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MALAT1 lncRNA and Parkinson's Disease: The role in the Pathophysiology and Significance for Diagnostic and Therapeutic Approaches

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Abstract

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder. PD is characterized by progressive loss of dopamine-producing neurons in the substantia nigra (SN) region of brain tissue followed by the α-synuclein-based Lewy bodies' formation. These conditions are manifested by various motor and non-motor symptoms such as resting tremor, limb rigidity, bradykinesia and posture instability, cognitive impairment, sleep disorders, and emotional and memory dysfunctions. Long non-coding RNAs (lncRNAs) are closely related to protein-coding genes and are involved in various biological processes. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA is involved in different pathways, including alternative splicing, transcriptional regulation, and post-transcriptional regulation, and also interacts with RNAs as a miRNA sponge. MALAT1 is highly expressed in brain tissues and several lines of evidence suggested it is probably involved in synapse generation and other neurophysiological pathways. This narrative review discussed all aspects of MALAT1-associated mechanisms involved in the PD pathogenesis, i.e., perturbed α-synuclein homeostasis, apoptosis and autophagy, and neuro-inflammation. Lastly, the possible applications of MALAT1 as a diagnostic biomarker and its importance to developing therapeutic strategies were highlighted. The literature search was conducted using neurodegeneration, neurodegenerative disorders, Parkinson's disease, lncRNA, and MALAT1 as search items in Google Scholar, Web of Knowledge, PubMed, and Scopus up to December 2021.

Keywords Parkinson's disease · Long non-coding RNA (lncRNA) · Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) · Neurodegenerative disorder · Neuro-inflammation

Abbreviations

AD	Alzheimer's disease
AMP	Adenosine monophosphate
ASO	Specific antisense oligonucleotide
CSF	Cerebro-spinal fluid
CNS	Central nervous system
DAPK1	Death-associated protein kinase1
EZH2	Enhancer of zeste homolog 2
GPNMB	Glycoprotein non-metastatic melanoma protein B
HD	Huntington's disease
HTR2A	5-Hydroxytryptamine receptor 2A
IFN-γ	Interferon-γ
IL	Interleukin
lncRNA	Long ncRNA
LPS	Lipopolysaccharide
LRRK2	Leucine-rich repeat kinase 2
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
mascRNA	MALAT1-associated small cytoplasmic RNA
MPP^+	Methyl-4-phenylpyridinium
MPTP	1-Methyl–4-phenyl-1, 2, 3, 6-tetrahydropyridine
N2a	Neuro 2A
nc-RNAs	Non-coding RNAs
NEAT2	Nuclear-enriched abundant transcript 2
NRF2	Nuclear factor erythroid 2-related factor 2
NLGN1	Neuroligin1
NLR	NOD-like receptor

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NLRP3	NLR family pyrin domain containing 3
NS	Nervous system
NSCLC	Non-small-cell lung cancer
PD	Parkinson's disease
PRC2	Polycomb repressive complex 2
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
SAA3	Serum amyloid A3
SN	Substantia nigra
SNCA	Alpha-synuclein
sncRNA	Small ncRNA
SNP	Single nucleotide polymorphism
SynCAM1	Synaptic cell adhesion molecule1
TH^+	Tyrosine hydroxylase positive
TNF-α	Tumor necrosis factor-α

Introduction

Parkinson's disease (PD) is the second most common chronic neurodegenerative disorder among the elderly, followed by Alzheimer's disease (AD). It affects 2–3% of people aged 65 and over worldwide. Approximately 8–18 out of every 100,000 people are diagnosed with new cases of PD every year. The number of patients is expected to double between 2005 and 2030, putting a heavy burden on society [1–4].

The main characteristic of PD is programmed cell death and progressive degradation of dopaminergic neurons in the substantia nigra (SN) region, followed by the α-synuclein-based Lewy bodies, leading to striatal dopamine deficiency and motor dysfunction [5–7]. Extensive loss of dopamine-producing neurons reduces the dopamine levels in the brain and leads to motor clinical manifestations including resting tremor, limb rigidity, akinesia, bradykinesia, posture instability, and ankyloses arthritis [8–10]. After the dopaminergic loss, various non-dopaminergic neurons degrade and result in non-motor or dopamine-resistant manifestations, i.e., cognitive impairment, autonomic nervous dysfunction, sleep disorders, depression, anxiety, olfactory dysfunction, and emotional and memory disorders [2, 11, 12].

