Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

Review

AMPK Signaling Pathway as a Potential Therapeutic Target for Parkinson's Disease

Seyed Zanyar Athari[1,2], Fereshteh Farajdokht[2]*, Rana Keyhanmanesh[1], Gisou Mohaddes[2,3]*

[1] *Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2] *Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[3] *Department of Biomedical Education, California Health Sciences University, College of Osteopathic Medicine, Clovis, CA,*

*Corresponding author:
Dr. Gisou Mohaddes
Email: gmohaddes@chsu.edu, gmohades@yahoo.com
Dr. Fereshteh Farajdokht
Email: farajdokhtf@tbzmed.ac.ir, farajdokht@gmail.com

ORCID:
Gisou Mohaddes: 0000-0002-3732-1663
Fereshteh Farajdokht: 0000-0001-5349-6028
Rana Keyhanmanesh: 0000-0002-6941-2690
Seyed Zanyar Athari: 0000-0001-8274-8570

Abstract
Parkinson's disease (PD) is the second most common neurodegenerative disease caused by the loss of dopaminergic neurons. Genetic factors, inflammatory responses, oxidative stress, metabolic disorders, cytotoxic factors, and mitochondrial dysfunction are all involved in neuronal death in neurodegenerative diseases. The risk of PD can be higher in aging individuals due to decreased mitochondrial function, energy metabolism, and AMP-activated protein kinase (AMPK) function. The potential of AMPK to regulate neurodegenerative disorders lies in its ability to enhance antioxidant capacity, reduce oxidative stress, improve mitochondrial function, decrease mitophagy and macroautophagy, and inhibit inflammation. In addition, it has been shown that modulating the catalytic activity of AMPK can protect the nervous system. This article reviews the mechanisms by which AMPK activation can modulate PD.

Keywords: Parkinson's disease, AMPK, α-synuclein, Oxidative stress, Inflammation

Abbreviations
PD: Parkinson's Disease
RBD: Rapid Eye Movement Sleep Behavior Disorder
SNpc: Substantia Nigra Pars Compacta

VTA: Ventral Tegmental Area
α-syn: α-synuclein
GABA: γ-aminobutyric acid
AMPK: AMP-Activated Protein Kinase
IL: Interleukin
TNF: Tumor Necrosis Factor
OxPh: Oxidative-Phosphorylation
ROS: Reactive Oxygen Species
MFN: Mitofusin
OPA: Optic Atrophy
Drp-1: Dynamin-Related Protein
PGC-1: Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1
FA: Fatty Acid
FOXO: Forkhead Box Class O Family Member Proteins
mTORC: Mammalian Target Of Rapamycin Complex 1
TSC-2: Tuberous Sclerosis Complex 2
Raptor: Regulatory-Associated Protein of mTOR
MFF: Mitochondrial Fission Factor
OMM: Outer Mitochondrial Membrane
TFAM: Mitochondrial Transcription Factor A
TFEB: Transcription Factor EB
ULK-1: Unc-51-like Autophagy Activating Kinase
UPS: Ubiquitin-Proteasome System
CMA: Chaperone-Mediated Autophagy
APPL1: Adaptor Protein, Phosphotyrosine Interacting With PH Domain And Leucine Zipper 1
NOX: NADPH Oxidase
NO: Nitric Oxide
iNOS: Nitric Oxide Synthase
PARK7: Parkinson Disease-7 Gene
NF-kB: Nuclear Factor Kappa B
NURR1: Nuclear Receptor-Related Protein 1

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease caused by the loss of dopaminergic neurons.[1–3] In 2016, it was estimated that PD affected 6.1 million people worldwide, up from 2.5 million in 1990, and this figure is predicted to more than double by 2040.[4] Moreover, PD is present in approximately 3% of individuals aged 65 and above, with the largest number of cases reported in those over 70 years old.[5]

Clinically, symptoms of PD can be categorized as non-motor signs and motor symptoms. The non-motor symptoms are more common and emerge years before motor symptoms.[6] Non-motor symptoms comprise loss of sense of smell, sensory disturbances (such as pain), sleep disorders, autonomic disorders (orthostatic hypotension), gastrointestinal disorders (constipation), urogenital disorders, sexual dysfunction, as well as cognitive deficits and dementia.[7] Motor symptoms include bradykinesia, tremors at rest, rigid muscles, impaired posture, and imbalance. In addition to the main symptoms, patients may show other motor symptoms like micrography, freezing, masked face, decreased blink rate, dysphagia, and softened voice.[8]

Pathologically, the key characteristics of PD are the damage to dopaminergic neurons in substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA), depletion of dopamine in the striatum, and the presence of Lewy bodies in the cytoplasm formed mainly by the α-synuclein (α-syn) protein. PD affects various neurotransmitters aside from the dopamine system, such as noradrenaline, serotonin, glutamate, γ-aminobutyric acid (GABA), acetylcholine, and neuropeptides. The development of PD may also be caused by the degeneration of cholinergic neurons in the mynert nucleus, norepinephrinergic neurons in the locus cereus, and serotoninergic neurons in the raphe nuclei.[9] Non-motor symptoms caused by non-dopaminergic neurotransmitter system dysfunction are unresponsive to dopaminergic therapy.[10]

Along with genetic factors, inflammation, oxidative stress, mitochondrial dysfunction, and cytotoxic factors [11,12], metabolism-related dysfunction is also involved in the pathophysiology of PD.[13] Evidence shows that impaired regulation of glucose metabolism, which occurs in early PD, reduces antioxidant capacity and neuronal survival.[14] Furthermore, during the initial stages of PD, oxidative stress, a crucial characteristic of metabolic

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

syndrome, leads to mitochondrial structural abnormalities and mutations in mitochondrial DNA, which worsen oxidative stress and ultimately cause neuronal death.[15]

Energy dysregulation is implicated as a possible trigger for PD, indicating that a deeper understanding of the molecular pathways controlling energy balance could lead to identifying therapeutic targets. The AMP-activated protein kinase (AMPK) signaling pathway regulates metabolism, cell growth, and autophagy,[16] and serves as a metabolic energy sensor and controls both lipid and carbohydrate metabolism inside the cell.[17,18] Moreover, inhibiting AMPK expression or activity results in an increase in pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α,[19] whereas stimulating AMPK pathway has been shown to boost neuroprotection.[20] AMPK is also involved in regulating macroautophagy,[21] mitochondrial biogenesis,[22] and gene expression.[23]

