosomal proteins upon inhibition of rRNA synthesis affects p53 turnover with dramatic consequences for cell proliferation, survival and stress response [37]. It seems obvious on the one hand that cells need proper nucleolar activity and protein synthesis to function correctly. On the other hand, down-regulation of rRNA transcription in response to stress conditions allows cells to limit energy expenditure and to keep conducting their functions under minimal regime [16]. However, protracted inhibition of rRNA synthesis results in severe cellular damage and cell death [37].

The nucleolar-dependent mechanisms that are responsible for the switch from life to death are still poorly investigated but they could allow a better understanding on how neurons manage to resist a neurodegenerative process under stress. In this context it is of particular interest that in most common neurodegenerative diseases, neurons are not equally affected by the disease process but rather display a so-called differential vulnerability of distinct neuronal populations to the neurodegenerative process, as illustrated for PD [1].

3. Increased nucleolar stress is present in PD and other neurodegenerative disorders

Decreased rRNA synthesis and nucleolar disintegration have been reported in a variety of neurodegenerative disorders [14]. In PD brain autopsies altered nucleolar function and morphology have been described in DA neurons [38]. Initial data show that nucleolar volume in DA neurons is decreased in PD subjects and this is inversely correlated with the disease duration, suggesting metabolic alterations in these neurons [39,40]. Indeed reduced nucleolar volume has been associated with reduced RNA synthesis [41].

As mentioned, age is the most prominent risk-factor for PD. Interestingly, 18S rRNA levels decrease with aging in humans and mice [42,43], and an increased nucleolar fragmentation with age is described [44]. Synthesis of rRNA is downregulated in DA neurons in a pharmacological mouse model of PD based on injection of MPTP, and it is associated with disruption of nucleolar integrity [38]. More recently, decreased nucleolar volume has been reported in the partial unilateral intrastriatal 6-hydroxydopamine (6-OHDA) oxidative stress rat model of PD [45]. Interestingly, in AD, there is also a significant atrophy of the nucleoli [46]; on the other side nucleolar hypertrophy has been linked to neurotoxic β-amyloid deposits and Aβ plaques in the hippocampus of asymptomatic AD subjects [46]. Reduced nucleolar volume and reduced RNA synthesis may reflect neuronal atrophy and in general a suffering neuron, however reduced or altered nucleolar activity could in addition play an active role in the disease progression.

Nucleolar proteins regulating rRNA synthesis and ribosome biogenesis could contribute to the pathophysiological mechanisms of different neurodegenerative diseases, e.g. by mutations or agents affecting their expression and activity [18,47–55]. DNA damage, a hallmark of neurodegenerative diseases, results in translocation to the nucleoplasm of nucleophosmin (NPM), a multifunctional protein with chaperone activity [56]. Although NPM role in neurodegeneration is not fully characterized, kainic acid-induced neurotoxicity promotes downregulation of NPM in rat hippocampus [47]. In turn, NPM overexpression is neuroprotective, at least in cellular models [47]. A pathogenic role in neurodegeneration has been clearly reported for nucleolin. Nucleolin is a phosphoprotein that interacts with mutant RNAs in polyglutaminopathies like HD, resulting in its reduced binding to rRNA promoters, reduced rRNA transcription and increased nucleolar stress [18,49]. Interestingly, nucleolin is downregulated in SN tissues from PD subjects and in a DA cellular model of PD upon treatment with rotenone [48]. Nucleolin associates with α-synuclein (PARK1/PARK4) and DJ-1 (PARK7), two genes whose mutations can cause familial forms of PD [50]. The impact of nucleolin on rRNA transcription has not been addressed in this model; nevertheless nucleolin overexpression is neuroprotective and its downregulation promotes neuronal death in a PD cellular model [48] and in various models of polyglutaminopathies [18,49]. Another example is the ribonuclease angiogenin that

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014

translocates to the nucleoli upon growth stimuli where it promotes rRNA transcription [51]. Angiogenin variants are frequent in PD and ALS and could be predisposing factors in both diseases [57]. Notably, angiogenin is downregulated in transgenic mice overexpressing human wildtype α-synuclein [58]. Angiogenin knockdown leads to cell death while its overexpression promotes neuronal survival in models of ALS [59]. Similarly angiogenin reduces cell death in cellular PD models based on MPP^+ and rotenone treatment [53]. However in a recent in vivo study in the MPTP mouse model of PD where angiogenin was overexpressed by stereotactic injection in DA neurons, these neurons were not protected from degeneration [60]. Nevertheless it is not only the level of angiogenin expression but also its localization that plays a role in the regulation of neuronal survival [61]. Indeed it has been shown that angiogenin promotes rRNA transcription under permissive growth conditions: under stress conditions angiogenin translocates to the cytoplasm reducing protein translation and increasing cell survival [61]. Survival motor neuron (SMN) protein is mutated in SMA [55]. Interestingly wild-type SMN is associated in a complex with NPM and nucleolin [62]. However in SMA patient-derived fibroblasts mutant SMN is not associated with NPM and nucleolin [62]. Future research should explain whether altered distribution of mutant SMN plays a role in the pathogenesis of SMA.

The role of relocalization of nucleolar proteins in neuronal survival has been demonstrated in other systems. Increased pre-rRNA biogenesis and reduced mature 18S and 28S rRNA have been recently reported in a cellular proteasomal inhibition model of PD [63]. In the nucleolus, TRAF and TNF receptor-associated protein (TTRAP) is a multifunctional protein that can control levels of rRNA precursor and processing intermediates [64,65]. In response to proteasome inhibition, TTRAP accumulates in nucleolar cavities and regulates rRNA processing [65]. Silencing TTRAP expression causes alterations in rRNA biogenesis during proteasome impairment, with a decrease of pre-rRNA and an accumulation of processing intermediates [65]. Notably the PD associated mutant protein DJ-1 L166P that results in a misfolded protein and aggregate formation impairs TTRAP localization in the nucleolar cavities and rRNA transcription [63]. Hence, these studies show that impaired nucleolar function may be specifically triggered by a disease-associated mutant protein and suggest a novel pathophysiological mechanism in PD. Interestingly, this mechanism is similar to that identified in polyglutaminopathies, like HD, in which mutant mRNAs interfere with RNA polymerase I transcription [18,49]. Noteworthy, these findings indicate that inhibition of rRNA transcription can be a primary event of the degenerative process.