For decades, the exact pathophysiology of PD was unknown. At the same time, different experimental and epidemiologic studies reported that both genetic predisposition and environmental factors play a crucial role in the pathogenesis of this brain disorder. Familial PD has resulted from dominant and/or recessive mutations in several genes, including alpha-synuclein (SNCA), ligase parkin, leucine-rich repeat kinase 2 (LRRK2), eglycase DJ-1 (or PD protein 7), and 5-hydroxytryptamine receptor 2A (HTR2A) [13, 14], while environmental factors (exogenous neurotoxins, age, diet, and lifestyle) also cause sporadic PD [15]. Old age is the leading risk factor for PD. Although Parkinson's disease is rare under 50, its prevalence increases 5 to 10 times in the sixth to ninth decades of life [10, 16]. It has been observed that these factors induce several changes in various cellular and molecular events that initiate neurodegeneration and neuroinflammation [2]. Events include mitochondrial dysfunction, autophagy, apoptosis, oxidative stress, calcium hemostasis, axonal transport, and neuro-inflammation. Altogether suggest that the progression and development of PD is a systemic and comprehensive process, and all these factors work together to eventually cause the death of dopaminergic neurons in substantia nigra [17–19].

Current diagnostic methods for PD are mainly based on clinical manifestations and can only be confirmed by autopsy [20]. Furthermore, the rate of primary degradation of motor function is rapid [21]. In addition, there is no effective treatment for PD, and further research is needed to identify the pathogenesis of the disease and improve early detection methods and targeted treatments in the future.

Recent progress in genome-wide transcriptome analysis revealed that only 2% of human transcripts are protein-coding genes, and a vast majority of transcripts are non-protein-coding [22, 23]. Generally, non-coding RNAs (ncRNAs) are categorized into small ncRNA (sncRNA) that are less than 200 bp in length (e.g., piRNA, siRNA, snoRNA, snRNA, miRNA, and rRNA); and long ncRNA (lncRNA), which are 200 bp to 100 kb in length. To date, more than 50,000 lncRNA has been identified in the human genome [24, 25]. These lncRNAs are located both in the nucleus and cytoplasm. They have a potentially crucial role in regulating protein-coding gene expressions in different levels, including epigenetic regulation, transcription regulation, and post-translation control, while they do not code any protein themselves [26–28].

Also, several lines of evidence showed that lncRNAs are involved in different biological processes, including organogenesis, cell proliferation and differentiation, survival, dosage compensation, genome imprinting, and chromatin remodeling [29–33]. The function of lncRNAs is associated with their interactions with DNA, RNA, and proteins [34]. Also, their complicated secondary and higher-order structures make them suitable and flexible to recognize proteins and other targets [35, 36]. It is noteworthy that their unique secondary structures make them tissue specific even at a level greater than protein-coding RNAs [37]. In the central nervous system (CNS), lncRNAs are highly expressed and regulated by several neuro-biologic processes, including neuron plasticity, neurogenesis, brain development, etc., via histone modifications, mRNA degradation, and alternative splicing [38–41]. Abnormal expression of lncRNAs and genetic variations and epigenetics dysregulation in them are associated with human neurologic disorders such as PD, AD, Huntington's disease (HD), and schizophrenia [42–44].

Alterations in the expression of lncRNAs in the brain of PD patients suggested that lncRNA impairment may occur in the early stages of the disease and highlighted its importance as a biomarker for early diagnosis of PD [10]. Also, the expression of lncRNAs altered during aging is highly associated with PD development [45, 46]. Ni et al. reported that 87 different lncRNAs expressed in the substantia nigra of PD patients [47]. Also, 13 lncRNAs had an altered expression in the peripheral blood leukocytes of PD patients [48]. High expression in the brain tissues and variated expression in different neuronal regions during neuropathological conditions support the idea that MALAT1 plays a crucial role in the pathogenesis of PD. Furthermore, microarray analysis revealed that MALAT1 is among the specific regulatory agents that are associated with the formation of neuronal synapses [49–51].