Energy balance in cells is maintained by AMPK, which inhibits energy consumption and activates energy production processes in response to specific conditions to restore ATP levels.[24] The mitochondrial oxidative-phosphorylation (OxPh) pathway is commonly used to produce ATP from glucose. Hence, increasing AMPK activity is a viable strategy to avoid bioenergetics failure and boost energy levels in vulnerable neurons.[25] AMPK stimulates glucose transport through glucose membrane vectors and the breakdown of stored glycogen in the cytoplasm.[25,26] AMPK also provides substrates for other OxPh sources like fatty acids (FA) and glutamine.[27] During calorie restriction, AMPK acutely increases the uptake and transfer of FAs to the mitochondria for catabolism, oxidation, and energy production. Long-term activation of AMPK can influence energy metabolism by activating regulatory factors like forkhead box transcription factors (FOXO) and peroxisomal proliferator-activated receptor-gamma coactivator (PGC)-1 α for energy production and consumption.[28–30]

Furthermore, AMPK regulates cellular ATP production and energy levels by restricting anabolic processes.[24] AMPK inhibits processes that require ATP, like new protein production and cell growth, to maintain the ATP level in energy-constrained conditions.[31] The mammalian target of rapamycin complex (mTORC)-1 is an essential cellular protein that promotes protein synthesis and growth and induces nutrient signals.[24] Evidence shows that AMPK inhibits mTORC-1 through activating tuberous sclerosis complex (TSC)-2 and inhibiting regulatory-associated protein of mTOR (RAPTOR).[32,33] Also, AMPK has the ability to decrease protein production by inhibiting the synthesis of ribosomal RNA.[34]

AMPK activation provides a significant neuroprotective effect and enhances cell survival against several cytotoxic agents. The mechanisms that AMPK activation may use to regulate PD-related pathology were summarized in this review (Table 1).

2. AMPK Effect on Mitochondrial Function

Cell metabolism relies on organelles called mitochondria, which provide energy through the OxPh process. The OxPh generates additional substances, particularly reactive oxygen species (ROS), that can negatively affect mitochondrial function when produced excessively. The decrease in cellular energy production following mitochondrial dysfunction creates a vicious cycle of chronic ROS production and worsens mitochondrial dysfunction.[35] Therefore, cells' essential functions are to control mitochondrial health, biogenesis, fission-fusion dynamics, and mitochondrial autophagy (mitophagy).[36] The process of mitochondrial quality control declines with age, particularly in those with PD.[37,38] Additionally, accumulated α-syn may be the reason for mitochondrial damage in PD.[39,40]

Mitochondria can change their structure, size, and shape through repetitive cycles of fission and fusion.[41] Mitochondrial dynamics can be influenced by calcium homeostasis, apoptosis, and respiration. Genetic mutations or exposure to toxins can lead to changes in mitochondrial dynamics, causing neurodegenerative disorders. The fusion of mitochondria is accomplished by two groups of GTPases: mitofusins (MFN1 and MFN2) located in the outer mitochondrial membrane and optic atrophy (OPA)-1 located in the inner mitochondrial membrane.[42] Fission is another alteration in mitochondrial dynamics where dynamin-related protein (DRP)-1 is the key factor.[43]

Dopaminergic neurons in the SNpc have limited mitochondrial content and rely heavily on energy balance for survival.[44] Sporadic and familial forms of PD affect diverse aspects of mitochondria, including their bioenergy capacity, quality control, life cycle, morphology (fission and fusion), transportation, and control of cellular apoptosis pathways.[45] Furthermore, *PINK1* and *PARKIN* genes play a key role in mitochondrial function and quality control as they detect damage in mitochondria and facilitate mitophagy to eliminate and replace dysfunctional mitochondrial components.[46,47] Ubiquitination of MFN1 and MFN2 proteins, which are involved in mitochondria fusion, depends on the Parkin/PINK1 pathway, wherein PINK1 phosphorylates MFN2, resulting in Parkin recruitment and protein ubiquitination.[48] This process is essential to identify mitochondria for degradation through mitophagy and prevent them from reintegrating into the mitochondrial network. However, this process is disturbed by PD, leading to the accumulation of abnormal mitochondria and respiratory dysfunction. Moreover,

loss of DRP-1 in dopaminergic neurons leads to the degeneration of SN neurons in mice and a Parkinson's-like phenotype due to depletion of axonal mitochondria.[49]

One of the primary regulators of mitochondrial biogenesis is a transcriptional activator called PGC-1.[50] According to prior studies, PD causes a decline in the expression of PGC-1 and its downstream genes responsible for controlling cellular bioenergy and mitochondrial biogenesis.[51,52] Interestingly, overexpression of PGC-1 can prevent dopaminergic neuron death caused by α-syn overexpression or rotenone-induced damage, potentially improving PD-like pathologies.[52]

As AMPK is vital for intracellular energy metabolism in response to energy depletion, it is expected that AMPK has a significant impact on mitochondrial homeostasis. An in vitro study has shown that α-syn overexpression reduces AMPK activity, leading to a decrease in cellular resistance to α-syn.[53] A deficiency in AMPK activity can lead to reduced mitochondria and abnormal mitochondrial biogenesis due to disruption of the AMPK/PGC-1 axis, putting dopaminergic neurons at risk of degeneration and causing symptoms similar to PD.[54,55] However, pharmacological AMPK activation provides neuroprotection.[55]

Through activating PGC-1α, AMPK promotes mitochondrial biogenesis, activating mitochondrial transcription factor A (TFAM), leading to increased transcription and replication of mitochondrial DNAs.[56,57] Furthermore, AMPK enhances mitochondrial fusion, leading to the development of extensive and highly branched mitochondrial networks in a PGC-1-dependent way.[58,59] Besides, AMPK activates mitochondrial fission factor (MFF) to promote mitochondrial fission but inhibits mTORC1 to suppress it.[60,61] Therefore, it seems that the role of AMPK in intervening mitochondrial homeostasis is context-dependent based on cellular energy status. In mild energy depletion, it may stimulate fusion to boost energy production, but under prolonged and intense cellular stress, it may trigger fission to promote mitophagy and initiate mitochondrial biogenesis to substitute the impaired ones.