4. Animal models of induced nucleolar stress

Although nucleolar stress appears to be a common component of neurodegenerative disorders [14,15], only recently the cellular and molecular consequences of impaired rRNA synthesis and nucleolar disruption have been systematically explored in the nervous system. Mouse models in which nucleolar stress is induced in specific neuronal populations at a defined time-point have been generated, based on the conditional ablation of the transcription factor TIF-IA [66]. TIF-IA is essential for the recruitment of RNA polymerase I to the rRNA promoters [66]. TIF-IA activity is tightly regulated by mitogenic signals, growth stimuli, oxidative stress, cellular energy status and ER stress, and it represents an essential crossroad in the control of rRNA transcription under stress conditions [41,67,68]. Therefore conditional ablation of TIF-IA by the Cre-loxP system is a convenient tool to mimic nucleolar stress in specific cellular and developmental/aging contexts (Table 1). Conditional TIF-IA ablation in embryonic neural progenitors using the Nestin-Cre transgenic line leads to rapid loss of developing neurons starting E11.5 by p53-dependent apoptosis and anencephaly [69]. On the contrary, cell-specific TIF-IA ablation in distinct postmitotic neurons results in their slowly progressive degeneration; in addition these studies reveal that hippocampal, DA and dopaminoceptive neurons can survive for several months under nucleolar stress [38,69–71]. This slow progression allows the analysis of the sequence of events triggered by nucleolar stress in distinct neuronal populations (Table 1). Interestingly, DA-specific TIF-IA ablation results in mutant mice, characterized by behavioral and cellular features reminiscent of PD, including progressive and preferential loss of DA neurons in the SN vs VTA DA neurons, as well as marked behavioral deficiencies (slowness of movement, gait and posture disturbances) [38]. Importantly, selective impairment of nucleolar activity at the age of two months in DA neurons leads to mitochondrial dysfunction and increased oxidative damage, characteristics shared by various neurodegenerative diseases, such as PD, HD, AD and ALS, and summarized in Table 2. This Table shows mechanisms either "associated" with a disease (meaning that they are described in human and/or animal models), or "directly related" to a disease (meaning that they are proven to be caused/triggered by mutant RNAs or proteins based on experimental evidence). We refer to recent reviews and original articles for detailed information (see Table 2). Interestingly, most of the mechanisms involved in these listed neurodegenerative diseases [31] are also described in conditional TIF-IA knock-out mice (cKO), in particular DA and striatal specific models (Table 2).

How nucleolar stress could lead to mitochondrial dysfunction, increased oxidative damage and finally neurodegeneration is discussed in the next paragraph.

5. Nucleolar stress can induce mitochondrial dysfunction and neurodegeneration in PD and other neurodegenerative diseases: role of mTOR

Abnormalities in protein synthesis are common to PD and may be related to impaired Akt-mTOR signaling [72–74]. First evidence that nucleolar stress also leads to downregulation of mTOR was indeed derived from the DA-specific inducible TIF-IA knock-out mice [38]. Recent analysis of conditional mutant mice lacking TIF-IA in striatal medium spiny neurons (MSNs) revealed that mTOR activity is inhibited also in these neurons and that p53 increases the phosphatase PTEN (phosphatase and tensin homolog deleted on chromosome 10), a well-known inhibitor of the mTOR signaling. Remarkably, a mouse model of spinocerebellar ataxia characterized by increased DNA damage and

Table 1
Temporal link between nucleolar stress, p53, oxidative damage and cell death in distinct TIF-IA conditional mutant mice.

Cre recombinase activity	Nucleolar stress	Increased p53 protein	Oxidative damage	Cell death
Neural and glial progenitors (E9.5)	E11.5	E11.5	n.d.	E11.5[a,b]
Adult hippocampal neurons[c]	1 month	3 months	n.d.	3 months[b,d]
DA neurons (E13.5)	E18.5	E18.5	n.d.	E18.5[a] P15[d]
Adult DA neurons[c]	2 weeks	2 weeks	1 month	2 months[d]
Dopaminoceptive neurons (E16.5)	1 month	2 months	2 months	3 months[b]

[a] Analyzed by activated caspase-3.
[b] Analyzed by Terminal deoxynucleotydil transferase dUTP end labeling, TUNEL assay.
[c] Induced by tamoxifen injection in 2-month old mice and analyzed at the indicated stages.
[d] Analyzed by neuronal loss.

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014

Table 2
Mechanisms involved in specific neurodegenerative disorders as well as in TIF-IA mouse models.

	Altered nucleolar function	Mitochondrial dysfunction	Oxidative damage	p53 activity	Aberrant autophagy	Aggregated/misfolded proteins	Neuroinflammation
PD (idiopatic /inherited)	Associated/directly related [38,63]	Associated/directly related [32]	Associated/directly related [96]	Associated/directly related [84,97]	Associated/directly related [98,99]	Associated/directly related [3]	Associated [100]
HD (inherited)	Directly related [18,20,49,70,101]	Associated/ directly related [32,102]	Associated [103]	Associated [104]	Associated [105]	Directly related [106]	Associated [107]
AD (idiopatic /inherited)	Associated [17,108,109]	Associated/ directly related [32]	Associated [110]	Associated [111]	Directly related [112]	Directly related [113]	Associated/directly related [114]
ALS (idiopatic /inherited) SMA (inherited)	Associated/directly related [51] Partially analyzed [54,55]	Associated/ directly related [32,115,116]	Associated/directly related [117]	Associated [118]	Associated/directly related [119]	Associated/directly related [120]	Associated[121]
TIF-IA cKO	Directly related [38,69,70]	Associated [38]	Associated [38,70]	Associated [38,69,70]	Associated [70]	Not analyzed	Associated [38,70]

nucleolar stress also shows increased level of p53 and PTEN in the affected cerebellum [75]. Moreover, mTOR inhibition in MSNs promotes autophagy highlighting an initial neuroprotective effect triggered by nucleolar stress [70]. Further analysis of the conditional mutant mice lacking both TIF-IA and PTEN indicates that this neuroprotective effect could depend on PTEN [70]. In fact the loss of TIF-IA and PTEN results in upregulation of mTOR, block of autophagy and accelerated neuronal death [70]. This is of particular importance as altered autophagy provides another trigger factor of PD [76,77]. Nevertheless, absence of PTEN and activation of the mTOR pathway are partially neuroprotective in adult DA neurons lacking TIF-IA [78]. Indeed double mutants lacking both TIF-IA and PTEN show improved motor performance on the rotarod test in comparison to TIF-IA single mutants [78]. These distinct findings for the role of PTEN and mTOR in MSN- or DA-specific postmitotic neurons under nucleolar stress point to a context- and time-specific role of the mTOR pathway for neuronal survival.

