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LncZFAS1 Inhibit MPP+-Induced Neuroinflammation Through TXNIP/MIB1 E3 Ubiquitin Ligase/NLRP3 Axis

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Abstract

Neuroinflammation is associated with the occurrence and progression of Parkinson's disease (PD). Nucleotide-binding domain-like receptor protein-3 (NLRP3) is closely related to pyroptosis in PD-related cells and animal models, such as microglia and SH-SY5Y cells. The novel lncRNA ZFAS1 (LncZFAS1) regulates a variety of signaling pathways and participates in the inflammatory response in various diseases. However, their role in PD remains unclear. Our research found LncZFAS1 overexpression directly interfered with mir590-3p to inhibit thioredoxin-interacting protein (TXNIP) the Mindbomb 1 (MIB1) E3 ubiquitin ligase/NLRP3 pathway, which might reveal a new research approach to the mechanism of PD.

Keywords: LncZFAS1, Parkinson's disease, Pyroptosis, MIB1, TXNIP, NLRP3

Abbreviations: PD: Parkinson's Disease; NLRP3: Nucleotide-binding domain-like Receptor Protein-3; LncZFAS1: Long-noncoding RNA ZFAS1; 6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Ca^{2+}: Calcium ion flux; TXNIP: Thioredoxin-Interacting Protein; TRX: Thioredoxin; ZFAS1: ZNFX1 Antisense RNA 1; ZNFX1: Zinc-finger structure, NFX1; miRNAs: MicroRNAs

Introduction

Recently researchers have focused on the role of neuroinflammation in neurodegenerative diseases such as Alzheimer's disease [1], atrophic lateral sclerosis [2], Huntington's disease [3], Multiple sclerosis [4] and Parkinson's disease (PD) [5]. PD is one of the leading neurodegenerative diseases in developed countries and the complete etiological scenario remains unknown. A-synuclein misfolding and aggregation, mitochondrial dysfunction, dysfunctional protein clearance and ubiquitin/proteasome systems, and neuroinflammation have been associated with PD. Harnessing inflammatory responses through targeted modulation of innate and adaptive immune responses has gained increasing interest in recent years as a potential therapeutic strategy. One of our articles, "A Novel Long-Noncoding RNA LncZFAS1 Prevents MPP+-Induced Neuroinflammation Through MIB1 Activation," was studied on this topic and published online in Molecular Neurobiology in December, 2021 [6]. We explored the interaction of the LncZFAS1 and miR590-3p/TXNIP/MIB1 E3 ubiquitin ligase/NLRP3 pathway in the inflammation of PD. TXNIP ubiquitination via MIB1 E3 ubiquitin ligase regulates NLRP3 inflammasome activation in SH-SY5Y cells. In contrast, MPTP activated NLPR3 inflammasome through miR590-3p upregulation and directly interfered with MIB1-dependent TXNIP ubiquitination. LncZFAS1 overexpression inhibits this entire pathway through direct interference with miR590-3p, suggesting a novel research idea in mechanism of PD [6].

An Appropriate Model for PD Neuroinflammatory Study

An appropriate model is the first and most important step in experimental neuropathological studies of PD. There is a clear criterion for PD model selection, but it needs to be further discussed in a PD non-neuroinflammatory study. The