The current narrative review summarized the role of MALAT1 lncRNA in the pathogenesis of PD and highlighted its importance as a biomarker that could be implicated for diagnostic, prognostic, and therapeutic approaches. For this purpose, neurodegeneration, neurodegenerative disorders, Parkinson's disease, lncRNA, and MALAT1 were considered search items. A comprehensive literature search was conducted using items in form of alone or combined in Google Scholar, Web of Knowledge, PubMed, and Scopus up to December 2021. Also, the references of main articles were searched to find further relevant studies.

MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1)

MALAT1 is a widely investigated lncRNA also identified as nuclear-enriched abundant transcript 2 (NEAT2), HCN, LINC00047, NCRN00047, PRO02853 [52]. The first time, it was identified in a screening for transcripts associated with metastasis and survival in patients with non-small-cell lung cancer (NSCLC) as a prognostic marker [22]. Evidence implied that MALAT1 is upregulated in various cancers and drives tumorigenesis via inducing tumor cell proliferation [51, 53–55]. MALAT1 gene primary sequence contains more than 8000 bp and showed high levels of conservation among 33 mammal species. MALAT1 is mainly located at the nucleus and expressed ubiquitously in approximately all tissues of humans, including skin, brain, bone marrow and immune cells, vascular endothelial cells, adipose, liver, lungs, pancreas, and bladder, and the highest expression is in the pancreas and lungs [54, 56, 57].

MALAT1 Biogenesis

MALAT1 gene is located on human 11q13 and mouse 19q1 chromosomes [58]. RNA polymerase II transcribes it, and the initial transcript is about 7–8 kb in humans and 6.7 kb in mice. Two RNase P and RNase Z act on the primary transcript to produce a 6.7-bp larger piece, and a smaller component contains 61 nucleotides known as MALAT1-associated small cytoplasmic RNA (mascRNA) [49, 52]. Unlike the typical cleavage and polyadenylation process, MALAT1 lacks a poly-A tail in the 3′ end and forms a triple-helix structure that protects the 3′ end against 3′–5′ exonuclease. The regulation of MALAT1 turnover is not thoroughly investigated. A recent study introduced the Drosha-DGCR8 complex (part of the microprocessor involved in the biogenesis of miRNA) to be involved in degradation by interacting with the 5′ end [59–61].

Nervous System (NS)-Associated Physiologic Function of MALAT1

The ubiquitous presence and evolutionary conservation of MALAT1 may indicate its essential functions, while MALAT1 knockdown showed no phenotypic effects in mice. An acceptable explanation for this could be that MALAT1 functionally activates under stress and is not a normal physiologic condition. Another possibility is that other vital lncRNAs compensate for the altered function of MALAT1 [56, 62]. MALAT1 can regulate the transcription of genes acting as a molecular scaffold on inter-chromatin granule clusters. These effects are due to interference in alternative splicing, transcriptional regulation, and post-transcriptional regulation. Also, MALAT1 could interact with RNAs and act as a miRNA sponge via binding to the RNA response elements [56, 63].

MALAT1 is highly expressed in brain tissues and especially in highly active human neo-cortex regions [50]. DNA microarray analysis showed that following the MALAT1 depletion, the expression profile of specific genes significantly associated with synapse and dendrite development of cultured neuron cells was altered. Moreover, in mice hippocampus and Purkinje cells, MALAT1 was first detected between post-natal day 0 (P0) and P7 and finally reached the peak at P28. These results suggest that MALAT1 is probably involved in synapse generation from the early post-natal weeks. Further in vitro studies showed that genetic depletion of MALAT1 reduces synaptic density. In contrast, MALAT1 over-expression leads to a cell-autonomous elevation in the synaptic density in mice primary hippocampus neuron cell culture. It should be noted that this process is accomplished by regulating neuroligin1 (NLGN1) and synaptic cell adhesion molecule1 (SynCAM1) that are involved in synapse formation [49].