The analysis of the conditional TIF-IA models indicates a dual role of that nucleolar stress: initially it could trigger a neuroprotective defense response, in particular by inducing autophagy [70]. However, enduring nucleolar stress also leads to impaired mitochondrial function and increased oxidative stress, and ultimately slowly progressing neuronal death [38,70]. In this view, these findings suggest that the identification of acute as well as chronic regulators and downstream effectors of impaired nucleolar function can help to better understand disease progression and might open avenues for the development of novel neuroprotective therapeutic strategies.

6. Nucleolar stress can induce mitochondrial dysfunction and neurodegeneration in PD: role of p53

Besides mTOR pathways, it is well known that the nucleolus transmits cellular stress signals to the p53 pathways [79]. Upon disruption of the nucleolus, several ribosomal proteins (RPs) are released into the nucleoplasm and bind to the E3 ubiquitin ligase Mdm2 [37]. Mdm2 promotes p53 degradation, but when bound to RPs it does not function correctly, leading to accumulation of p53 with context-dependent consequences on cell viability and metabolism [80]. Inhibition of p53 has been shown to be neuroprotective in the MPTP model of PD [81]. Interestingly p53 activity is linked to several genes with a causative role in PD [82]. For example, in response to oxidative stress, p53 transcriptionally upregulates the ubiquitin ligase parkin (PARK2) and promotes mitochondrial respiration and antioxidant defense [83]. In turn parkin downregulates p53 transcription limiting the negative consequences of its increased activity [84]. These results show that parkin can function also as transcriptional repressor by interacting with p53 promoter. However mutant parkin loses this neuroprotective function, offering an explanation how this mutation could result in p53 induction and apoptotic cell death [84,85]. Interestingly parkin positively regulates another gene with a causative role in PD DJ-1 (PARK7) by inhibiting p53; again this neuroprotective function is lost by mutant parkin [86]. These findings link these (and additional) factors to a complex signaling network, that might be jointly altered in a cell-specific fashion in neurodegenerative disease, like PD.

To add complexity, p53 also plays a role in the downregulation of mTOR activity, observed in both DA and dopaminoceptive MSNs upon nucleolar stress [38,70]. In *Drosophila*, mutations in PINK1 (PARK6), parkin (PARK2) or leucine-rich repeat kinase 2 (LRRK2/PARK8) genes result in dysregulated translation, increased sensitivity to oxidative stress and age-related loss of DA neurons [87,88]. This phenotype is linked to abnormal phosphorylation of the eukaryotic initiation factor 4E (eIF4E)-binding protein (4E-BP1) [88]. Hypophosphorylation of 4E-BP1 is required for its function as a repressor of protein translation [24]. By phosphorylating 4E-BP1 mTOR promotes protein translation [24]. Interestingly in these *Drosophila* mutants inhibition of TOR by rapamycin represses protein translation and prolong neuronal survival [87,88]. In line with these results, PINK1 (PARK6) knock-out mice

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014

show reduced mTOR activity and decreased levels of phosphorylated ribosomal S6 protein, another target of mTOR [89]. However 4E-BP1 has not been confirmed as a substrate of LRRK2 in mammalian brain and it is not clear whether mutant LRRK2 participates to the abnormal protein translation observed in PD [90]. Nevertheless other regulators of protein translation are emerging in PD in particular variants in the eukaryotic translation initiation factor 4-gamma 1 gene (EIF4G1) are associated with familial PD forms [91]. It is tempting to speculate that deficits of protein translation are common to several neurodegenerative diseases. As strongly indicated by a recent study, e.g. increased phosphorylation of α-subunit of eukaryotic translation initiation factor 2 (eIF2α) reduces protein translation in PD mouse models [92].

7. Open questions and perspectives

This review summarizes a series of intriguing studies that link PD to alterations in nucleolar function, and it offers mechanisms by which nucleolar stress could lead to selective neurodegeneration. However, in particular the selective neurodegeneration of distinct neuronal populations, a hallmark of all neurodegenerative diseases, needs further investigation.

The animal models based on inducible nucleolar stress at a defined time-point in specific neuronal populations offer one novel and unique tool to further study functional and molecular consequences of nucleolar stress in different contexts, and to identify central regulatory — and potentially neuroprotective pathways [38,69,70,78]. Interestingly, the characteristic differential vulnerability of DA midbrain subpopulations observed in PD and its animal models (SN versus VTA) [93,94], is indeed present in the DA-specific TIF-IA models, despite induction of nucleolar stress and increased p53 also in *all* DA midbrain neurons [38]. This finding points to an additional intrinsic factor that renders SN DA neurons particularly vulnerable to nucleolar stress and other neurodegenerative triggers. Another explanation could be that TIF-IA expression and function might be lower in more resistant (e.g. VTA DA) neurons compared to highly vulnerable (e.g. SN DA) neurons. In this context, it is interesting to note that neurotrophins like BDNF control TIF-IA [95]. However, up to now a cell-specific analysis of neuronal TIF-IA expression in health, aging, and disease is missing.

Other open questions are related to the age- or disease-stage-specific effects of nucleolar stress and the neuroprotective role of rRNA synthesis. It would be important to establish at what levels nucleolar stress might trigger protective responses, or might become deleterious to a certain neuron, and what factors could contribute to those nucleolar stress levels. For example, do PARK gene mutations chronically alter nucleolar activity and integrity selectively in the most vulnerable population of SN DA neurons? And can reduction of nucleolar stress reduce the distinct phenotypes of the PARK mouse models? To start answering to these questions the cellular and molecular consequences of nucleolar stress in combination with genetic mutations underlying PD should be addressed. These studies could open avenues to identify novel disease pathways, and also to novel therapeutic approaches. However, to reach that desired goal, much further research and insight into the emerging converging role of nucleolar dysfunction – in interplay with other environmental and genetic factors and disease pathways – in PD and other neurodegenerative disease are essential.

Funding

This work was supported by the program for medical genome research (NGFNplus) with financial support from the German Federal Ministry for Education and Research (BMBF), under the support code 01GS08141, the DFG (LI 1745/1-1) and the Alfried Krupp Prize (to B.L.).

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Profs. G. Auburger, Drs. S. Gispert and K.L. Tucker for the insightful and constructive discussions related to the content of this review.

