Activation of Nrf2 alleviates Parkinson’s disease-like pathology: a new strategy targeting the C/EBPβ/α-Syn pathway

Ze-Fang Lin¹,², Wei Yao*¹

¹Department of Physiology, School of Medicine, Jinan University, Guangzhou 510632, China. ²Guangzhou Key Laboratory of Formula-pattern Research Center, School of Traditional Chinese Medicine, Jinan University, Guangzhou 510632, China.

*Corresponding to: Wei Yao, Guangzhou Key Laboratory of Formula-pattern Research Center, School of Traditional Chinese Medicine, Jinan University, No. 601, Huanggou Avenue West, Tianhe District, Guangzhou 510632, China. E-mail: weiyao@jnu.edu.cn.

Parkinson’s disease (PD) is a prevalent neurological disorder around the globe, currently affecting over 6 million people globally [1]. It is estimated that by 2040, this number may double to more than 12 million [2]. Aging is strongly associated with PD, as it is a significant risk factor for its development [3].

Clinically, PD presents with various motor and non-motor signs. Movement-related issues mainly consist of slowed motion, involuntary shaking at rest, stiff muscles, and balance difficulties. At the same time, non-movement-related issues include impaired sense of smell, sleep disturbances, bowel irregularities, feelings of sadness, and problems with the body’s automatic functions [4]. The typical pathological features of PD patients include the gradual loss of dopaminergic neurons within the substantia nigra pars compacta, coupled with the buildup of α-synuclein (α-Syn) in neurons, the aggregates of which form inclusions known as Lewy bodies [5]. The A53T mutant of human α-Syn has a propensity to aggregate, a characteristic closely associated with the neurotoxicity seen in familial PD [6]. A synthesis of both in vitro and in vivo research indicates that the misfolding and aggregation of α-Syn are key pathogenic mechanisms in the development of PD [7–9].

The CCAAT/enhancer-binding protein β (C/EBPβ) belongs to the CCAAT/enhancer-binding protein group and is categorized within the basic-leucine zipper family of proteins [10]. The mRNA of C/EBPβ is extensively expressed in neurons throughout the mature brain, where it significantly influences the adaptability of synapses and the development of memory [11–14]. A range of pro-inflammatory cytokines, including interleukin-6, interleukin-1β, and tumor necrosis factor-α, are capable of triggering the activation of C/EBPβ [15, 16]. Given the central role of C/EBPβ in brain function, it is implicated in the pathogenesis of several neurodegenerative diseases. For instance, in patients with Alzheimer’s disease, the levels of both mRNA and protein of C/EBPβ are found to be increased, and its upregulation mediates the pathological processes of amyloid-β and Tau, thereby accelerating the progression of Alzheimer’s disease [17, 18]. Similarly, in amyotrophic lateral sclerosis, the upregulation of C/EBPβ also promotes the expression of pro-inflammatory genes, exacerbating the condition [19]. It has been reported that C/EBPβ can regulate the transcription of α-Syn in an age-dependent manner, thus mediating the pathogenesis of PD [20]. However, the specific impact of C/EBPβ on the pathophysiology of PD is not well understood at present. Consequently, studying the inhibitory effects of irregular C/EBPβ expression may offer a new potential avenue for developing effective therapeutic strategies to prevent the progression of PD.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor found throughout the brain, playing a key role in managing responses to oxidative stress. Nrf2 can combat various oxidative and stress-related neurodegenerative damages by binding to antioxidant response elements [21, 22]. Given the crucial role of Nrf2 as a transcriptional mediator for antioxidants, its potential to inhibit the transcriptional activity of C/EBPβ warrants further attention. Sulforaphane is a natural antioxidant derived from cruciferous vegetables and is an activator of Nrf2 [23, 24]. Research indicates that pro-inflammatory cytokines stimulate C/EBPβ, which then controls the expression of α-Syn in the brains of PD [20]. Consequently, investigating how activating Nrf2 affects the aberrant C/EBPβ/α-Syn signaling pathway in PD mouse models may offer crucial understanding into alleviating the pathological hallmarks of PD.

In the paper of Aging Cell, Lin et al. observed in SH-SY5Y cells that activating Nrf2 with sulforaphane could inhibit the transcription of C/EBPβ triggered by 1-methyl-4-phenylpyridinium (MPP+). Furthermore, using C/EBPβ-DNA/RNA heteroduplex oligonucleotides (HDO) has been shown to effectively silence C/EBPβ. Both methods successfully reduced the MPP+-induced expression of α-Syn in primary neuronal cells. Moreover, in PD mouse models treated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine and preformed α-synuclein fibrils, it was observed that either prolonged activation of Nrf2 or the application of C/EBPβ-HDO could suppress C/EBPβ activity. This led to a reduction in α-Syn expression, ameliorating the degeneration of dopaminergic neurons in the substantia nigra pars compacta and consequently alleviating the PD-like symptoms in A53T mice.

The study results highlight the potential application of Nrf2 activators in the field of neuroprotection, particularly as a novel strategy for treating PD. Nrf2 activators, by modulating oxidative stress responses and inhibiting inflammatory pathways, hold promise in combating the neurodegenerative processes in PD. Additionally, Nrf2 activators can also block the critical C/EBPβ/α-Syn signaling pathway involved in PD pathology. Therefore, activators targeting the Nrf2 pathway such as sulforaphane, as well as C/EBPβ-HDO, demonstrate significant promise as potential therapeutic agents for treating PD.

References


Author contribution
Conceptualization: Wei Yao; Original draft preparation: Zefang Lin, Wei Yao; Review and editing: Zefang Lin and Wei Yao.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This study was financially supported by the National Natural Science Foundation of China (No.82271563 and No.82204786); The National Science Foundation of Guangdong Province of China (No.2022A1510121512); The Academic Promotion Program of Shandong First Medical University.

Abbreviations
PD, Parkinson’s disease; α-Syn, α-synuclein; C/EBPβ, CCAAT/enhancer-binding protein β; Nrf2, nuclear factor erythroid 2-related factor 2; MPP+, 1-methyl-4-phenylpyridinium; HDQ, heteroduplex oligonucleotides.

Citation

Executive editor: Xin-Yun Zhang.

Received: 24 December 2023; Accepted: 24 December 2023; Available online: 25 December 2023. © 2023 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (https://creativecommons.org/licenses/by/4.0/).