Potential Pathophysiological Crosstalk between Parkin and FBXO7 Signalling Pathways

Zhi Dong Zhou1,3,*, Eng King Tan1-3

1 National Neuroscience Institute of Singapore, 11 Jalan Tan Tock Seng, Singapore;
2 Department of Neurology, Singapore General Hospital, Outram Road, Singapore;
3 Signature Research Program in Neuroscience and Behavioral Disorders, Duke-NUS Graduate Medical School Singapore, 8 College Road, Singapore.

*Corresponding author. Tel: 91-9717968020; E-mail: Zhideong_zhou@nni.com.sg

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Abstract

Mutations of F-box protein 7 [FBXO7] and Parkin, two proteins related to Ubiquitin-Proteasome System [UPS], are implicated in the pathogenesis of Dopamine [DA] neuron degeneration in Parkinson's Disease [PD], possibly involving impairment of UPS and mitophagy. Parkin is a HECT/RING hybrid ubiquitin E3 ligase that physically receives ubiquitin on its catalytic centre and passes ubiquitin onto its substrates, whereas FBXO7 is an adaptor protein in Skp-Cullin-F-box [SCF] SCF\textsubscript{FBXO7} ubiquitin E3 ligase complex to recognize substrates and mediate substrates ubiquitination by SCF\textsubscript{FBXO7} E3 ligase. There are overlapping clinical features in Parkin and FBXO7 linked PD. One recent study demonstrates that FBXO7 can mediate mitochondrial translocation of Parkin under mitochondria impairment to initiate neuroprotective mitophagy (Figure 1A) [12]. Therefore, it can be hypothesized that stress-induced mitochondrial impairment leads to exposure of certain mitochondrial targets of FBXO7. FBXO7 can be first recruited to impaired mitochondria to initiate mitophagy that clear away the impaired mitochondria and protect cells against stress [12]. In this case, FBXO7 and Parkin cooperate to protect DA neurons against stress, while mutations in FBXO7 and Parkin lose their functions, leading to mitophagy inhibition and DA neuron degeneration.

Keywords: FBXO7; Mitochondria; Mitophagy; Parkin; Parkinson's disease; Proteotoxicity; Ubiquitin proteasome system.

Parkinson's disease [PD] is a common neurodegenerative disorder characterized by chronic and progressive loss of dopaminergic neurons in substantia nigra pars compacta [SN]. PD can affect about 2% of the population above 65 years of age [1-3]. PD symptoms include rigidity, postural instability, tremor at rest and slowness or absence of voluntary movement, and even neuropsychiatric symptoms [4,5]. The pathological hallmarks of PD include progressive degeneration of Dopamine [DA] neurons in SN as well as accumulation of α-synuclein [α-syn] positive Lewy bodies in afflicted brain regions [4,6]. Most PD cases are late onset and may be classified as Sporadic PD [SPD]. However, gene mutations or variations can lead to early onset inherited familial PD [FPD] [3,7]. Parkin gene mutations are associated with classic Levodopa responsive FPD [PARK2] [8]. However, recessive gene mutations of F-box protein 7 [FBXO7] are associated with juvenile onset Parkinsonism [PARK15], frequently accompanied by atypical features including dementia, dystonia, hyperreflexia and pyramidal signs [9,10]. Both Parkin and FBXO7 are involved in Ubiquitin-Proteasome System [UPS] and neuroprotective mitophagy process [11]. There are overlapping pathways in Parkin and FBXO7 linked disease (Figure 1).