PD model includes toxin-based, gene-based, and synuclein-based models [7-11]. The toxin model imitates dopaminergic neurodegeneration by injecting neurotoxins, studying oxidative stress, mitochondrial respiratory defects, and abnormal protein aggregation among the three potentially important roles in PD pathogenesis [12,13]. The injected toxins include 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, rotenone, and so on [14,15]. Rotenone and MPTP show little difference in their ability to use and inhibit the respiratory chain in animals [16]. However, only MPTP has a clear association with the onset of human PD; in other words, human exposure to MPTP results in a syndrome similar to the core neurological symptoms of PD and relatively selective dopaminergic neurodegeneration [17]. In addition, animal models based on modification of the gene or synaptic nuclear protein, including mice, rats, and fruit flies, cannot obtain stable dopaminergic nerve cell degeneration (i.e., cell death). Instead, they present a variety of neuropathological changes, including neuronal atrophy, malnutrition of neurites, and astrocytic proliferation with α-synaptic nuclear protein-positive LB-like inclusions [18]. Nevertheless, dopaminergic cell neurodegeneration changes are consistent in these models; α-synaptic nuclear proteins in the neurotoxin model represented by MPTP demonstrate a higher fitting degree of human PD [19, 20]. The misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway, leading to the production of α-synaptic nuclear proteins, is critical to the pathogenesis of PD [21,22]. Neurotoxin-based models (particularly MPTP models) are important for elucidating the molecular cascade of cell death in dopaminergic neurons. Our study explored the TXNIP/MIB1 E3 ubiquitin ligase/NLRP3 pathway as one of the ubiquitin-proteasome pathways; therefore, the adopted SH-SY5Y cell model (MPTP-induced) is appropriate. Gene expression is intact in the SH-SY5Y genome of major PD pathways, such as ROS metabolic columns, ubiquitin-proteasome system, dopamine metabolism, calcium signaling, mitochondria, and glycolysis [23]. Retinoic acid is often used to make SH-SY5Y cells morphologically similar to mature primary neurons and present a dopaminergic phenotype in PD [24-26]. Furthermore, SH-SY5Y cells have the advantages of high-throughput screening capacity of high proliferation cell lines, availability of clonal cells, and avoidance of ethical problems caused by human primary neural cell culture [27].

The Role of NLRP3 in PD Neuroimmunology

Neuroinflammation-mediated pyroptosis in PD neurological cells has been extensively studied [8,29,30]. Pyroptosis of NLRP3 activation in primary microglial cells is the core of PD progression in an MPTP-induced mouse model [31-35]. NLRP3 is an inflammatory complex mainly present in microglia and contains a caspase activation recruitment domain and caspase-1, which promotes the secretion of IL-1/IL-18 and induces pyroptosis to destroy microglia to further release IL-1 [36-38]. Our results showed that SH-SY5Y cells generated and activated NLRP3 to induce cellular pyroptosis [6], revealing the role of NLRP3 and cells other than microglia in the neuroinflammatory response in PD. Besides, NLRP3 inflammasome activation may aggravate dopaminergic neuronal loss in Parkinson's disease [39]. There is a link between the aggregation of α-synuclein, increased mitochondrial ROS, and cathepsin B release with the activation of microglial NLRP3 inflammation-mediated pyroptotic cell death of dopaminergic neurons in the substantia nigra[40]. Mitochondrial generation of ROS, mitophagy, loss of function of dopaminergic receptors, and lncRNA, are frequently connect with microglial NLRP3 inflammasome activation [41]. Activators with different biological activities and molecular structures can activate NLRP3, indicating that NLRP3 is activated by common cellular events rather than by physical interactions [42-46]. Common activators induce cell stress, and NLRP3 senses these cell pressures. However, it remains unclear how NLRP3 senses cell stress and which pathways induce climax in the process of NLRP3 activation and inflammatory body formation [47,48]. Multiple upstream signals are involved in these processes, including K^+ or Cl^- efflux [49], calcium ion flux (Ca^{2+}) [50], lysosomal destruction [51], mitochondrial dysfunction [52], metabolic changes [53] and trans-Golgi disassembly [54]. Thioredoxin-interacting protein (TXNIP), an endogenous inhibitor of the thioredoxin (TRX) system, is associated with importin-α, Jab1, E3 ubiquitin ligase ITCH, Mybbp1a, and NLRP3 [55]. TXNIP expression was increased and TXNIP knockdown by siRNA weakened the NLRP3 inflammasome activation response in αSynagg-stimulated mouse microglial cells, suggesting that TXNIP plays a nodal role in PD inflammation [56]. A TXNIP centered inflammasome regulation mechanism has not yet been reported. In our study, NLPR3 activation, ASC recruitment, caspase-1 cleavage, and IL-1 release were found to be dependent on TXNIP/TRX1 interaction. Increased TXNIP ubiquitination by MIB1 E3 ubiquitin ligase can regulate NLRP3 inflammasome activation in SH-SY5Y cell [6]. In the above chapter, we mention innate immunity and adaptive immunity. Microglia, the core of the innate immune network, secrete both anti- and proinflammatory cytokines and chemokines together with other factors that regulate not only adaptive immunity, but also neural function and neural homeostasis [28]. In PD, a- synuclein is associated with activated microglia and dopaminergic neuronal death. During disease, dopaminergic neurons accumulate α-synuclein together with other misfolded proteins (intracellular Lewy body). On injury or death, neurons release these proteins to the surrounding neuroenvironment and the modified proteins find their way to the peripheral lymphatic system. In our study, SH-SY5Y cell model (MPTP-induced) was used to simulate the partial process of dopamine neurons immune injury. Microglia was not involved in this process, which show certain value to understand the role of other cells in innate and adaptive immune responses.