MALAT1 also expressed in the cerebrospinal fluid (CSF) and neuro-pathological changes affect its levels. CSF analysis in AD patients compared to the healthy controls showed that MALAT1 levels were decreased due

to neurodegenerative consequences [64]. Recent studies showed that MALAT1 levels are different in various regions of the brain and pathologic conditions occurred, while the expression of MALAT1 altered to an abnormal level due to exogenous or endogenous inducers. For instance, it was reported that increased expression of MALAT1 in the brain of human alcoholic is limited to the hippocampus, brain stem, and cerebellum regions and MALAT1 expression is normal in frontal and motor cortices. Also, in alcohol-subjected rats, MALAT1 overexpression was observed in the cortex [65]. MALAT1 is expressed in different types of neurons in the brain. Since it plays an essential role in the normal development of the brain and its physiological activities, it is not surprising that dysregulated MALAT1 is associated with CNS disorders [22].

MALAT1 and Parkinson's Disease

Abnormal expression of MALAT1 was demonstrated in PD. It was reported that MALAT1 was up-regulated in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced mice model of PD and methyl-4-phenylpyridinium (MPP +)-induced cells [66–68]. Theo et al. conducted a comprehensive analysis on 90 well-annotated lncRNA in the brain of PD patients compared to healthy controls. They proved that several lncRNAs, including TncRNA, SNGH1, MALAT1, and lincRNA-p21, were significantly up-regulated in patients. In this case, the MALAT1 expression was elevated threefold of the normal levels, and most alterations occurred in the primary stages even before the disease course [66]. MALAT1 dysregulation in PD resulted in pathologic conditions and affected multiple pathways, including perturbed α-synuclein hemostasis, apoptosis and autophagy, and neuro-inflammation. Here, we categorized studies conducted in association with MALAT-1 and PD (Table 1).

Perturbed α-Synuclein Hemostasis

The α-synuclein (SNCA) is a presynaptic neuronal protein associated with neurodegenerative disorders. Aberrant oligomeric conformational structures of α-synuclein lead to Lewy bodies' formation and involve the cellular hemostasis disturbance and neuronal death [69, 70]. Abnormal aggregation of this protein is associated with PD, Lewy body dementia, and multisystem atrophy [71] and leads to abnormal deposition of other proteins in brain tissue [72]. Intra-neuronal aggregation of α-synuclein as a result of risk SNCA variants was reported in PD patients [73, 74] (Fig. 1).

Zhang et al. showed that MALAT1 was upregulated in the midbrain tissue of the MPTP neurotoxin-induced PD mice model and resulted in reeling gait, slow motion, and less activity as well as perturbed α-synuclein hemostasis. In this case, they investigated the neuroprotective effects of cis-2, 4, 5-trimethoxy-1-allyl phenyl (β-asarone), the main component of *Acorus tatarinowii Schott*; both in a murine model of PD and MPP + -exposed SH-SY5Y cells. The PD mice model was induced by intraperitoneal injection of MPP + (20 mg/kg) in a total of four doses over an 8-h period. They showed that intra-gastric administration of β-asarone (10 mg/kg) for 28 days dramatically improves cell line viability and significantly increases the number of tyrosine hydroxylase positive (TH +) neurons in animals, which results in MALAT1 inhibition followed by α-synuclein regulation [67].

In another study, Xia et al. reported that MALAT1 binds to miR-129 (a negative regulator of SNCA) and inhibits its expression. In this case, MALAT1 induces SNCA overexpression and α-synuclein aggregation that develops neuronal apoptosis in the murine model of PD. The PD mice model was established using MPTP (20 mg/kg) in four doses at 8-h periods and a 3-week period observation. Also, they demonstrated that resveratrol (50 mg/kg/day, intra-gastric, for 3 weeks) increases the number of TH + cells and the expression of miR-129 due to MALAT1 inhibition. It seems that the inhibitory effect of resveratrol occurs through a blockage in the transcription of the MALAT1 promoter. Thus, modulation of MALAT1/miR-129/SNCA and inhibition of α-synuclein dysregulation could be considered the therapeutic effects of resveratrol in PD [68].

Apoptosis and Autophagy

Autophagy and apoptosis are essential contributors to developing neurodegenerative disorders, e.g., PD [75, 76]. Increasing evidence implied that autophagy plays a crucial role in disease pathogenesis; likewise, apoptosis is considered an important signal for the degradation of dopaminergic neurons [77, 78] (Fig. 1).