AMPK also facilitates mitochondrial function by controlling the direct phosphorylation of target proteins and transcriptional regulation of the relevant genes.[62] Mitophagy is a physiological process that eliminates damaged mitochondria while promoting mitochondrial biogenesis pathways to replenish mitochondrial levels.[63,64] Through the phosphorylation of Unc-51-like autophagy activating kinase (ULK)-1, AMPK promotes mitophagy by facilitating autophagosome formation and directing damaged mitochondria to lysosomes.[65] AMPK activation also couples mitochondria fission with mitophagy by phosphorylating MFF and activating DRP-1 to maintain energy bioavailability and high-quality mitochondria.[66,67]

The mitochondrial electron transport chain is the major source of ROS, and cells rely on antioxidant mechanisms to prevent damage from ROS and maintain redox homeostasis. Proper cellular function and metabolic stress adaptation necessitate the regulation of ROS generated by mitochondria.[68,69] Damage to essential cellular components caused by excessive free radical production and impaired redox balance in neurons contributes to the degeneration of dopaminergic neurons in the SN. The low glutathione levels, high levels of oligomeric α-syn, high iron and calcium contents, mitochondrial dysfunction, and dopamine degradation and oxidation are responsible for ROS production in PD.[70,71] Genetic mutations in *SNCA*, *PARKIN*, *PINK1*, *LRRK2*, *FBXO7*, *ATP13A2*, *GIGYF2* and *HTRA2* are also responsible for impairing mitochondrial function and morphology, leading to ROS formation.[72] The connection between oxidative stress and PD pathogenesis is backed up by neurotoxin-induced animal models (6-hydroxydopamine (6-OHDA), rotenone, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)), which result in ROS generation and gradual loss of nigrostriatal dopaminergic system.[73–76]

Aberrant production of ROS and imbalanced redox status activate AMPK to maintain redox homeostasis. AMPK promotes the expression of antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) to mitigate ROS generation by activating Sirt1/PGC-1α/FOXO-1 pathway (Fig.1). However, pharmacological or genetic inactivation of AMPK leads to elevated mitochondrial ROS levels, promoting cytotoxicity.[69] Nuclear factor E2-related factor 2 (Nrf2) maintains redox balance and protects cells from oxidative damage. Nrf2 is usually kept in the cytoplasm during stress-free conditions, but it translocates to the nucleus on exposure to oxidative stress. Once bound to the antioxidant response element, it activates the expression of several antioxidative enzymes, including heme oxygenase-1 (HO-1), SOD, and GPx, which help to detoxify free radicals. Through phosphorylation, AMPK also enhances Nrf2 nuclear translocation, thus reducing ROS levels and inhibiting oxidative stress.[77,78] Therefore, activating the AMPK pathway may serve as a therapeutic approach for inhibiting oxidative stress in PD.
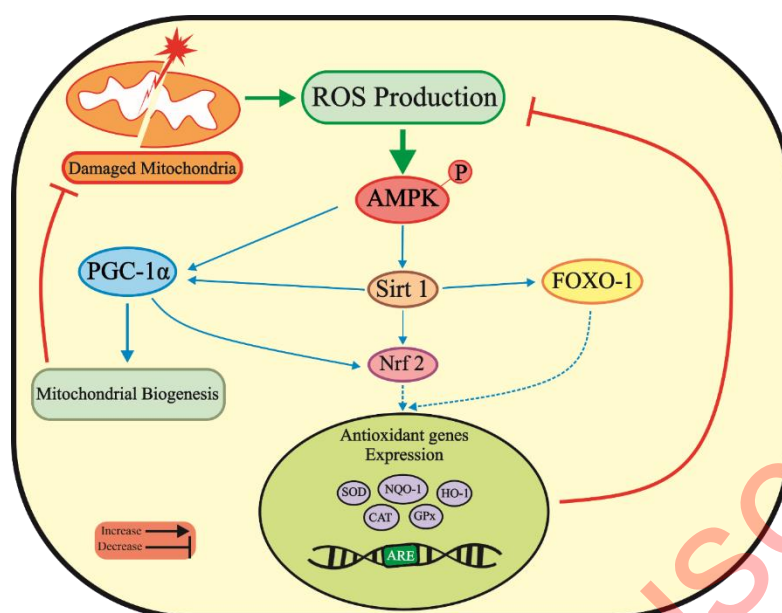
Figure 1. Activated AMPK suppresses oxidative stress pathways related to PD by activating PGC-1α and Sirt 1 pathways, resulting in increased antioxidant gene expression and inhibition of mitochondrial damages. ROS, Reactive oxygen species; AMPK, AMP-activated protein kinase; FOXO-1, Forkhead box class O family member proteins-1; Sirt 1, Sirtuin 1; PGC-1α, Peroxisome Proliferator-activated receptor-gamma coactivator-1; Nrf2, Nuclear factor E2-related factor 2; SOD, Superoxide dismutase; NQO-1, NAD(P)H quinone dehydrogenase 1; HO-1, Heme oxygenase-1;CAT, Catalase; GPx, Glutathione peroxidase.

3. Effect of AMPK on macroautophagy

Autophagy is a process that transfers waste products, cellular components, and large molecules to the lysosome for decomposition and ingestion.[24] Autophagy disturbance is one of the etiologies of PD, leading to α-syn accumulation in the brain.[79] Moreover, deleting essential genes involved in autophagy, such as autophagy-related gene-7 (*ATG-7*), can induce neurodegeneration similar to PD in mice.[80] A recent study has shown that tricin, a natural flavonoid, can improve autophagy and ATG-7-dependent clearance of α-syn via an AMPK/mTOR pathway.[81]

There are three main ways to remove α-syn from neurons: the ubiquitin-proteasome system (UPS), chaperone-mediated autophagy (CMA), and macroautophagy.[82] Removing α-syn oligomers requires macroautophagy-mediated degradation because UPS and CMA are ineffective. To accomplish this, autophagosomes are formed to separate cytoplasmic components and carry them to lysosomes.[83,84] In both PD patients and animal models, macroautophagy is stimulated by transcription factor EB (TFEB), which mediates lysosomal biogenesis and macroautophagy development due to increased α-syn levels.[85,86] In the PD mice model, overexpression of α-syn causes macroautophagy dysfunction and increases dopaminergic neuron degeneration in SNpc and movement disorders. These defects can be improved by overexpression of TFEB or Beclin-1 (another autophagy regulator), suggesting that macroautophagy regulation can be helpful in the PD to reduce α-syn accumulation and neuronal damage.[86,87]

