Molecular and Cellular Neuroscience xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

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

Pathologic and therapeutic implications for the cell biology of parkin

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ARTICLE INFO

Article history:
Received 13 November 2014
Revised 7 February 2015
Accepted 15 February 2015
Available online xxxx

Keywords:
Parkin
PD
Mitophagy
Apoptosis
Therapy
Neurodegeneration

ABSTRACT

Mutations in the E3 ligase parkin are the most common cause of autosomal recessive Parkinson's disease (PD), but it is believed that parkin dysfunction may also contribute to idiopathic PD. Since its discovery, parkin has been implicated in supporting multiple neuroprotective pathways, many revolving around the maintenance of mitochondrial health quality control and governance of cell survival. Recent advances across the structure, biochemistry, and cell biology of parkin have provided great insights into the etiology of parkin-linked and idiopathic PD and may ultimately generate novel therapeutic strategies to slow or halt disease progression. This review describes the various pathways in which parkin acts and the mechanisms by which parkin may be targeted for therapeutic intervention. This article is part of a Special Issue entitled 'Neuronal Protein'.

Contents

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http://dx.doi.org/10.1016/j.mcn.2015.02.008
1044-7431/

1. Introduction

Of all neurodegenerative disorders, Parkinson's disease (PD) is the second most prevalent affecting about 9.5 per 1000 of the population aged at least 65 or older (Dauer and Przedborski, 2003; Hirtz et al., 2007). Since the first identification of a monogenic, inherited form of PD in 1997, researchers have made great strides in elucidating the biochemical pathways that underlie this disease. Yet the precise etiologies of inherited and sporadic PD still remain unknown. Patients present with a wide range of pathological symptoms that include bradykinesia, resting tremor, postural instability and rigidity (Wirdefeldt et al., 2011). The classic pathological manifestations of the disease include the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of intracellular cytoplasmic aggregates called Lewy bodies (Forno, 1996). However, it is now appreciated that both the pathology and symptomology extend far beyond the nigrostriatal system (Hornykiewicz and Kish, 1987; Kupsky et al., 1987; Braak et al., 2004; Langston, 2006; Jain, 2011). Unfortunately, available treatments to date are mostly geared towards the movement disturbances while the non-nigral features of PD are less well addressed.

The majority of PD cases are idiopathic, but about 5–10% of the cases have a known underlying genetic basis (Dawson and Dawson, 2003). Leucine-rich repeat kinase 2 (LRRK2) and α-synuclein are associated with autosomal dominant forms of PD, whereas parkin, PINK1 (PTEN-induced kinase 1), DJ-1 and ATP13a2 are associated with autosomal recessive forms. Of these, mutations in the gene encoding parkin are the most common cause of autosomal recessive PD, comprising about 50% of all recessive forms of the disease (Lucking et al., 2000). While the biochemical function of some proteins implicated in PD is not known (e.g. α-synuclein, DJ-1, LRRK2), parkin is a well-established ubiquitin E3 ligase whose crystal structure was recently solved (Riley et al., 2013; Trempe et al., 2013; Wauer and Komander, 2013). The wealth of information surrounding parkin structure and function, and particularly the strides made in the last two years, make parkin biology an attractive target for therapeutic intervention in sporadic PD, where wild-type parkin expression is preserved but may be functionally compromised or amenable to facilitation. In this review, we will detail the various molecular pathways affected by parkin, as well as the possible upstream and downstream interactors that could be targeted not only for PD, but also for other neurodegenerative diseases.