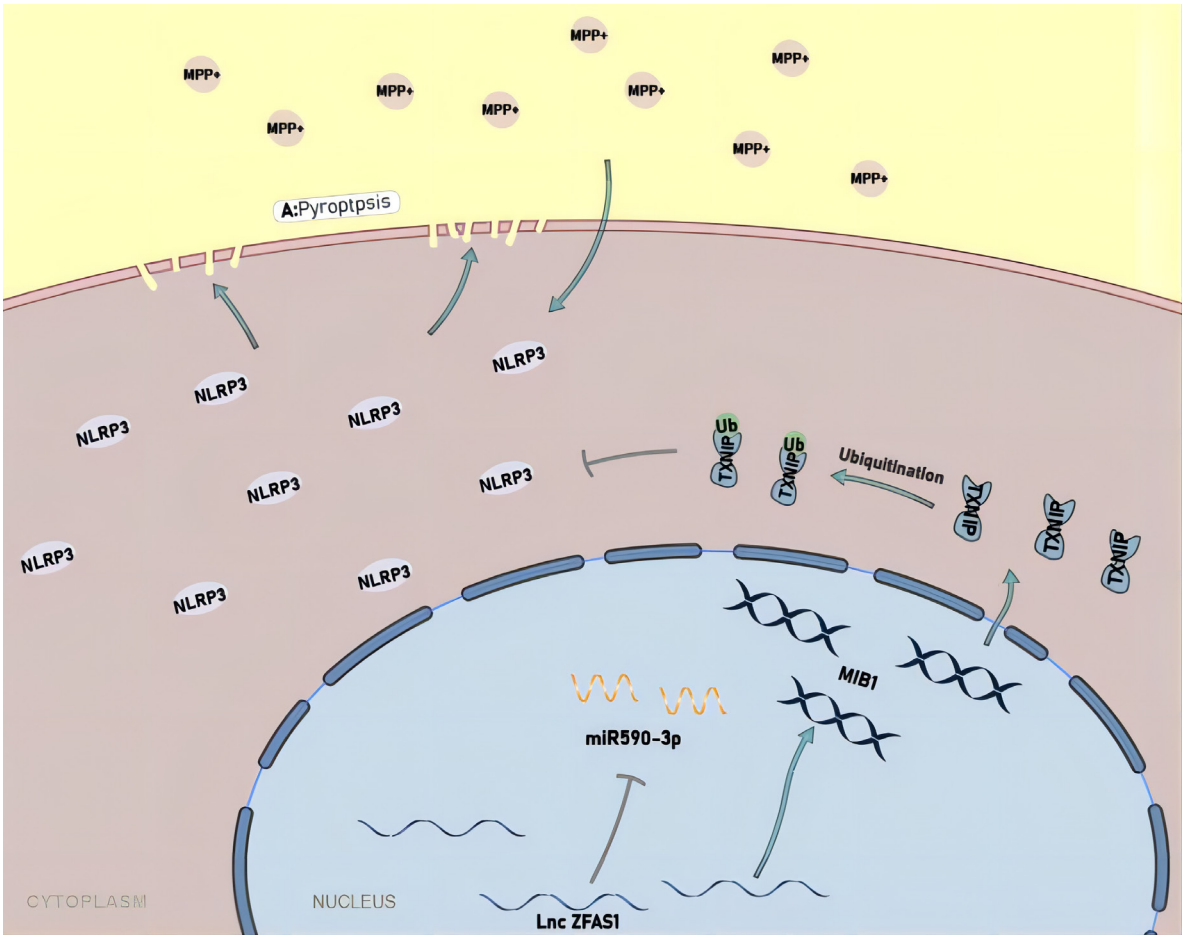

Figure 1: Molecular mechanism for LncZFAS1 mediated inflammasome regulation in neuronal cells.