References

[1] M.P. Mattson, T. Magnus, Ageing and neuronal vulnerability, Nat. Rev. Neurosci. 7 (2006) 278–294.
[2] C.F. Lippa, J.E. Duda, M. Grossman, H.I. Hurtig, D. Aarsland, B.F. Boeve, D.J. Brooks, D.W. Dickson, B. Dubois, M. Emre, S. Fahn, J.M. Farmer, D. Galasko, J.E. Galvin, C.G. Goetz, J.H. Growdon, K.A. Gwinn-Hardy, J. Hardy, P. Heutink, T. Iwatsubo, K. Kosaka, V.M. Lee, J.B. Leverenz, E. Masliah, I.G. McKeith, R.L. Nussbaum, C.W. Olanow, B.M. Ravina, A.B. Singleton, C.M. Tanner, J.Q. Trojanowski, Z.K. Wszolek, DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers, Neurology 68 (2007) 812–819.
[3] H. Braak, E. Ghebremedhin, U. Rub, H. Bratzke, K. Del Tredici, Stages in the development of Parkinson's disease-related pathology, Cell Tissue Res. 318 (2004) 121–134.
[4] C.H. Hawkes, K. Del Tredici, H. Braak, A timeline for Parkinson's disease, Parkinsonism Relat. Disord. 16 (2010) 79–84.
[5] V. Moskvina, D. Harold, G. Russo, A. Vedernikov, M. Sharma, M. Saad, P. Holmans, J.M. Bras, F. Bettella, M.F. Keller, N. Nicolaou, J. Simon-Sanchez, J.R. Gibbs, C. Schulte, A. Durr, R. Guerreiro, D. Hernandez, A. Brice, H. Stefansson, K. Majamaa, T. Gasser, P. Heutink, N. Wood, M. Martinez, A.B. Singleton, M.A. Nalls, J. Hardy, M.J. Owen, M.C. O'Donovan, J. Williams, H.R. Morris, N.M. Williams, Analysis of genome-wide association studies of Alzheimer disease and of Parkinson disease to determine if these 2 diseases share a common genetic risk, JAMA Neurol. (2013) Aug 5. http://dx.doi.org/10.1001/jamaneurol.2013.448. [Epub ahead of print].
[6] V.K. Ramanan, A.J. Saykin, Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders, Am. J. Neurodegener. Dis. 2 (2013) 145–175.
[7] E. Teuling, A. Bourgonje, S. Veenje, K. Thijssen, J. de Boer, J. van der Velde, M. Swertz, E. Nollen, Modifiers of mutant huntingtin aggregation: functional conservation of *C. elegans*-modifiers of polyglutamine aggregation, PLoS Curr. 3 (2011) RRN1255.
[8] P.M. Andersen, A. Al-Chalabi, Clinical genetics of amyotrophic lateral sclerosis: what do we really know? Nat. Rev. Neurol. 7 (2011) 603–615.
[9] A.H. Burghes, C.E. Beattie, Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nat. Rev. Neurosci. 10 (2009) 597–609.
[10] S.M. Goldman, Environmental toxins and Parkinson's disease, Annu. Rev. Pharmacol. Toxicol. 54 (2014) 141–164.
[11] Y. Lee, V.L. Dawson, T.M. Dawson, Animal models of Parkinson's disease: vertebrate genetics, Cold Spring Harb. Perspect. Med. 2 (2012).
[12] A. Johri, M.F. Beal, Mitochondrial dysfunction in neurodegenerative diseases, J. Pharmacol. Exp. Ther. 342 (2012) 619–630.
[13] J.J. Hoozemans, W. Scheper, Endoplasmic reticulum: the unfolded protein response is tangled in neurodegeneration, Int. J. Biochem. Cell Biol. 44 (2012) 1295–1298.
[14] R. Parlato, G. Kreiner, Nucleolar activity in neurodegenerative diseases: a missing piece of the puzzle? J. Mol. Med. (Berl.) 91 (2013) 541–547.
[15] M. Hetman, M. Pietrzak, Emerging roles of the neuronal nucleolus, Trends Neurosci. 35 (2012) 305–314.
[16] I. Grummt, The nucleolus-guardian of cellular homeostasis and genome integrity, Chromosoma 122 (6) (2013) 487–497.
[17] M. Pietrzak, G. Rempala, P.T. Nelson, J.J. Zheng, M. Hetman, Epigenetic silencing of nucleolar rRNA genes in Alzheimer's disease, PLoS One 6 (2011) e22585.
[18] H. Tsoi, T.C. Lau, S.Y. Tsang, K.F. Lau, H.Y. Chan, CAG expansion induces nucleolar stress in polyglutamine diseases, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 13428–13433.
[19] L.M. Garcia Moreno, J.M. Cimadevilla, H. Gonzalez Pardo, M.C. Zahonero, J.L. Arias, NOR activity in hippocampal areas during the postnatal development and ageing, Mech. Ageing Dev. 97 (1997) 173–181.
[20] J. Lee, Y.J. Hwang, J.H. Boo, D. Han, O.K. Kwon, K. Todorova, N.W. Kowall, Y. Kim, H. Ryu, Dysregulation of upstream binding factor-1 acetylation at K352 is linked to impaired ribosomal DNA transcription in Huntington's disease, Cell Death Differ. 18 (2011) 1726–1735.
[21] N. Ammal Kaidery, S. Tarannum, B. Thomas, Epigenetic landscape of Parkinson's disease: emerging role in disease mechanisms and therapeutic modalities, Neurotherapeutics 10 (4) (2013) 698–708.
[22] E. Masliah, W. Dumaop, D. Galasko, P. Desplats, Distinctive patterns of DNA methylation associated with Parkinson disease: identification of concordant epigenetic changes in brain and peripheral blood leukocytes, Epigenetics 8 (2013).
[23] K.H. Vousden, C. Prives, Blinded by the light: the growing complexity of p53, Cell 137 (2009) 413–431.
[24] M. Laplante, D.M. Sabatini, mTOR signaling in growth control and disease, Cell 149 (2012) 274–293.
[25] P. Calabresi, A. Castrioto, M. Di Filippo, B. Picconi, New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease, Lancet Neurol. 12 (2013) 811–821.
[26] T. Wichmann, M.R. DeLong, J. Guridi, J.A. Obeso, Milestones in research on the pathophysiology of Parkinson's disease, Mov. Disord. 26 (2011) 1032–1041.