Autophagy initiation is mainly driven by ULK-1, while the inhibition of ATG-13 phosphorylation by mTORC-1 leads to a decrease in the ULK-1 complex activity, ultimately suppressing autophagy.[88,89] ULK-1 factor initiates the formation and maturation of autophagosomes through the Beclin-1 phosphorylation.[90] Evidence suggests that AMPK boosts autophagic degradation by activating ULK-1 through phosphorylation and inhibiting mTORC1 and blocking its inhibitory effect on ULK-1.[91] Moreover, AMPK promotes lysosomal biogenesis by increasing the activity of TFEB[92] and improving the transcription of proteins required for macroautophagy by FOXO-3.[93] Preclinical studies indicate that autophagy-promoting agents can improve α-syn clearance and provide neuroprotection.[94] Metformin has been shown to stimulate autophagy and protect nigrostriatal neurons in PD models by activating the AMPK/FOXO-3 pathway.[53,95,96] Moreover, resveratrol exhibits neuroprotective properties in PD models by inducing autophagy via AMPK activation and mTOR inhibition.[97,98] Therefore, AMPK-dependent stimulation of autophagy may hold promising potential for developing new therapeutic strategies in PD.

4. **Effect of AMPK on Genetic PD**

Genetic PD is rare; however, several types are identified that account for almost 30% of familial cases.[99] Genetic mutations in *LRRK2*, *PARK2*, *PARK7*, *PINK1*, or the *SNCA* gene can lead to familial cases of PD. Accumulating studies show that mutations in *SNCA*, *GBA*, and *LRRK2* genes result in overexpression of α-syn and increased secretion of pro-inflammatory cytokines, leading to the development of motor dysfunction.[92,100–102]

PARK7 (also known as DJ-1) is the gene responsible for the expression of DJ-1 protein, and its mutation causes genetic form and early onset of PD.[103] A critical function of DJ-1 is nuclear communication with mitochondria.[104] The wild-type DJ-1 enzyme prevents glycolysis metabolite damage in cells metabolizing carbohydrates.[105] It protects cells from oxidative stress-induced cytotoxicity by enhancing Nrf2 transcriptional activity and preventing Nrf2 inactivation.[106,107] Moreover, DJ-1 is one of the influential factors in cellular signals, including transcription of tyrosine hydroxylase, dopamine receptor, and p53 signaling pathway.[104] *PINK1* is also transcriptionally up-regulated by Nrf2, which shields dopamine neurons from neurotoxicity induced by oxidative stress.[106,107] AMPK can enhance Nrf2 nuclear translocation through phosphorylation and inhibiting oxidative stress.[77,78]

PARKIN, *PINK1*, *LRRK2,* and *PARK7* genetic mutations cause mitochondrial morphology and function abnormalities.[108] Point mutations in the *PARK7* (NM_007262.5) gene include p.Leu166Pro (c.497T>C), p.Ala104Thr (c.310G>A), p.Met26Ile (c.78G>A), p.Asp149Ala (c.446A>C), p.Glu64Asp (c.192G>C), p.Leu10Pro (c.29T>C), and p.Pro158del (c.471_473del).[109] Activation of AMPK by adaptor protein phosphotyrosine interacting with PH domain and leucine zipper (APPL)-1, an endosomal adapter protein, can protect against the p.Leu166Pro (c.497T>C) mutation of the *PARK7* gene.[110]

5. **Effect of AMPK on inflammation**

Both preclinical and clinical PD studies have proved that the onset and progression of PD involve neuroinflammation and immune dysfunction.[111] The causes of inflammation in PD include exposure to heavy metals, environmental toxins, bacterial and viral infections, and pesticides.[112]

Microglia, a part of the innate immune system in the central nervous system (CNS), are categorized into M1 and M2 subtypes. The M2 phenotype has anti-inflammatory and cytoprotective properties, essential for maintaining CNS homeostasis. Upon microglia activation, the M2 subtype is transformed into the M1 subtype, known to be cytotoxic and pro-inflammatory.[113–115] In the pathology of PD, the accumulation of α-syn and the increase of ROS in dopaminergic cells promote neuronal death, followed by the release of damage-associated molecular patterns (DAMPs) from neurons, resulting in an increase in the activity of M1 microglia in the CNS.[116] Preclinical PD models have shown that microglial activation and secretion of pro-inflammatory cytokines, particularly IL-6 and IL-1β, precede the degeneration of dopamine neurons.[117,118] Additionally, there is a connection between pathological α-syn accumulation and the PD brain's heightened inflammation.[119,120]

The blood-brain barrier becomes weaker when inflammation increases in the brain, leading to the penetration of harmful substances like ROS and NO, which cause further damage.[121] In a 6-OHDA-induced PD model, the amount of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and INF-γ were increased, while anti-inflammatory cytokines such as IL-10 was decreased, indicating dysregulation in the immune system and the occurrence of inflammation in the CNS.[122] In basal condition, nuclear factor kappa B (NF-κB) is inactive, localizes in the cytoplasm, and tightly bound to an inhibitor of nuclear κB (IκB). Upon activation by DAMPs, IκB kinase (IKK) targets IκB for degradation, resulting in translocation of NF-κB to the nucleus, pro-inflammatory gene expression, and damage to dopaminergic neurons through impaired mitochondrial function and autophagy by suppressing Sirt1/FOXO-PGC-1α pathway.[123,124]

On the other hand, nuclear receptor-related protein 1 (NURR1) controls the expression of genes essential for the survival of dopaminergic neurons and has the potential to inhibit NF-κB activity when activated.[125] Nrf2 transcription factor not only boosts antioxidative defense but also plays a critical role in regulating inflammation and has been substantiated to obstruct inflammatory responses prompted by inflammatory factors. Typically, Nrf2 is expressed at high levels in glial cells, and its activation reduces neuroinflammation.[121] The survival of dopaminergic neurons is influenced by Nrf2 and NF-κB, which behave as antagonistic transcription factors. Nrf2 negates NF-κB signaling, while NF-κB silences Nrf2 target genes and deprives it of necessary co-transcription factors. However, a lack of Nrf2 results in an increase in NF-κB levels through proteasome-mediated IκB degradation. Therefore, activation of the Nrf2 pathway can alleviate PD symptoms by reducing cellular damage from oxidative stress and neuroinflammation, as well as improving mitochondrial function.[126,127]