In PD, miR-124 regulates cell apoptosis and autophagy processes in dopamine-producing neurons. It protects them via modulation of adenosine monophosphate (AMP)-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR) pathway [79]. MALAT1 can directly bind and inhibits miR-124 expression (51). Liu et al. reported that MALAT1 interacts with and negatively regulates miR-124 expression in a murine model of PD and SH-SY5Y cells. The murine model was induced using 30 mg/kg/day MPTP for 4 days. miR-124 downregulation leads to phosphatase and tensin homolog (PTEN)-induced kinase1 protein stability, and dopaminergic neuron apoptosis was accelerated [80]. In another study, Lu et al. reported that MALAT1/mir-124-3p/death-associated protein kinase1 (DAPK1) signaling cascade mediates cellular apoptosis and could be considered a therapeutic approach for PD.

Table 1 Summary of studies conducted on the association between MALAT1 and PD pathogenesis

Author	Experimental model	Findings	Ref.
Zhang et al *(2016)*	MPTP-induced mice model	Following the PD induction, MALAT1 upregulated and α-synuclein stabilized The β-asarone administration increased the number of TH + cells and regulated the α-synuclein due to inhibition of MALAT1	[67]
Xia et al *(2019)*	MPTP-induced mice model	Following the PD induction, MALAT1 upregulated, miR-129 inhibited, SNCA elevated, and neuronal apoptosis increased Resveratrol administration modulated the MALAT1/miR-129/SNCA signaling pathway	[68]
Liu et al *(2017)*	MPTP-induced mice model and MPP^+-treated SH-SY5Y cell line	MALAT1 suppressed the miR-124 and stabilized PTEN-induced kinase1 protein that lead to dopaminergic neurons apoptosis	[80]
Lu et al *(2020)*	MPTP-induced mice model and MPP^+-treated SH-SY5Y cell line	MALAT1 sponged miR-124-3p and leads to DAPK1 overexpression and accelerated cell apoptosis	[81]
Chen et al *(2018)*	MPTP-induced mice model and MPP^+-treated MN9D cell line	MALAT1 sponged miR-205-5p and leads to LRRK2 overexpression and accelerated cell apoptosis	[82]
Lv et al *(2021)*	MPP^+-treated SK-N-Sh and SK-N-BE cell lines	MALAT1 targeted miR-135b-5p/GPNMB axis and leads to cell apoptosis	[86]
Cai et al *(2020)*	MPTP-induced mice model and LPS/ATP-induced N2a human and BV2 murine microglial cells	MALAT1 involved NRF2, NLRP3, EZH2, and PRC2 and induced ROS overexpression and subsequent activation of NLRP3 inflammasome	[95]
Yang et al *(2021)*	Serum of sporadic PD patients and LPS-treated PC12 cell line	Significant association between serum levels of MALAT1 and MMSE scores was observed in PD patients Also serum levels of IFN-γ, TNF-α, IL-6, and IL-1β inflammatory cytokines were associated with MALAT1 serum levels in PD patients A significant association between mutant alleles in rs3200401 (C > T) and rs4102217 (G > C) SNPs and susceptibility to PD was observed Higher secretion of inflammatory cytokines in pcDNA3.1-MALAT1/si-MALAT1-transfected PC 12 cells was observed	[96]

ATP adenosine triphosphate, *DAPK1* death-associated protein kinase1, *EZH2* enhancer of zeste homolog 2, *GPNMB* glycoprotein non-metastatic melanoma protein B, *IFN-γ* interferon-γ, *IL-1β* interleukin-1β, *IL-6* interleukin-6, *LPS* lipopolysaccharide, *LRRK2* leucine-rich repeat kinase 2, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *MMSE*, mini-mental state examination, MPP^+ 1-methyl-4-phenylpyridinium, *MPTP*, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, *N2a* neuro 2A, *NLRP3* NOD-like receptor (NLR) family pyrin domain containing 3, *NRF2* nuclear factor erythroid 2-related factor, *PD* Parkinson's disease, *PRC2* polycomb repressive complex 2, *PTEN* to phosphatase and tensin homolog, *ROS* reactive oxygen species, *SNCA* alpha-synuclein, *SNP* single nucleotide, *TH* + tyrosine hydroxylase positive, *TNF-α* tumor necrosis factor-α

