



Activation of p62-Keap1-Nrf2 Pathway Protects 6-Hydroxydopamine-Induced Ferroptosis in Dopaminergic Cells

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Received: 8 May 2020 / Accepted: 28 July 2020

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder primarily caused by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). However, the manner of death of dopaminergic neurons remains indistinct. Ferroptosis is a form of cell death involving in the iron-dependent accumulation of glutathione depletion and lipid peroxide. Besides, previous studies indicated that ferroptosis might be involved in the death of dopaminergic neurons. In this study, we aim to explore the protective effect of the p62-Keap1-Nrf2 pathway against 6-hydroxydopamine (6-OHDA)-induced ferroptosis in dopaminergic cells. Firstly, our results demonstrated that 6-OHDA-induced ferroptosis could be observed in vivo zebrafish and in vitro human dopaminergic cell line (SH-SY5Y cells) model. Moreover, ferroptosis induced by 6-OHDA mitigates in SH-SY5Y cells upon ferrostatin-1 (Fer, an inhibitor of ferroptosis) treatment via upregulating the protein expression of glutathione peroxidase 4 (GPX4). Then, we found that high p62/SQSTM1 (p62) expression could protect SH-SY5Y cells against ferroptosis through promoting Nrf2 nuclear transfer and upregulating the expression of the antioxidant protein heme oxygenase-1 (HO-1). Ultimately, high p62 expression activates the Nrf2/HO-1 signaling pathway through binding to Kelch-like ECH-associated protein 1 (Keap1). Collectively, the activation of the p62-Keap1-Nrf2 pathway prevents 6-OHDA-induced ferroptosis in SH-SY5Y cells, targeting this pathway in combination with a pharmacological inhibitor of ferroptosis can be a potential approach for PD therapy.

Keywords Parkinson's disease · 6-OHDA · Ferroptosis · p62-Keap1-Nrf2

Abbreviations

PD Parkinson's disease
ROS Reactive oxygen species
6-OHDA 6-Hydroxydopamine
Fer Ferrostatin-1

HO-1 Heme oxygenase-1
Nrf2 Nuclear factor erythroid 2-like 2
SNpc Substantia nigra pars compacta
GPX4 Glutathione peroxidase 4
ACSL4 Acyl-CoA synthetase-4
 α -syn α -Synuclein
Nec Necrosulfonamide
Keap1 Kelch-like ECH-associated protein 1
ZnPP Zn-protoporphyrin
p62 p62/SQSTM1
BCA Bicinchoninic acid

Yiran Sun, Libo He, Taoyu Wang and Wan Hua contributed equally to this work.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12035-020-02049-3>) contains supplementary material, which is available to authorized users.

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Introduction

Parkinson's disease (PD), a common neurodegenerative disorder, is characterized by progressive motor disability and cognitive dysfunction resulting from the degeneration of dopaminergic neurons and abnormal aggregation of α -synuclein