Evidence suggests that chronic inflammation leads to a gradual decrease in AMPK function[128], while an increase in AMPK activity encourages microglial anti-inflammatory M2 polarization.[129] Furthermore, AMPK suppresses NF-κB activation in the brain to inhibit inflammatory responses.[130,131] In an MPTP-induced PD model, liraglutide was shown to modulate the AMPK/NF-κB pathway, leading to improvements in PD-related motor symptoms, rescue of dopaminergic neurons, and diminished activated microglia in the SN.[132] Another pathway

by which AMPK regulates inflammation is sirtuin1 (Sirt1). Indole-3-carbinol was reported to activate the AMPK/Sirt1 pathway and reduce nervous system inflammation in PD model mice.[133] Moreover, AMPK reduces inflammation by inhibiting NOX-mediated ROS production and decreasing nitric oxide synthase (iNOS)-mediated nitric oxide (NO) production.[134–137] AMPK also acts as a cofactor for Sirt1 activity and Sirt1 activation protects dopaminergic neurons through inhibiting iNOS, p53, and NF-κB expression, and increasing FOXO-3/PGC-1α pathway.[138–141] The next target of AMPK in nerve cells to deal with neuroinflammation is activation of Nrf2.[142] As shown in Figure 2, AMPK activation through modulation of several pathways can protect dopaminergic neurons from inflammation.
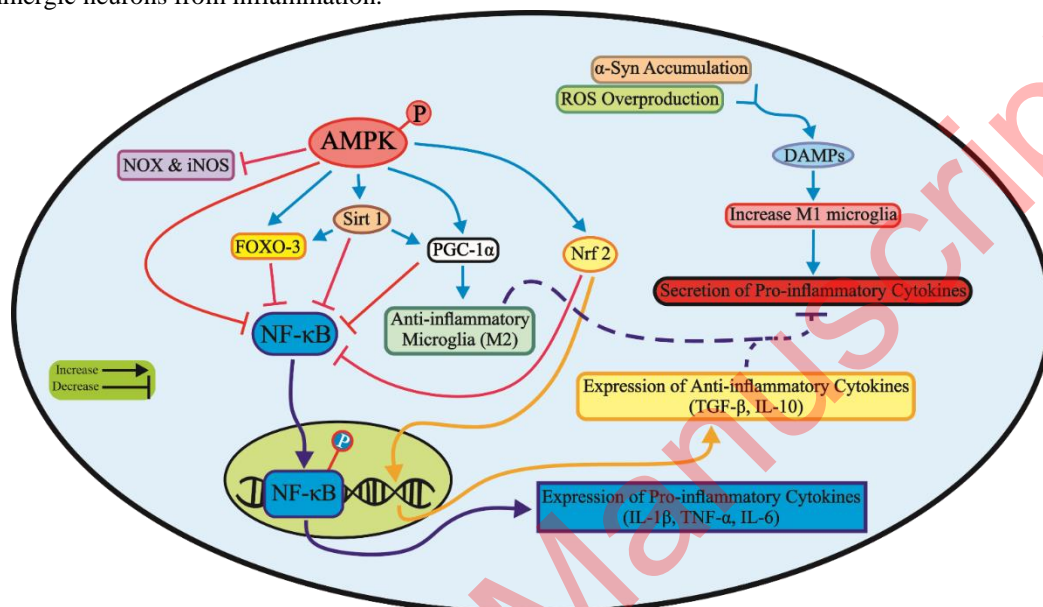

Figure 2. The phosphorylation of AMPK targets multiple signaling pathways to inhibit neuroinflammation responses related to PD. This results in the suppression of NF-κB translocation to the nucleus and expression of pro-inflammatory cytokines while enhancing the expression of anti-inflammatory cytokines. AMPK, AMP-activated protein kinase; NOX, NADPH oxidase; iNOS, Inducible nitric oxide synthase; FOXO-3, Forkhead box class O family member proteins-3; Sirt 1, Sirtuin 1; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator-1; Nrf2, Nuclear factor E2-related factor 2; NF-κB, Nuclear factor kappa B; IL, Interleukine; TNF-α, Tumor necrosis factor-α; DAMP, Damage-associated molecular patterns; ROS, Reactive oxygen species; α-Syn: α-Synuclein.

6. Effect of AMPK on cell survival and apoptosis

In PD, the activation of the intrinsic apoptotic pathway induces the death of dopaminergic neurons in the SNpc. Many studies suggest that PD is connected with mitochondrial-mediated apoptosis, leading to an increase in pro-apoptotic factors like BAX and cytochrome c, caspase-9, and caspase-3, and a decrease in anti-apoptotic factors such as Bcl-2 and Bcl-XL. As mentioned, PD is associated with a chain of events that drive cells toward apoptosis, including genetic mutation, accumulation of α-syn, neuroinflammation, ROS production, and mitochondrial dysfunction.[48,143–145] Besides, genetic mutation of PD-related genes, namely *Parkin*, *LRRK2*, *PINK1*, and *PARK7*, contribute to mitochondrial impairment and apoptosis.[99,143]

AMPK plays a dual role in regulating cell death and survival, depending on the type of stress and cells, and duration of exposure.[146–148] Some studies have shown that the activation of AMPK for a prolonged duration can activate c-Jun N-terminal protein kinase (JNK), leading to apoptosis in liver cells and pancreas beta cells.[149,150] However, another study showed that activation of AMPK inhibited dexamethasone-induced apoptosis in thymocytes.[151] Conversely, some studies suggest that the activation of AMPK-related pathways could prevent the apoptosis pathway, particularly in neurons, by correcting mitochondrial abnormalities. Furthermore, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) triggers AMPK activation that prevents apoptosis while inhibiting AMPK activity induces cell apoptosis.[152–156] Additionally, an in vitro study demonstrated that disruption of the AMPK/Sirt1 signaling pathway by sevoflurane caused an increase in the apoptosis rate in neural cells while promoting AMPK level can improve apoptosis.[157] In the intracerebral hemorrhage model, activating the αVβ5/AMPK pathway by Irisin, a myokine, inhibited apoptosis in the brain.[158] In an MPTP-induced PD model, activation of the AMPK/MAPK pathway by osmotin administration reduced α-syn and apoptosis-related

proteins.[159] Besides, treatment with the AMPK agonist, GSK621, attenuated mitochondrial dysfunction and apoptotic neuronal death in the SNpc in the MPTP-induced PD mice model by activating the AMPK/GSK-3β/PP2A.[160] Therefore, the regulation of apoptosis by AMPK is a controversial topic that requires more study.

Table 1. The AMPK downstream pathways to protect dopaminergic neurons.