DAPK1 is a critical factor in neuronal cell dysfunction and was initially discovered in progression of interferon-γ (IFN-γ)-induced programmed cell death. They showed that DAPK1 expression is associated with MALAT1 levels and significantly upregulated in MPTP-induced mice (30 mg/kg/day for 5 consecutive days) and MPP^+-induced SH-SY5Y cell models of PD, while was negatively correlated with miR-124-3p levels. In other words, miR-124-3p mimic could efficiently inhibit the expression of DAPK1 and alleviates cell apoptosis, while MALAT1 knockdown improved behavioral changes and reduced apoptosis in mice via miR-124-3p upregulation and DAPK1 downregulation. Also, it should be noted that following MPTP administration, behavioral tests were significantly impaired, with slower average speed and shorter total distance. Surprisingly, MALAT1 knockdown attenuated behavioral deficits [81].

Chen et al. introduced the MALAT1/miR-205-5p/LRRK2 axis as another pathway that MALAT1 is involved in PD pathogenesis. The PD mice model was induced by intraperitoneal administration of 20 mg/kg/dose MPTP in four doses at 2-h intervals. They showed that MALAT1 sponges miR-205-5p in PD murine models' midbrain, leading to elevated LRRK2 levels. Also, they reported that LRRK2 overexpression reduces viability and promotes apoptosis in MPP^+-induced MN9D cells (dopaminergic neuron cell line) [82].

Glycoprotein non-metastatic melanoma protein B (GPNMB) is a glycoprotein associated with tissue injury and inflammation and directly targeted by miR-135b-5p.

