Editorial Highlight: Iron promotes the clearance of α-synuclein

Qing-Zhang Tuo, Peng Lei*

Department of Neurology and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China

Correspondence to:

Dr. Peng Lei, Department of Neurology and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China.

Email: peng.lei@scu.edu.cn

Abstract

Both elevated iron and α-synuclein (α-syn) aggregates are neuropathological hallmarks of Parkinson's disease (PD). It has been previously shown that iron promotes α-synuclein aggregation, and α-synuclein dysfunction impairs iron metabolism. In their latest work, Kim et al. have shown that the H63D variant of the homeostatic iron regulator (HFE) facilitates α-syn degradation via REDD1-mediated autophagy. Mice
with the H63D variant of \textit{HFE} were protected against \( \alpha \)-syn toxicity. These results may shed light on recent clinical studies of PD using iron chelation therapy.

Parkinson’s disease (PD) is a neurodegenerative disorder that affects predominately dopaminergic neurons in substantia nigra (SN), and both iron accumulation and \( \alpha \)-syn aggregation in the region are neuropathological hallmarks of PD (Ayton & Lei 2014). Iron can provoke \( \alpha \)-synuclein fibrillation by inducing conformational changes (Ayton & Lei 2014), while \( \alpha \)-syn regulates iron metabolism through its ferrireductase activity (Davies \textit{et al.} 2011). However, the causal relationship between iron and \( \alpha \)-synuclein pathologies is still in debate.

The homeostatic iron regulator protein, HFE, limits iron uptake into cells through its interaction with the transferrin receptor (Connor & Lee 2006). Polymorphisms in the \textit{HFE} gene have been identified to be disease modifiers in several neurodegenerative diseases such as Alzheimer’s disease (Connor & Lee 2006). In the current issue of \textit{Journal of Neurochemistry}, Kim and colleagues (Kim \textit{et al.} 2020) have investigated the effects of commonly occurring H63D variant of the \textit{HFE} gene on \( \alpha \)-syn pathology in cell culture and animal models of PD, and have found that H63D \textit{HFE} cells accumulate iron while promoting \( \alpha \)-syn clearance. Further evidence has suggested that the \textit{HFE} variant may promote autophagy through regulated in development and DNA damage responses 1 (REDD1) inhibition of the mammalian target of rapamycin complex 1 (mTORC1) \textit{in vitro}, which consequently causes \( \alpha \)-syn degradation (\textit{Figure 1}).

Considering the critical involvement of \( \alpha \)-syn in the pathogenesis of PD, Kim and colleagues have examined the consequences of having an H63D variant of \textit{HFE} in cells and mice. They have found that H63D \textit{HFE} decreased pre-formed fibril (PFF) induced \( \alpha \)-syn aggregation in cells, and H67D \textit{Hfe} mice (homologous to human H63D \textit{HFE}) are resistant to PFF-mediated loss of motor function, consistent with the previous report (Nixon \textit{et al.} 2018).

Kim and colleagues also have reported that H63D \textit{HFE} expressing cells have lower endogenous \( \alpha \)-syn comparing with the control cells. It has been previously reported that
α-syn mRNA contains a putative iron-responsive element (IRE) in the 5’-UTR of that has a sequence homology in mRNA for ferritin (Friedlich et al. 2007), without demonstrating of its interactions with an iron response element-binding proteins (IRPs). Accordingly, the H63D HFE variant should increase α-syn mRNA translation since it increases the labile iron pool. The controversy data support the hypothesis that the IRE in α-syn may not be functional, which should be further investigated.

Excessive iron within a cell can cause stress-induced autophagy. In mutated SH-SY5Y cells overexpressing divalent metal transporter 1 with dramatically enhanced iron uptake, excessive autophagic activity is observed, and pharmacological inhibition of autophagy reverses cell death mediated by iron overloading (Chew et al. 2011). Recently, iron-dependent ferroptosis has been described as an autophagic cell death process (Gao et al. 2016). Therefore, enhanced autophagy can promote the clearance of α-syn as shown by Kim and colleagues, but it can also directly engulf healthy neuronal cells or trigger ferroptosis. It is yet to be determined the sequence of events between iron accumulation and enhanced autophagy with H63D HFE variant, and how to modulate autophagy to achieve beneficial effects is challenging.

Brain iron overload is sufficient to cause parkinsonism in animal models of PD and humans (Ayton & Lei 2014). The iron chelator deferiprone (DFP) was shown to benefit PD patients in the phase II clinical trial (Devos et al. 2014). Iron chelation has been shown to activate autophagy by inhibiting mTOR activity (Ohyashiki et al. 2009), and autophagy promotes the clearance of α-syn (Moors et al. 2017). Consistently, Kim and colleagues have shown that the H63D HFE variant, modulating cellular iron by extension, can enhance autophagy-mediated α-syn clearance. More importantly, Kim and colleagues have found that neuroprotection offered by DFP is affected by the H63D HFE variant in SH-SY5Y cells, where a low concentration of DFP (1μM) can even enhance the PEF-mediated toxicity in cells. DFP at a lower dose may inhibit autophagy-induced α-syn clearance since it prevents the iron influx that is needed for REDD1-mTORC1-related autophagy activation, which is offset by direct activation of autophagy with higher doses of iron chelator (Ohyashiki et al. 2009).
Kim and colleagues have shown that regulating iron uptake can promote autophagy to degrade α-syn, indicating that PD patients with the H63D HFE variant may respond differently to iron chelation therapy. The highly prevalent H63D HFE variant is estimated to be 5-22% globally (Hanson et al. 2001), and therefore, pre-screening of PD patients for the H63D HFE variant may be warranted before iron chelation therapy.

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CONFLICT OF INTEREST

Peng Lei is an editor for the Journal of Neurochemistry. Qing-zhang Tuo has no conflict of interest to declare.

REFERENCES


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Figure Legend

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Figure 1 Iron promotes the clearance of α-synuclein. H63D HFE variant increases REDD1 and subsequently inhibits mTORC1 to induce autophagy, and promotes the clearance of α-syn. The low-dose of DFP can inhibit autophagy-induced α-syn clearance. The high-dose of DFP can directly activate autophagy, therefore offsetting the inhibitory effect of iron reduction on autophagy, which ultimately promotes α-syn clearance.
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