Signaling pathways	Outcome	References
AMPK/mTORC-1 AMPK/mTOR/ULK-1 AMPK/Sirt1/PGC-1α	Increases Autophagy Increases Mitophagy	161–163 164,165
AMPK/Nrf2 AMPK/Sirt1/PGC-1α AMPK/Sirt1/Nrf2 AMPK/Nrf2/TXNIP AMPK/Sirt1/FOXO-1	Reduces Oxidative Stress	130,133,164–167
AMPK/PGC-1α/NF-κB AMPK/Sirt1/FOXO-3 AMPK/Sirt1/NF-κB AMPK/AKT/NF-κB AMPK/Nrf2/TXNIP	Reduces Inflammation	130,133,166,167
AMPK/Akt/mTOR AMPK/Sirt1/NF-κB AMPK/FOXO-3 AMPK/Sirt1/mTOR AMPK/MAPK/mTOR AMPK/GSK-3β/PP2A	Inhibits apoptosis	95,133,161–163,168,169

Conclusion

The pathophysiology of PD is complex and mulifactorial, involving abnormalities in mitochondrial function and morphology, impaired energy metabolism, genetic mutation, aggregation of α-syn, resulting in loss of dopaminergic neurons. AMPK can regulate multiple biological functions, including mitochondrial homeostasis, mitophagy, autophagy, oxidative stress, inflammation, and apoptosis, by which effectively prevents PD-related pathology (Fig. 3). To treat PD effectively, conducting additional preclinical research is necessary to gain a better understanding of the potential benefits and drawbacks of AMPK activation. This will help identify specific downstream pathways of AMPK and avoid activating any detrimental pathways.
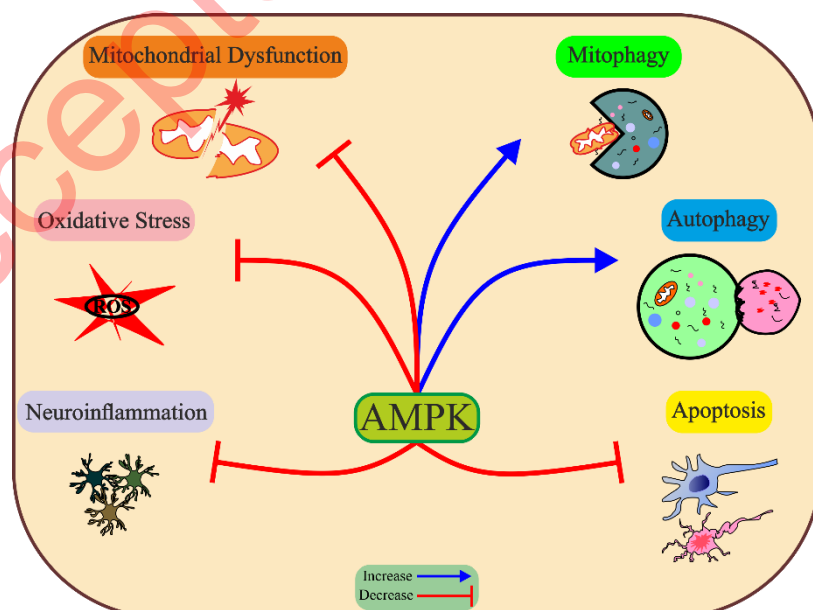

Figure 3. Protective effect of AMPK against Parkinson's disease etiologies. Activated AMPK target Parkinson's disease-related etiology by decreasing neuroinflammation, oxidative stress and apoptosis, and improving mitochondrial function, mitophagy, and autophagy. ROS, reactive oxygen species.

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

References

1. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Prim* 2021;7(1):47. doi: 10.1038/s41572-021-00280-3

2. Hu LF, Lu M, Tiong CX, Dawe GS, Hu G, Bian JS. Neuroprotective effects of hydrogen sulfide on Parkinson's disease rat models. *Aging Cell* 2010;9(2):135-46. doi: 10.1111/j.1474-9726.2009.00543.x

3. Hashempour-Baltork F, Farshi P, Mirza Alizadeh A, Eskandarzadeh S, Abedinzadeh S, Azadmard-Damirchi S, et al. Effect of Refined Edible Oils on Neurodegenerative Disorders. *Adv Pharm Bull* Published online November 2, 2022. doi: 10.34172/apb.2023.060

4. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018;17(11):939-53. doi: 10.1016/S1474-4422(18)30295-3

5. Armstrong MJ, Okun MS. Time for a New Image of Parkinson Disease. *JAMA Neurol* 2020;77(11):1345. doi: 10.1001/jamaneurol.2020.2412

6. Elfil M, Kamel S, Kandil M, Koo BB, Schaefer SM. Implications of the Gut Microbiome in Parkinson's Disease. *Mov Disord* 2020;35(6):921-33. doi: 10.1002/mds.28004

7. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem* 2016;139:318-24. doi: 10.1111/jnc.13691

8. Mazzoni P, Shabbott B, Cortes JC. Motor Control Abnormalities in Parkinson's Disease. *Cold Spring Harb Perspect Med* 2012;2(6):a009282-a009282. doi: 10.1101/cshperspect.a009282

9. Jameson JL; Fausi AS et al. *Harrison's Principles of Internal Medicine*. 20th ed.; 2018.

10. Bonnet AM. Involvement of non-dopaminergic pathways in Parkinson's disease. *CNS Drugs* 2000;13(5):351-64. doi: 10.2165/00023210-200013050-00005

11. Spatola M, Wider C. Genetics of Parkinson's disease: the yield. *Parkinsonism Relat Disord* 2014;20:S35-S38. doi: 10.1016/S1353-8020(13)70011-7

12. Surmeier DJ. Calcium, ageing, and neuronal vulnerability in Parkinson's disease. *Lancet Neurol* 2007;6(10):933-8. doi: 10.1016/S1474-4422(07)70246-6

13. Zhang P, Tian B. Metabolic Syndrome: An Important Risk Factor for Parkinson's Disease. *Oxid Med Cell Longev* 2014;2014:1-7. doi: 10.1155/2014/729194

14. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, et al. Diabetes mellitus and Parkinson disease. *Neurology* 2018;90(19):e1654-62. doi: 10.1212/WNL.0000000000005475

15. Yan MH, Wang X, Zhu X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med* 2013;62:90-101. doi: 10.1016/J.FREERADBIOMED.2012.11.014

16. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. *Nat Cell Biol* 2011;13(9):1016-23. doi: 10.1038/ncb2329

17. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol* 2012;13(4):251-62. doi: 10.1038/nrm3311