2. Parkin and parkinsonism

Over a decade and a half ago, parkin was identified by the investigation of a chromosomal deletion in Japanese patients diagnosed with autosomal recessive-juvenile Parkinson's disease (AR-JP) (Matsumine et al., 1997; Kitada et al., 1998). Patients diagnosed with AR-JP exhibited the same characteristic symptoms as those with typical late-onset PD and were L-DOPA responsive, but postmortem analyses revealed the surprising lack of expected Lewy bodies (Takahashi et al., 1994; Mori et al., 1998; Yokochi, 2000). Later studies, however, did report the presence of Lewy bodies in the substantia nigra and the locus coeruleus of patients with compound heterozygous parkin mutations (Farrer et al., 2001; Pramstaller et al., 2005; Sharp et al., 2014). Patients with AR-JP possessed large deletions in chromosome 6 within the coding region of parkin (Matsumine et al., 1997; Kitada et al., 1998). However, later studies revealed that parkin mutations were found not only in early-onset AR-JP, but also in late-onset PD (Oliveira et al., 2003). Following the discovery of this genetic disruption, it was shown that the gene product was a RING domain E3 ubiquitin ligase (Shimura et al., 2000; Zhang et al., 2000). Parkin is a large (1.3 Mb) gene that is translated to a 465 amino-acid protein that is expressed in various tissues including the heart, testis and skeletal muscle. It is also abundantly expressed in the brain, especially in the substantia nigra (Kitada et al., 1998; Huynh et al., 2001). There have been over 200 mutations in parkin identified in patients which span all domains of the protein (Corti et al., 2011) and include point mutations, exon rearrangements and small deletions (Mata et al., 2004). Given that some of the disease-associated mutations abrogate translation of a functional protein, it has been presumed that the more subtle missense mutations would likewise cause loss-of-function, and some experimental evidence would support this assertion (Henn et al., 2005; Sriram et al., 2005; Schlehe et al., 2008; Bosco et al., 2011). However, not all the mutations may directly affect E3 ligase activity, as it has been argued that some point mutations lead to decreased solubility and the propensity for aggregation of the protein (Henn et al., 2005; Schlehe et al., 2008), which may be particularly true of the truncated mutants.

2.1. New insights from parkin structure

Parkin is a multi-domain protein, belonging to a class of RING domain E3 ligases. Parkin is unusual in that it has two RING domains, an inverted RBR (RING-InbetweenRING-RING) domain and an ubiquitin-like motif (Ubl) within its N-terminus (Sakata et al., 2003). It also contains a unique parkin-specific domain (UPD) containing the RING0 domain (Kahle et al., 2000; Hristova et al., 2009). The crystal structure of parkin was recently solved by multiple groups (Riley et al., 2013; Trempe et al., 2013; Wauer and Komander, 2013), and these impressive efforts have provided valuable insights into the behavior of parkin in the cell (Dove and Klevit, 2013). These structures agreed in finding that parkin exists natively in an auto-inhibited state; the N-terminal region of parkin is folded over the RING1 and RING2 domains, occluding the active site, which requires a conformational change in order to execute an ubiquitination reaction (Riley et al., 2013; Trempe et al., 2013). The structure also reveals how specific mutations in parkin affect its enzymatic activity and its folding capacity. Interestingly, even though PD-associated parkin mutations are widespread and not confined to any particular domain of the protein, they can be categorized according to predicted effects on zinc binding and protein folding, catalytic efficiency, or association with E2s, substrates, or cofactors (Trempe et al., 2013).

2.2. Solubility: role for parkin deficiency in sporadic PD?

Parkin contains 35 cysteine residues, making up almost 8% of the protein, which is high when considered against the proteomic average of 2% (Bosco et al., 2011; Dove and Klevit, 2013). This characteristic is likely at least partially responsible for the protein's susceptibility to stress-induced aggregation or misfolding (Bosco et al., 2011). Studies have also shown that various PD-linked stressors including oxidative, nitrosative and dopamine stresses altered parkin structure, making it more insoluble (Winklhofer et al., 2003; LaVoie et al., 2005; Wang et al., 2005b; Meng et al., 2011). Perhaps consistent with these in vitro studies, there is an age-dependent decrease in parkin solubility in human brain (Pawlyk et al., 2003). Parkin solubility was also found to be decreased in brain tissue from sporadic PD and Diffuse Lewy Body disease patients compared to otherwise healthy controls (LaVoie et al., 2005; Wang et al., 2005a; Kawahara et al., 2008; Lonskaya et al., 2013a), as well as in the blood of PD patients (Vinish et al., 2010). Interestingly, soluble parkin levels were also significantly decreased in cortices from post-mortem Alzheimer's disease (AD) patients, compared to healthy controls (Lonskaya et al., 2013b). This study also reported that insoluble parkin co-localized with intracellular amyloid beta. Collectively, these findings suggest that stress-induced or aging-dependent decreases in soluble, active parkin in the brain may serve as a biochemical phenocopy of loss-of-function mutations in the protein, and contribute to risk of idiopathic PD.

2.3. Animal models

Several in vivo models have been generated to date to understand the molecular pathways affected due to loss of a functional parkin

Please cite this article as: Charan, R.A., LaVoie, M.J., Pathologic and therapeutic implications for the cell biology of parkin, Mol. Cell. Neurosci. (2015), http://dx.doi.org/10.1016/j.mcn.2015.02.008