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014

[27] C. Schulte, T. Gasser, Genetic basis of Parkinson's disease: inheritance, penetrance, and expression, Appl. Clin. Genet. 4 (2011) 67–80.
[28] M.A. Nalls, M. Saad, A.J. Noyce, M.F. Keller, A. Schrag, J.P. Bestwick, B.J. Traynor, J.R. Gibbs, D.G. Hernandez, M.R. Cookson, H.R. Morris, N. Williams, T. Gasser, P. Heutink, N. Wood, J. Hardy, M. Martinez, A.B. Singleton, Genetic comorbidities in Parkinson's disease, Hum. Mol. Genet. (2013) Oct 22. [Epub ahead of print].
[29] P.M. Antony, N.J. Diederich, R. Kruger, R. Balling, The hallmarks of Parkinson's disease, FEBS J. 280 (23) (2013) 5981–5993.
[30] F. Cicchetti, J. Drouin-Ouellet, R.E. Gross, Environmental toxins and Parkinson's disease: what have we learned from pesticide-induced animal models? Trends Pharmacol. Sci. 30 (2009) 475–483.
[31] S. Gandhi, N.W. Wood, Genome-wide association studies: the key to unlocking neurodegeneration? Nat. Neurosci. 13 (2010) 789–794.
[32] R.K. Chaturvedi, M. Flint Beal, Mitochondrial diseases of the brain, Free Radic. Biol. Med. 63 (2013) 1–29.
[33] K.S. McNaught, D.P. Perl, A.L. Brownell, C.W. Olanow, Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson's disease, Ann. Neurol. 56 (2004) 149–162.
[34] J. Trinh, M. Farrer, Advances in the genetics of Parkinson disease, Nat. Rev. Neurol. 9 (2013) 445–454.
[35] L. Greenbaum, M. Lorberboym, E. Melamed, A. Rigbi, Y. Barhum, Y. Kohn, A. Khlebtovsky, B. Lerer, R. Djaldetti, Perspective: identification of genetic variants associated with dopaminergic compensatory mechanisms in early Parkinson's disease, Front. Neurosci. 7 (2013) 52.
[36] F.M. Boisvert, S. van Koningsbruggen, J. Navascues, A.I. Lamond, The multifunctional nucleolus, Nat. Rev. Mol. Cell Biol. 8 (2007) 574–585.
[37] S. Boulon, B.J. Westman, S. Hutten, F.M. Boisvert, A.I. Lamond, The nucleolus under stress, Mol. Cell 40 (2010) 216–227.
[38] C. Rieker, D. Engblom, G. Kreiner, A. Domanskyi, A. Schober, S. Stotz, M. Neumann, X. Yuan, I. Grummt, G. Schutz, R. Parlato, Nucleolar disruption in dopaminergic neurons leads to oxidative damage and parkinsonism through repression of mammalian target of rapamycin signaling, J. Neurosci. 31 (2011) 453–460.
[39] D.M. Mann, P.O. Yates, Pathogenesis of Parkinson's disease, Arch. Neurol. 39 (1982) 545–549.
[40] H.J. Gertz, A. Siegers, J. Kuchinke, Stability of cell size and nucleolar size in Lewy body containing neurons of substantia nigra in Parkinson's disease, Brain Res. 637 (1994) 339–341.
[41] C. Mayer, I. Grummt, Cellular stress and nucleolar function, Cell Cycle 4 (2005) 1036–1038.
[42] M. Zampieri, F. Ciccarone, T. Guastafierro, M.G. Bacalini, R. Calabrese, M. Moreno-Villanueva, A. Reale, M. Chevanne, A. Burkle, P. Caiafa, Validation of suitable internal control genes for expression studies in aging, Mech. Ageing Dev. 131 (2010) 89–95.
[43] E. Boda, A. Pini, E. Hoxha, R. Parolisi, F. Tempia, Selection of reference genes for quantitative real-time RT-PCR studies in mouse brain, J. Mol. Neurosci. 37 (2009) 238–253.
[44] L. Guarente, Link between aging and the nucleolus, Genes Dev. 11 (1997) 2449–2455.
[45] M. Healy-Stoffel, S.O. Ahmad, J.A. Stanford, B. Levant, Altered nucleolar morphology in substantia nigra dopamine neurons following 6-hydroxydopamine lesion in rats, Neurosci. Lett. 546 (2013) 26–30.
[46] D. Iacono, R. O'Brien, S.M. Resnick, A.B. Zonderman, O. Pletnikova, G. Rudow, Y. An, M.J. West, B. Crain, J.C. Troncoso, Neuronal hypertrophy in asymptomatic Alzheimer disease, J. Neuropathol. Exp. Neurol. 67 (2008) 578–589.
[47] E.M. Marquez-Lona, Z. Tan, S.S. Schreiber, Nucleolar stress characterized by down-regulation of nucleophosmin: a novel cause of neuronal degeneration, Biochem. Biophys. Res. Commun. 417 (2012) 514–520.
[48] W.M. Caudle, E. Kitsou, J. Li, J. Bradner, J. Zhang, A role for a novel protein, nucleolin, in Parkinson's disease, Neurosci. Lett. 459 (2009) 11–15.
[49] H. Tsoi, H.Y. Chan, Expression of expanded CAG transcripts triggers nucleolar stress in Huntington's disease, Cerebellum 12 (2013) 310–312.
[50] J. Jin, G.J. Li, J. Davis, D. Zhu, Y. Wang, C. Pan, J. Zhang, Identification of novel proteins associated with both alpha-synuclein and DJ-1, Mol. Cell. Proteomics 6 (2007) 845–859.
[51] S. Li, G.F. Hu, Angiogenin-mediated rRNA transcription in cancer and neurodegeneration, Int. J Biochem. Mol. Biol. 1 (2010) 26–35.
[52] A. Dranovsky, I. Vincent, L. Gregori, A. Schwarzman, D. Colflesh, J. Enghild, W. Strittmatter, P. Davies, D. Goldgaber, Cdc2 phosphorylation of nucleolin demarcates mitotic stages and Alzheimer's disease pathology, Neurobiol. Aging 22 (2001) 517–528.
[53] T.U. Steidinger, D.G. Standaert, T.A. Yacoubian, A neuroprotective role for angiogenin in models of Parkinson's disease, J. Neurochem. 116 (2011) 334–341.
[54] Y. Piao, T. Hashimoto, S. Takahama, A. Kakita, T. Komori, T. Morita, H. Takahashi, T. Mizutani, K. Oyanagi, Survival motor neuron (SMN) protein in the spinal anterior horn cells of patients with sporadic amyotrophic lateral sclerosis, Brain Res. 1372 (2011) 152–159.
[55] K.A. Wehner, L. Ayala, Y. Kim, P.J. Young, B.A. Hosler, C.L. Lorson, S.J. Baserga, J.W. Francis, Survival motor neuron protein in the nucleolus of mammalian neurons, Brain Res. 945 (2002) 160–173.
[56] K. Kalita, D. Makonchuk, C. Gomes, J.J. Zheng, M. Hetman, Inhibition of nucleolar transcription as a trigger for neuronal apoptosis, J. Neurochem. 105 (2008) 2286–2299.
[57] M.A. van Es, H.J. Schelhaas, P.W. van Vught, N. Ticozzi, P.M. Andersen, E.J. Groen, C. Schulte, H.M. Blauw, M. Koppers, F.P. Diekstra, K. Fumoto, A.L. LeClerc, P. Keagle, B.R. Bloem, H. Scheffer, B.F. van Nuenen, M. van Blitterswijk, W. van Rheenen, A.M. Wills, P.P. Lowe, G.F. Hu, W. Yu, H. Kishikawa, D. Wu, R.D. Folkerth, C. Mariani, S. Goldwurm, G. Pezzoli, P. Van Damme, R. Lemmens, C. Dahlberg, A. Birve, R. Fernandez-Santiago, S. Waibel, C. Klein, M. Weber, A.J. van der Kooi, M. de Visser, D. Verbaan, J.J. van Hilten, P. Heutink, E.A. Hennekam, E. Cuppen, D. Berg, R.H. Brown Jr., V. Silani, T. Gasser, A.C. Ludolph, W. Robberecht, R.A. Ophoff, J.H. Veldink, R.J. Pasterkamp, P.I. de Bakker, J.E. Landers, B.P. van de Warrenburg, L.H. van den Berg, Angiogenin variants in Parkinson disease and amyotrophic lateral sclerosis, Ann. Neurol. 70 (2011) 964–973.
