Biochimica et Biophysica Acta 1842 (2014) 791–797

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

How Parkinson's disease meets nucleolar stress ☆

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ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 13 December 2013
Accepted 31 December 2013
Available online 8 January 2014

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.

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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

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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

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