First, FBXO7 was found to facilitate Parkin mitochondrial translocation under mitochondria impairment to initiate neuroprotective mitophagy (Figure 1A) [12]. Therefore, it can be hypothesized that stress-induced mitochondrial impairment leads to exposure of certain mitochondrial targets of FBXO7. FBXO7 can be first recruited to impaired mitochondria and subsequently FBXO7 in mitochondria can further attract Parkin to damaged mitochondria. Finally, the accumulated FBXO7 and Parkin in mitochondria may act together to mediate ubiquitination of targets in impaired mitochondria and initiate mitophagy that clear away the impaired mitochondria and protect cells against stress [12]. In this case, FBXO7 and Parkin cooperate to protect DA neurons against stress, while mutations in FBXO7 and Parkin lose their functions, leading to mitophagy inhibition and DA neuron degeneration.
Second, FBXO7 may recognize Parkin as its ubiquitination substrate (Figure 1B). The FBXO7 is an adaptor protein in Skp-Cullin-F-box [SCF] SCF$^{FBXO7}$ ubiquitin E3 ligase complex to recognize substrates and mediate substrates ubiquitination by SCF$^{FBXO7}$ E3 ligase [11]. After binding with Parkin, the protein complex of FBXO7 and Parkin can be further recruited into SCF$^{FBXO7}$ E3 ligase [formed by Cullin1, Skp1, ROC1 and FBXO7] (Figure 1B). Then Parkin can be ubiquitinated by SCF$^{FBXO7}$ E3 ligase and undergo subsequent proteasomal degradation. In this case, FBXO7 may promote degradation of Parkin and maintain the physiological metabolism of Parkin in DA neurons.

Third, FBXO7 may act as an adaptor protein for potential Parkin$^{FBXO7}$ SCF-like E3 ligase complex (Figure 1C). After binding with FBXO7, Parkin may use FBXO7 as its adaptor protein to interact with more substrates. The substrates caught by FBXO7 can be subsequently ubiquitinated by Parkin$^{FBXO7}$ SCF-like E3 ligase and undergo proteasomal degradation. In this case, the adaptor protein FBXO7 can expand the substrate spectrum of Parkin. This hypothesis can be supported by previous finding that Parkin can exert its E3 ligase activity to induce ubiquitination and subsequent proteasome degradation of FBXO7 proteins.

Fourth, after binding of Parkin with FBXO7, Parkin may exert its E3 ligase activity to promote ubiquitination of FBXO7 (Figure 1D). This possibility can be supported by previous finding that Parkin can exert its E3 ligase activity to promote ubiquitination of FBXO7 and promote subsequent proteasome degradation of FBXO7 [14]. In this case, Parkin promotes ubiquitination and clearance of FBXO7,
therefore controls the physiological metabolism of FBXO7 protein in DA neurons.

Fifth, FBXO7 may act as an E4 ligase to modulate Parkin E3 ligase activity (Figure 1E) [18]. We recently found that overexpression of R498X FBXO7 mutant, but not WT FBXO7, promotes WT Parkin aggregates formation [18]. Our findings also demonstrated that mutant FBXO7 can form deleterious protein aggregates in mitochondria, suggesting the mutant FBXO7 can be an aggregation-prone protein [18]. There are accumulated suggestions linking deleterious protein aggregation [proteotoxicity] to disease onset of PD and other human neuron degenerative diseases [19-23]. In this case, mutated FBXO7 proteins may bind with and induce protein aggregates formation of Parkin, leading to diffusion of protein aggregation and down regulation of available functional Parkin under FBXO7 mutations, which can contribute to DA neuron vulnerability under stress.

Sixth, mutant FBXO7 can interact with Parkin and promote protein aggregates formation of Parkin (Figure 1F) [18]. We recently found that overexpression of R498X FBXO7 mutant, but not WT FBXO7, promotes WT Parkin aggregates formation [18]. Our findings also demonstrated that mutant FBXO7 can form deleterious protein aggregates in mitochondria, suggesting the mutant FBXO7 can be an aggregation-prone protein [18]. There are accumulated suggestions linking deleterious protein aggregation [proteotoxicity] to disease onset of PD and other human neuron degenerative diseases [19-23]. In this case, mutated FBXO7 proteins may bind with and induce protein aggregates formation of Parkin, leading to diffusion of protein aggregation and down regulation of available functional Parkin under FBXO7 mutations, which can contribute to DA neuron vulnerability under stress.

There are increasing evidences to support interactions between Parkin and FBXO7 linked pathways. Parkin and FBXO7 are both implicated in tumorigenesis [24,25]. Both WT Parkin and FBXO7 can be cytoprotective, whereas their PD-linked mutants are all deleterious to DA neurons. Further evidence is needed to verify these hypotheses and unravel the complicated crosstalk between the signaling pathways of Parkin and FBXO7, which may open to development of newer therapeutics in PD.

References