18. Srivastava RAK, Pinkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res* 2012;53(12):2490-514. doi: 10.1194/jlr.R025882

19. Sag D, Carling D, Stout RD, Suttles J. Adenosine 5′-Monophosphate-Activated Protein Kinase Promotes Macrophage Polarization to an Anti-Inflammatory Functional Phenotype. *J Immunol* 2008;181(12):8633-41. doi: 10.4049/jimmunol.181.12.8633

20. Ronnett G V., Ramamurthy S, Kleman AM, Landree LE, Aja S. AMPK in the brain: its roles in energy balance and neuroprotection. *J Neurochem* 2009;109:17-23. doi: 10.1111/j.1471-4159.2009.05916.x

21. Curry DW, Stutz B, Andrews ZB, Elsworth JD. Targeting AMPK Signaling as a Neuroprotective Strategy in Parkinson's Disease. *J Parkinsons Dis* 2018;8(2):161-81. doi: 10.3233/JPD-171296

22. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat Rev Mol Cell Biol* 2018;19(2):121-35. doi: 10.1038/nrm.2017.95

23. Sukumaran A, Choi K, Dasgupta B. Insight on Transcriptional Regulation of the Energy Sensing AMPK and Biosynthetic mTOR Pathway Genes. *Front Cell Dev Biol* 2020;8. doi: 10.3389/fcell.2020.00671

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

24. Garcia D, Shaw RJ. AMPK: Mechanisms of Cellular Energy Sensing and Restoration of Metabolic Balance. *Mol Cell* 2017;66(6):789-800. doi: 10.1016/j.molcel.2017.05.032

25. Berndt N, Bulik S, Holzhütter HG. Kinetic modeling of the mitochondrial energy metabolism of neuronal cells: The impact of reduced _ ketoglutarate dehydrogenase activities on ATP production and generation of reactive oxygen species. *Int J Cell Biol* 2012;2012:1-11. doi: 10.1155/2012/757594

26. Wu N, Zheng B, Shaywitz A, Dagon Y, Tower C, Bellinger G, et al. AMPK-Dependent Degradation of TXNIP upon Energy Stress Leads to Enhanced Glucose Uptake via GLUT1. *Mol Cell* 2013;49(6):1167-75. doi: 10.1016/j.molcel.2013.01.035

27. Chaube B, Bhat MK. AMPK, a key regulator of metabolic/energy homeostasis and mitochondrial biogenesis in cancer cells. *Cell Death Dis* 2016;7(1):e2044-e2044. doi: 10.1038/cddis.2015.404

28. Hardie DG, Pan DA. Regulation of fatty acid synthesis and oxidation by the AMP-activated protein kinase. *Biochem Soc Trans* 2002;30(6):1064-70. doi: 10.1042/bst0301064

29. Cantó C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, et al. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. *Nature* 2009;458(7241):1056-60. doi: 10.1038/nature07813

30. Cantó C, Auwerx J. AMP-activated protein kinase and its downstream transcriptional pathways. *Cell Mol Life Sci* 2010;67(20):3407-23. doi: 10.1007/s00018-010-0454-z

31. Tarasiuk O, Miceli M, Di Domizio A, Nicolini G. AMPK and Diseases: State of the Art Regulation by AMPK-Targeting Molecules. *Biology (Basel)* 2022;11(7):1041. doi: 10.3390/biology11071041

32. Inoki K, Zhu T, Guan KL. TSC2 Mediates Cellular Energy Response to Control Cell Growth and Survival. *Cell* 2003;115(5):577-90. doi: 10.1016/S0092-8674(03)00929-2

33. Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, et al. AMPK Phosphorylation of Raptor Mediates a Metabolic Checkpoint. *Mol Cell* 2008;30(2):214-26. doi: 10.1016/j.molcel.2008.03.003

34. Hoppe S, Bierhoff H, Cado I, Weber A, Tiebe M, Grummt I, et al. AMP-activated protein kinase adapts rRNA synthesis to cellular energy supply. *Proc Natl Acad Sci* 2009;106(42):17781-6. doi: 10.1073/pnas.0909873106

35. Franco-Iborra S, Vila M, Perier C. The Parkinson Disease Mitochondrial Hypothesis: Where Are We at? *Neuroscientist* 2016;22(3):266-77. doi: 10.1177/1073858415574600

36. Fischer F, Hamann A, Osiewacz HD. Mitochondrial quality control: an integrated network of pathways. *Trends Biochem Sci* 2012;37(7):284-92. doi: 10.1016/j.tibs.2012.02.004

37. Shi R, Guberman M, Kirshenbaum LA. Mitochondrial quality control: The role of mitophagy in aging. *Trends Cardiovasc Med* 2018;28(4):246-60. doi: 10.1016/j.tcm.2017.11.008

38. de Castro IP, Martins LM, Loh SHY. Mitochondrial Quality Control and Parkinson's Disease: A Pathway Unfolds. *Mol Neurobiol* 2011;43(2):80-6. doi: 10.1007/s12035-010-8150-4

39. Kamp F, Exner N, Lutz AK, Wender N, Hegermann J, Brunner B, et al. Inhibition of mitochondrial fusion by α-synuclein is rescued by PINK1, Parkin and DJ-1. *EMBO J* 2010;29(20):3571-89. doi: 10.1038/emboj.2010.223

40. Ordonez DG, Lee MK, Feany MB. α-synuclein Induces Mitochondrial Dysfunction through Spectrin and the Actin Cytoskeleton. *Neuron* 2018;97(1):108-124.e6. doi: 10.1016/j.neuron.2017.11.036

41. Twig G, Shirihai OS. The Interplay Between Mitochondrial Dynamics and Mitophagy. *Antioxid Redox Signal* 2011;14(10):1939-51. doi: 10.1089/ars.2010.3779

42. Frezza C, Cipolat S, Martins de Brito O, Micaroni M, Beznoussenko G V., Rudka T, et al. OPA1 Controls Apoptotic Cristae Remodeling Independently from Mitochondrial Fusion. *Cell* 2006;126(1):177-89. doi: 10.1016/j.cell.2006.06.025

43. Clinton RW, Francy CA, Ramachandran R, Qi X, Mears JA. Dynamin-related Protein 1 Oligomerization in Solution Impairs Functional Interactions with Membrane-anchored Mitochondrial Fission Factor. *J Biol Chem* 2016;291(1):478-92. doi: 10.1074/jbc.M115.680025