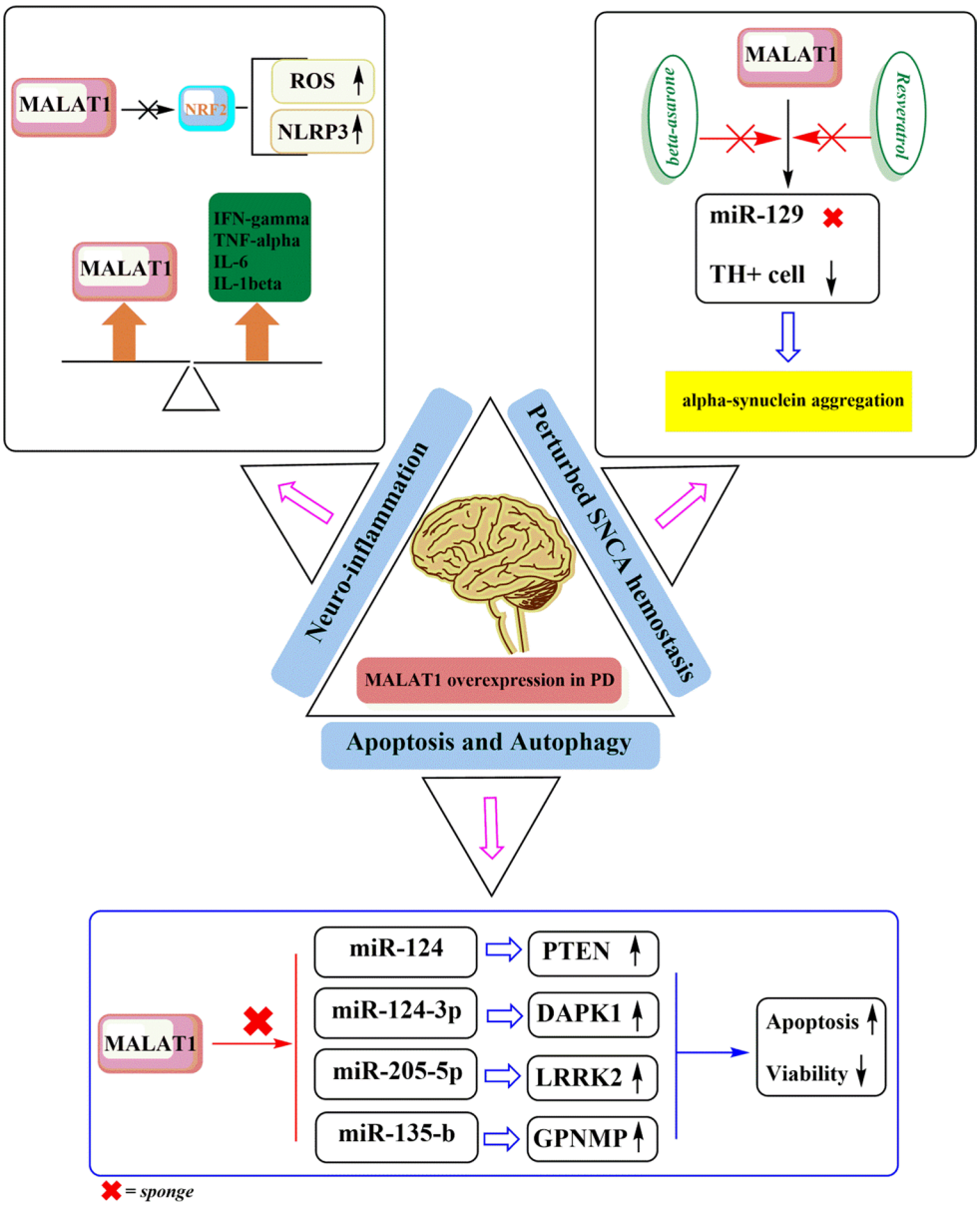

Fig. 1 Schematic of various pathways that are affected by MALAT1 dysregulation in PD. In case of perturbed SNCA hemostasis, MALAT1 dysregulation is associated with SNCA aggregation and Lewy bodies' formations. Resveratrol and beta-asarone are two candidates that inhibit SNCA aggregation in a MALAT1/miR-129/SNCA-dependent manner. While they inhibit MALAT1 expression, dramatic improvement in the TH + neurons viability and miR-129 overexpression leads to inhibition of SNCA aggregation. In case of apoptosis and autophagy, MALAT1 overexpression inhibits the expression of different miRNAs including miR-124, miR-124-3p, miR-205-5p, and miR-135b that leads to elevation in PTEN, DAPK1, LRRK2, and GPNMP elements and reduces cell viability and increases apoptosis. In case of neuro-inflammation, a correlation between MALAT1 levels and IFN-γ, TNF-α- IL-1β, and IL-6 inflammatory cytokines was observed. Also, it was shown that MALAT1 suppressed NRF2 and leads to NLRP3 and ROS production. Abbreviations. DAPK1, death-associated protein kinase; GPNMB, glycoprotein non-metastatic melanoma protein B; IFN-γ, interferon-γ; IL-6, interleukin-6; IL-1β, interleukin-1β; LRRK2, leucine-rich repeat kinase 2; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; NLRP3, NOD-like receptor (NLR) family pyrin domain containing 3; NRF2, nuclear factor erythroid 2-related factor; PD, Parkinson's disease; PTEN, to phosphatase and tensin homolog; ROS, reactive oxygen species; SNCA, alpha-synuclein; TH+, tyrosine hydroxylase positive; TNF-α, tumor necrosis factor-α

GPNMB increased selectively in PD patients, while miR-135b has a protective effect against PD pathogenesis via inducing pyroptosis [83–85]. Lv et al. investigated the regulatory effects of MALAT1 on the proliferation and apoptosis in MPP^+-treated SK-N-SH and SK-N-BE cells as PD in vitro model. They showed that MALAT1 targeted

miR-135b-5p/GPNMB axis. As MALAT1 is increasingly expressed in the treated cells, its downregulation accelerates proliferation and inhibits cell apoptosis [86].

Neuro-inflammation

Neuroinflammation and neurodegeneration are closely associated with neurologic disorders. Inflammation is considered an essential contributor to PD pathogenesis [87–89]. The expression of inflammasome was demonstrated in the brain tissue of PD patients and seems to accelerate PD development [90, 91]. Besides, studies proved that various lncRNAs, i.e., LincRA-Cox-2, lncRNA THRIL, and lncRNA NEAT1, are widely involved in the differentiation of immune cells and regulation of immune responses [10, 92]. MALAT1 interacts with serum amyloid A3 (SAA3) and accelerates the secretion of inflammatory mediators, i.e., tumor necrosis factor α (TNF-α) and interleukin (IL)-6 from high glucose-exposed endothelial cells [93]. Also, it was shown that MALAT1 knockdown inhibits severe inflammation in lipopolysaccharide (LPS)-induced mice model of septic via upregulation in the expression of miR-146a and reduced NFκB (p65) phosphorylation [94] (Fig. 1).