Interaction between lncRNA ZFAS1 and miRNAs in PD Neuroimmunology

ZNFX1 antisense RNA 1 (ZFAS1) is transcribed from the antisense direction of the zinc-finger structure NFX1 (ZNFX1), located on chromosome 20q13 [29]. LncZFAS1 has 14 transcripts created through alternative splicing (http://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000177410;r=20:49278178–49299600).NR_003604.3, NR_036658.2, NR_003606.3, NR_003605.2 and NR_036659.2 transcripts are 1008, 946, 860, 689 and 504 nucleotides length, respectively [57]. LncZFAS1 is considered as an oncogene in almost all types of cancers, and therefore it is possible to forecast the clinical outcome of patients with different neoplasms by using expression amounts of ZFAS1 [57]. What's more, lncZFAS1 is involved in inflammatory response processes in a variety of diseases, such as rheumatoid arthritis [58], acute lung injury [59], sepsis [60] and atherosclerosis [61]. ZFAS1 silencing has decreased proliferation, inflammation, autophagy, and enhanced apoptosis via miR-2682–5p/ ADAMTS9 axis in fibroblast-like synoviocytes of rheumatoid arthritis patients [58]. ZFAS1 up-regulation has increased inflammatory responses and hindered cholesterol effluence through sponging miR-654–3p and increasing ADAM10 and RAB22A expressions in the cell line model of atherosclerosis [61]. Inhibition of lncRNA ZFAS1 expression promotes the recovery of neurological function in traumatic brain injury [62]. Silencing of lncRNA ZFAS1, activation of the PI3K/AKT pathway, and increased expression of miR-421 regulate apoptosis and autophagy in epilepsy-related hippocampal neurons [63]. High expression of lncRNA ZFAS1 is associated with low levels of CRP, TNF-α, IL-1, and IL-6 in acute stroke patients [64], possibly because lncRNA ZFAS1 reduces miR-582 expression and upregulates nitric oxide synthase 3 expression to reduce pro-inflammatory cytokine production, thereby reducing inflammation in patients with acute brain stroke [65]. The relationship between LncZFAS1 and the NLRP3 inflammasome requires further investigation. MicroRNAs (miRNAs) target immune transcripts to fine-tune gene expression and turn on negative feedback loops, which help limit co-stimulation, set precise cellular activation thresholds, curtail inflammation, and control lymphocyte growth [66,67]. In a sepsis model,

LncZFAS1 aggravates sepsis-induced progression of cardiac insufficiency by targeting miR-590-3p/NLRP3-mediated autophagy and pyroptosis [68]. Thus, we hypothesized that LncZFAS1 might regulate inflammasome activation and pyroptosis during Parkinson's disease. E3 ubiquitin ligases act as the effectors of ubiquitination, a posttranslational modification characterized by the attachment of ubiquitin to a target protein. Modification cause protein rapid degradation by the proteasome or altering its localization or binding partners. As a member of the RING family of E3 ligases, MIB1 plays an important role in various biological processes by mediating the degradation of the different substrates. At the N terminus of MIB1 are two substrate-binding domains termed MZM (Mib-Herc2/ZZ Zinc Finger/ Mib-Herc2) and REP (consisting of two Mib-repeat domains) that are cumulatively designated the "MIB" domain and which serve as the primary determinants of target specificity. These domains then connect via a series of ankyrin repeats to a C terminus comprised of three RING finger domains [69]. MIB1 expression was increased in pancreatic carcinoma tissues and MIB1 overexpression reinforced the proliferative and invasive capacity through the ubiquitin-proteasome pathway [70]. Seo et al. [71] found that MIB1 was responsible for the proteasomal degradation-dependent regulation of α-actinin 3 in skeletal muscle maintenance. Recently, Qin et al. reported that MIB1 overexpression relieved apoptosis and inflammation of cardiac microvascular endothelial cells during coronary microvascular dysfunction by targeting the ASK1/p38 pathway [72]. In agreement with the hypothesis, lncZFAS1 overexpression directly interfered with mir590-3p to inhibit TXNIP the MIB1 E3 ubiquitin ligase/NLRP3 pathway [6]. Finally, we consider that LncZFAS1 can be used as an important regulatory target for neuroinflammatory pathways in PD.

Conclusion

In conclusion, LncZFAS1 is involved in inflammation and pyroptosis in PD through the TXNIP/MIB1 E3 ubiquitin ligase/ NLRP3 axis. This study revealed the potential beneficial role of lncZFAS1 in the progression of PD, which might serve as a new research approach to explore the pathogenesis of PD.

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Consent for Publication

All authors whose names appear on the submission agree with the version to be published.

Competing Interests

The authors declare no competing interests.

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