[58] T.A. Yacoubian, I. Cantuti-Castelvetri, B. Bouzou, G. Asteris, P.J. McLean, B.T. Hyman, D.G. Standaert, Transcriptional dysregulation in a transgenic model of Parkinson disease, Neurobiol. Dis. 29 (2008) 515–528.
[59] D. Kieran, J. Sebastia, M.J. Greenway, M.A. King, D. Connaughton, C.G. Concannon, B. Fenner, O. Hardiman, J.H. Prehn, Control of motoneuron survival by angiogenin, J. Neurosci. 28 (2008) 14056–14061.
[60] T.U. Steidinger, S.R. Slone, H. Ding, D.G. Standaert, T.A. Yacoubian, Angiogenin in Parkinson disease models: role of Akt phosphorylation and evaluation of AAV-mediated angiogenin expression in MPTP treated mice, PLoS One 8 (2013) e56092.
[61] S. Li, G.F. Hu, Emerging role of angiogenin in stress response and cell survival under adverse conditions, J. Cell. Physiol. 227 (2012) 2822–2826.
[62] S. Lefebvre, P. Burlet, L. Viollet, S. Bertrandy, C. Huber, C. Belser, A. Munnich, A novel association of the SMN protein with two major non-ribosomal nucleolar proteins and its implication in spinal muscular atrophy, Hum. Mol. Genet. 11 (2002) 1017–1027.
[63] S. Vilotti, M. Codrich, M. Dal Ferro, M. Pinto, I. Ferrer, L. Collavin, S. Gustincich, S. Zucchelli, Parkinson's disease DJ-1 L166P alters rRNA biogenesis by exclusion of TTRAP from the nucleolus and sequestration into cytoplasmic aggregates via TRAF6, PLoS One 7 (2012) e35051.
[64] S. Zucchelli, S. Vilotti, R. Calligaris, Z.S. Lavina, M. Biagioli, R. Foti, L. De Maso, M. Pinto, M. Gorza, E. Speretta, C. Casseler, G. Tell, G. Del Sal, S. Gustincich, Aggresome-forming TTRAP mediates pro-apoptotic properties of Parkinson's disease-associated DJ-1 missense mutations, Cell Death Differ. 16 (2009) 428–438.
[65] S. Vilotti, M. Biagioli, R. Foti, M. Dal Ferro, Z.S. Lavina, L. Collavin, G. Del Sal, S. Zucchelli, S. Gustincich, The PML nuclear bodies-associated protein TTRAP regulates ribosome biogenesis in nucleolar cavities upon proteasome inhibition, Cell Death Differ. 19 (2012) 488–500.
[66] X. Yuan, Y. Zhou, E. Casanova, M. Chai, E. Kiss, H.J. Grone, G. Schutz, I. Grummt, Genetic inactivation of the transcription factor TIF-IA leads to nucleolar disruption, cell cycle arrest, and p53-mediated apoptosis, Mol. Cell 19 (2005) 77–87.
[67] C. Mayer, J. Zhao, X. Yuan, I. Grummt, mTOR-dependent activation of the transcription factor TIF-IA links rRNA synthesis to nutrient availability, Genes Dev. 18 (2004) 423–434.
[68] C. Mayer, H. Bierhoff, I. Grummt, The nucleolus as a stress sensor: JNK2 inactivates the transcription factor TIF-IA and down-regulates rRNA synthesis, Genes Dev. 19 (2005) 933–941.
[69] R. Parlato, G. Kreiner, G. Erdmann, C. Rieker, S. Stotz, E. Savenkova, S. Berger, I. Grummt, G. Schutz, Activation of an endogenous suicide response after perturbation of rRNA synthesis leads to neurodegeneration in mice, J. Neurosci. 28 (2008) 12759–12764.
[70] G. Kreiner, H. Bierhoff, M. Armentano, J. Rodriguez-Parkitna, K. Sowodniok, J.R. Naranjo, L. Bonfanti, B. Liss, G. Schutz, I. Grummt, R. Parlato, A neuroprotective phase precedes striatal degeneration upon nucleolar stress, Cell Death Differ. 20 (2013) 1455–1464.
[71] A. Kiryk, K. Sowodniok, G. Kreiner, J. Rodriguez-Parkitna, A. Sonmez, T. Gorkiewicz, H. Bierhoff, M. Wawrzyniak, A.K. Janusz, B. Liss, W. Konopka, G. Schutz, L. Kaczmarek, R. Parlato, Impaired rRNA synthesis triggers homeostatic responses in hippocampal neurons, Front. Cell. Neurosci. 7 (2013) 207.
[72] R.E. Burke, Intracellular signalling pathways in dopamine cell death and axonal degeneration, Prog. Brain Res. 183 (2010) 79–97.
[73] L.S. Tain, A.J. Whitworth, Translating translation: regulated protein translation as a biomedical intervention, Fly (Austin) 3 (2009).
[74] V. Dorval, S.S. Hebert, LRRK2 in transcription and translation regulation: relevance for Parkinson's disease, Front. Neurol. 3 (2012) 12.
[75] F.C. Baltanas, I. Casafont, E. Weruaga, J.R. Alonso, M.T. Berciano, M. Lafarga, Nucleolar disruption and cajal body disassembly are nuclear hallmarks of DNA damage-induced neurodegeneration in purkinje cells, Brain Pathol. 21 (2011) 374–388.
[76] A. Ramirez, A. Heimbach, J. Grundemann, B. Stiller, D. Hampshire, L.P. Cid, I. Goebel, A.F. Mubaidin, A.L. Wriekat, J. Roeper, A. Al-Din, A.M. Hillmer, M. Karsak, B. Liss, C.G. Woods, M.I. Behrens, C. Kubisch, Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase, Nat. Genet. 38 (2006) 1184–1191.
[77] I. Ahmed, Y. Liang, S. Schools, V.L. Dawson, T.M. Dawson, J.M. Savitt, Development and characterization of a new Parkinson's disease model resulting from impaired autophagy, J. Neurosci. 32 (2012) 16503–16509.
[78] A. Domanskyi, C. Geissler, I.A. Vinnikov, H. Alter, A. Schober, M.A. Vogt, P. Gass, R. Parlato, G. Schutz, Pten ablation in adult dopaminergic neurons is neuroprotective in Parkinson's disease models, FASEB J. 25 (2011) 2898–2910.
[79] C.P. Rubbi, J. Milner, Disruption of the nucleolus mediates stabilization of p53 in response to DNA damage and other stresses, EMBO J. 22 (2003) 6068–6077.
[80] Y. Zhang, H. Lu, Signaling to p53: ribosomal proteins find their way, Cancer Cell 16 (2009) 369–377.
[81] W. Duan, X. Zhu, B. Ladenheim, Q.S. Yu, Z. Guo, J. Oyler, R.G. Cutler, J.L. Cadet, N.H. Greig, M.P. Mattson, p53 inhibitors preserve dopamine neurons and motor function in experimental parkinsonism, Ann. Neurol. 52 (2002) 597–606.
[82] A.J. Levine, C.R. Harris, A.M. Puzio-Kuter, The interfaces between signal transduction pathways: IGF-1/mTor, p53 and the Parkinson disease pathway, Oncotarget 3 (2012) 1301–1307.