In the case of PD, Cai et al. investigated the role of MALAT1 in neuro-inflammatory processes involved in the MPTP-induced mice model of PD and cell models, including LPS/ATP-induced neuro 2A (N2a) human cell line and BV2 murine microglial cells. The PD mice model was induced using 20 mg/kg MPTP, 3 times each day. They reported that MALAT1 is highly expressed both in vivo and in vitro models of PD. Also, several factors, i.e., nuclear factor erythroid 2-related factor 2 (NRF2), NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3), enhancer of zeste homolog 2 (EZH2), and a catalytic subunit of polycomb repressive complex 2 (PRC2), are involved in MALAT1-associated neuroinflammation. They proved that MALAT1 interacted with EZH2 in NRF2 gene promoter loci and repressed the NRF2 transcription, which results in reactive oxygen species (ROS) overexpression and subsequent activation of NLRP3 inflammasome [95].

In another study, Yang investigated the serum expression of MALAT1 and analyzed the MALAT1 single-nucleotide polymorphisms (SNPs), i.e., rs3200401, rs11227209, rs4102217, rs591291, rs619586, and rs664589, in serum of sporadic PD patients compared to healthy controls. They showed that higher serum levels of MALAT1 are significantly associated with lower mini-mental state examination (MMSE) scores and higher IFN-γ, TNF-α, IL-6, and IL-1β serum levels. Also, mutant alleles in rs3200401 (C > T) and rs4102217 (G > C) SNPs are dramatically associated with susceptibility to PD and facilitated the production of inflammatory cytokines, compared to wild-type alleles. In the other part of the study, the inflammation cell model was developed using PC12 cells treated with LPS, and the cytokine production was measured in pcDNA3.1-MALAT1/si-MALAT1-transfected PC 12 cells. In this case, they reported higher secretion of inflammatory cytokines in the pcDNA3.1-MALAT1 groups compared to the Mock group [96].

Concluding Remarks

Following an increase in the elderly population, the number of PD patients increases year by year and widely influences the quality of life, and puts a heavy burden on society. In clinical cases, the diagnosis of PD is based on tissue pathology, and existing strategies have only limited effectiveness in the early stages of the disease. Therefore, finding early diagnostic and effective treatment strategies is urgently needed.

Increasing results demonstrated that MALAT1 lncRNA is closely associated with PD pathogenesis, and while the symptoms were manifested, the expression of MALAT1 alters in PD patients. The cerebrospinal fluid (CSF) is closely associated with the leading site of PD pathology, and CSF contents could significantly reflect the molecular alterations on the brain tissue. In this case, CSF is an optimal source for diagnostic biomarkers. Also, various studies reported that the expression of lncRNAs in the leukocyte samples of PD patients is significantly associated with disease progression. Since the expression level of MALAT1 can be considered a diagnostic and prognostic biomarker.

On the other hand, therapeutically targeting MALAT1 in different ways seems to be a potential approach to regulate its expression. Multiple studies reported that MALAT1-specific antisense oligonucleotide (ASO) efficiently represses MALAT1 expression and inhibits tumor progression and metastasis [97, 98]. Likewise, application of MALAT1-inhibiting siRNA could be implicated in the case of PD to reduce neuroinflammation, apoptosis and autophagy, and α-synuclein aggregation as consecutive results of MALAT1 overexpression in PD. It is noteworthy that MALAT1 is highly expressed in almost all human tissues and is involved in crucial physiologic mechanisms, including synapse formation, skeletal myogenesis, and vascular growth. Also, the pathogenesis of PD is complicated, and further investigations are needed to clearly explain the exact cellular and molecular mechanisms that MALAT1 and other factors involved in PD. So, MALAT1 targeting in pathologic conditions is more complex than a simple silencing to be an efficient treatment procedure.

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and contributed to the preparation of the figure and manuscript. MR revised the article.

Declarations

Ethics Approval This is a review article. There is not ethical approval applicable.

Consent to Participate Not applicated.

Consent for Publication This is a review article. There is no consent to publish applicable.

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