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014

[83] C. Zhang, M. Lin, R. Wu, X. Wang, B. Yang, A.J. Levine, W. Hu, Z. Feng, Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 16259–16264.
[84] C.A. da Costa, C. Sunyach, E. Giaime, A. West, O. Corti, A. Brice, S. Safe, P.M. Abou-Sleiman, N.W. Wood, H. Takahashi, M.S. Goldberg, J. Shen, F. Checler, Transcriptional repression of p53 by parkin and impairment by mutations associated with autosomal recessive juvenile Parkinson's disease, Nat. Cell Biol. 11 (2009) 1370–1375.
[85] F. Checler, C. Alves da Costa, Interplay between Parkin and p53 governs a physiological homeostasis that is disrupted in Parkinson's disease and cerebral cancer, Neurodegener. Dis. (2013) Sep 4. [Epub ahead of print].
[86] E. Duplan, E. Giaime, J. Viotti, J. Sevalle, O. Corti, A. Brice, H. Ariga, L. Qi, F. Checler, C. Alves da Costa, ER-stress-associated functional link between Parkin and DJ-1 via a transcriptional cascade involving the tumor suppressor p53 and the spliced X-box binding protein XBP-1, J. Cell Sci. 126 (2013) 2124–2133.
[87] L.S. Tain, H. Mortiboys, R.N. Tao, E. Ziviani, O. Bandmann, A.J. Whitworth, Rapamycin activation of 4E-BP prevents parkinsonian dopaminergic neuron loss, Nat. Neurosci. 12 (2009) 1129–1135.
[88] Y. Imai, S. Gehrke, H.Q. Wang, R. Takahashi, K. Hasegawa, E. Oota, B. Lu, Phosphorylation of 4E-BP by LRRK2 affects the maintenance of dopaminergic neurons in *Drosophila*, EMBO J. 27 (2008) 2432–2443.
[89] R.S. Akundi, L. Zhi, H. Bueler, PINK1 enhances insulin-like growth factor-1-dependent Akt signaling and protection against apoptosis, Neurobiol. Dis. 45 (2012) 469–478.
[90] A. Trancikova, A. Mamais, P.J. Webber, K. Stafa, E. Tsika, L. Glauser, A.B. West, R. Bandopadhyay, D.J. Moore, Phosphorylation of 4E-BP1 in the mammalian brain is not altered by LRRK2 expression or pathogenic mutations, PLoS One 7 (2012) e47784.
[91] M.C. Chartier-Harlin, J.C. Dachsel, C. Vilarino-Guell, S.J. Lincoln, F. Lepretre, M.M. Hulihan, J. Kachergus, A.J. Milnerwood, L. Tapia, M.S. Song, E. Le Rhun, E. Mutez, L. Larvor, A. Duflot, C. Vanbesien-Mailliot, A. Kreisler, O.A. Ross, K. Nishioka, A.I. Soto-Ortolaza, S.A. Cobb, H.L. Melrose, B. Behrouz, B.H. Keeling, J.A. Bacon, E. Hentati, L. Williams, A. Yanagiya, N. Sonenberg, P.J. Lockhart, A.C. Zubair, R.J. Uitti, J.O. Aasly, A. Krygowska-Wajs, G. Opala, Z.K. Wszolek, R. Frigerio, D.M. Maraganore, D. Gosal, T. Lynch, M. Hutchinson, A.R. Bentivoglio, E.M. Valente, W.C. Nichols, N. Pankratz, T. Foroud, R.A. Gibson, F. Hentati, D.W. Dickson, A. Destee, M.J. Farrer, Translation initiator EIF4G1 mutations in familial Parkinson disease, Am. J. Hum. Genet. 89 (2011) 398–406.
[92] E. Colla, P. Coune, Y. Liu, O. Pletnikova, J.C. Troncoso, T. Iwatsubo, B.L. Schneider, M.K. Lee, Endoplasmic reticulum stress is important for the manifestations of alpha-synucleinopathy *in vivo*, J. Neurosci. 32 (2012) 3306–3320.
[93] P. Anglade, S. Vyas, F. Javoy-Agid, M.T. Herrero, P.P. Michel, J. Marquez, A. Mouatt-Prigent, M. Ruberg, E.C. Hirsch, Y. Agid, Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease, Histol. Histopathol. 12 (1997) 25–31.
[94] T.M. Dawson, H.S. Ko, V.L. Dawson, Genetic animal models of Parkinson's disease, Neuron 66 (2010) 646–661.
[95] C. Gomes, S.C. Smith, M.N. Youssef, J.J. Zheng, T. Hagg, M. Hetman, RNA polymerase 1-driven transcription as a mediator of BDNF-induced neurite outgrowth, J. Biol. Chem. 286 (2011) 4357–4363.
[96] M.F. Beal, Experimental models of Parkinson's disease, Nat. Rev. Neurosci. 2 (2001) 325–334.
[97] V.D. Nair, K.S. McNaught, J. Gonzalez-Maeso, S.C. Sealfon, C.W. Olanow, p53 mediates nontranscriptional cell death in dopaminergic cells in response to proteasome inhibition, J. Biol. Chem. 281 (2006) 39550–39560.
[98] Y.C. Su, X. Qi, Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation, Hum. Mol. Genet. 22 (2013) 4545–4561.
[99] A.R. Winslow, D.C. Rubinsztein, The Parkinson disease protein alpha-synuclein inhibits autophagy, Autophagy 7 (2011) 429–431.
[100] E.C. Hirsch, S. Vyas, S. Hunot, Neuroinflammation in Parkinson's disease, Parkinsonism Relat. Disord. 18 (Suppl. 1) (2012) S210–S212.
[101] J. Lee, Y.J. Hwang, H. Ryu, N.W. Kowall, H. Ryu, Nucleolar dysfunction in Huntington's disease, Biochim. Biophys. Acta (2013), pii: S0925-4439(13)00305-0.
[102] P.H. Reddy, U.P. Shirendeb, Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease, Biochim. Biophys. Acta 1822 (2012) 101–110.
[103] S.E. Browne, M.F. Beal, Oxidative damage in Huntington's disease pathogenesis, Antioxid. Redox Signal. 8 (2006) 2061–2073.
[104] B.I. Bae, H. Xu, S. Igarashi, M. Fujimuro, N. Agrawal, Y. Taya, S.D. Hayward, T.H. Moran, C. Montell, C.A. Ross, S.H. Snyder, A. Sawa, p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease, Neuron 47 (2005) 29–41.
[105] M. Martinez-Vicente, Z. Talloczy, E. Wong, G. Tang, H. Koga, S. Kaushik, R. de Vries, E. Arias, S. Harris, D. Sulzer, A.M. Cuervo, Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease, Nat. Neurosci. 13 (2010) 567–576.
[106] M. Arrasate, S. Finkbeiner, Protein aggregates in Huntington's disease, Exp. Neurol. 238 (2012) 1–11.
[107] T. Moller, Neuroinflammation in Huntington's disease, J. Neural Transm. 117 (2010) 1001–1008.
[108] A.M. da Silva, S.L. Payao, B. Borsatto, P.H. Bertolucci, M.A. Smith, Quantitative evaluation of the rRNA in Alzheimer's disease, Mech. Ageing Dev. 120 (2000) 57–64.
[109] H. Donmez-Altuntas, H. Akalin, Y. Karaman, H. Demirtas, N. Imamoglu, Y. Ozkul, Evaluation of the nucleolar organizer regions in Alzheimer's disease, Gerontology 51 (2005) 297–301.
[110] X. Wang, W. Wang, L. Li, G. Perry, H.G. Lee, X. Zhu, Oxidative stress and mitochondrial dysfunction in Alzheimer's disease, Biochim. Biophys. Acta (2013), pii: S0925-4439(13)00323-2.
[111] C. Hooper, E. Meimaridou, M. Tavassoli, G. Melino, S. Lovestone, R. Killick, p53 is upregulated in Alzheimer's disease and induces tau phosphorylation in HEK293a cells, Neurosci. Lett. 418 (2007) 34–37.
[112] D. Ling, P.M. Salvaterra, A central role for autophagy in Alzheimer-type neurodegeneration, Autophagy 5 (2009) 738–740.
[113] D.J. Selkoe, Alzheimer's disease, Cold Spring Harb. Perspect. Biol. 3 (2011).
[114] C.K. Glass, K. Saijo, B. Winner, M.C. Marchetto, F.H. Gage, Mechanisms underlying inflammation in neurodegeneration, Cell 140 (2010) 918–934.
[115] M.K. Jaiswal, B.U. Keller, Cu/Zn superoxide dismutase typical for familial amyotrophic lateral sclerosis increases the vulnerability of mitochondria and perturbs Ca2 + homeostasis in SOD1G93A mice, Mol. Pharmacol. 75 (2009) 478–489.
[116] G. Acsadi, I. Lee, X. Li, M. Khaidakov, A. Pecinova, G.C. Parker, M. Huttemann, Mitochondrial dysfunction in a neural cell model of spinal muscular atrophy, J. Neurosci. Res. 87 (2009) 2748–2756.
[117] L. Rossi, C. Valle, M.T. Carri, Altered gene expression, mitochondrial damage and oxidative stress: converging routes in motor neuron degeneration, Int. J. Cell Biol. 2012 (2012) 908724.
[118] L.J. Martin, p53 is abnormally elevated and active in the CNS of patients with amyotrophic lateral sclerosis, Neurobiol. Dis. 7 (2000) 613–622.
[119] A. Otomo, L. Pan, S. Hadano, Dysregulation of the autophagy-endolysosomal system in amyotrophic lateral sclerosis and related motor neuron diseases, Neurol. Res. Int. 2012 (2012) 498428.
[120] S. Carra, V. Crippa, P. Rusmini, A. Boncoraglio, M. Minoia, E. Giorgetti, H.H. Kampinga, A. Poletti, Alteration of protein folding and degradation in motor neuron diseases: implications and protective functions of small heat shock proteins, Prog. Neurobiol. 97 (2012) 83–100.
[121] F. Rizzo, G. Riboldi, S. Salani, M. Nizzardo, C. Simone, S. Corti, E. Hedlund, Cellular therapy to target neuroinflammation in amyotrophic lateral sclerosis, Cell. Mol. Life Sci. (2013) Oct 8. [Epub ahead of print].

Please cite this article as: R. Parlato, B. Liss, How Parkinson's disease meets nucleolar stress, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2013.12.014