44. Liang CL, Wang TT, Luby-Phelps K, German DC. Mitochondria mass is low in mouse substantia nigra dopamine neurons: Implications for Parkinson's disease. *Exp Neurol* 2007;203(2):370-80. doi: 10.1016/j.expneurol.2006.08.015

45. Park JS, Davis RL, Sue CM. Mitochondrial Dysfunction in Parkinson's Disease: New Mechanistic Insights and Therapeutic Perspectives. *Curr Neurol Neurosci Rep* 2018;18(5):21. doi: 10.1007/s11910-018-0829-3

46. Ge P, Dawson VL, Dawson TM. PINK1 and Parkin mitochondrial quality control: a source of regional vulnerability in Parkinson's disease. *Mol Neurodegener* 2020;15(1):20. doi: 10.1186/s13024-020-00367-7

47. Jin SM, Youle RJ. PINK1- and Parkin-mediated mitophagy at a glance. *J Cell Sci* 2012;125(4):795-9.

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

doi: 10.1242/jcs.093849

48. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. *J Neurochem* 2016;139(S1):216-31. doi: 10.1111/jnc.13731

49. Berthet A, Margolis EB, Zhang J, Hsieh I, Zhang J, Hnasko TS, et al. Loss of Mitochondrial Fission Depletes Axonal Mitochondria in Midbrain Dopamine Neurons. *J Neurosci* 2014;34(43):14304-17. doi: 10.1523/JNEUROSCI.0930-14.2014

50. Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim Biophys Acta - Mol Cell Res* 2011;1813(7):1269-78. doi: 10.1016/j.bbamcr.2010.09.019

51. Corona JC, Duchen MR. PPARγ and PGC-1α as Therapeutic Targets in Parkinson's. *Neurochem Res* 2015;40(2):308-16. doi: 10.1007/s11064-014-1377-0

52. Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, et al. PGC-1 , A Potential Therapeutic Target for Early Intervention in Parkinson's Disease. *Sci Transl Med* 2010;2(52):52ra73-52ra73. doi: 10.1126/scitranslmed.3001059

53. Dulovic M, Jovanovic M, Xilouri M, Stefanis L, Harhaji-Trajkovic L, Kravic-Stevovic T, et al. The protective role of AMP-activated protein kinase in alpha-synuclein neurotoxicity in vitro. *Neurobiol Dis* 2014;63:1-11. doi: 10.1016/j.nbd.2013.11.002

54. Hang L, Wang Z, Foo ASC, Goh GWY, Choong HC, Thundyil J, et al. Conditional disruption of AMP kinase in dopaminergic neurons promotes Parkinson's disease-associated phenotypes in vivo. *Neurobiol Dis* 2021;161:105560. doi: 10.1016/j.nbd.2021.105560

55. Hang L, Thundyil J, Goh GWY, Lim KL. AMP Kinase Activation is Selectively Disrupted in the Ventral Midbrain of Mice Deficient in Parkin or PINK1 Expression. *NeuroMolecular Med* 2019;21(1):25-32. doi: 10.1007/s12017-018-8517-7

56. Marcinko K, Steinberg GR. The role of AMPK in controlling metabolism and mitochondrial biogenesis during exercise. *Exp Physiol* 2014;99(12):1581-5. doi: 10.1113/expphysiol.2014.082255

57. Kang C, Li Ji L. Role of PGC- 1α signaling in skeletal muscle health and disease. *Ann N Y Acad Sci* 2012;1271(1):110-7. doi: 10.1111/j.1749-6632.2012.06738.x

58. Peng K, Yang L, Wang J, Ye F, Dan G, Zhao Y, et al. The Interaction of Mitochondrial Biogenesis and Fission/Fusion Mediated by PGC-1α Regulates Rotenone-Induced Dopaminergic Neurotoxicity. *Mol Neurobiol* 2017;54(5):3783-97. doi: 10.1007/s12035-016-9944-9

59. Robb EL, Moradi F, Maddalena LA, Valente AJF, Fonseca J, Stuart JA. Resveratrol stimulates mitochondrial fusion by a mechanism requiring mitofusin-2. *Biochem Biophys Res Commun* 2017;485(2):249-54. doi: 10.1016/j.bbrc.2017.02.102

60. Morita M, Prudent J, Basu K, Goyon V, Katsumura S, Hulea L, et al. mTOR Controls Mitochondrial Dynamics and Cell Survival via MTFP1. *Mol Cell* 2017;67(6):922-935.e5. doi: 10.1016/j.molcel.2017.08.013

61. Toyama EQ, Herzig S, Courchet J, Lewis TL, Loson OC, Hellberg K, et al. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science (80-)* 2016;351(6270):275-81. doi: 10.1126/science.aab4138

62. Marin TL, Gongol B, Zhang F, Martin M, Johnson DA, Xiao H, et al. AMPK promotes mitochondrial biogenesis and function by phosphorylating the epigenetic factors DNMT1, RBBP7, and HAT1. *Sci Signal* 2017;10(464). doi: 10.1126/scisignal.aaf7478

63. Ma K, Chen G, Li W, Kepp O, Zhu Y, Chen Q. Mitophagy, Mitochondrial Homeostasis, and Cell Fate. *Front Cell Dev Biol* 2020;8. doi: 10.3389/fcell.2020.00467

64. Zhu J, Wang KZQ, Chu CT. After the banquet: mitochondrial biogenesis, mitophagy, and cell survival. *Autophagy* 2013;9(11):1663-76. doi: 10.4161/auto.24135

65. Park JS, Lee DH, Lee YS, Oh E, Bae KH, Oh KJ, et al. Dual roles of ULK1 (unc-51 like autophagy activating kinase 1) in cytoprotection against lipotoxicity. *Autophagy* 2020;16(1):86-105. doi: 10.1080/15548627.2019.1598751

66. Wang S, Tan J, Miao Y, Zhang Q. Mitochondrial Dynamics, Mitophagy, and Mitochondria–Endoplasmic Reticulum Contact Sites Crosstalk Under Hypoxia. *Front Cell Dev Biol* 2022;10. doi: 10.3389/fcell.2022.848214

67. Laker RC, Drake JC, Wilson RJ, Lira VA, Lewellen BM, Ryall KA, et al. Ampk phosphorylation of Ulk1 is required for targeting of mitochondria to lysosomes in exercise-induced mitophagy. *Nat Commun* 2017;8(1):548. doi: 10.1038/s41467-017-00520-9

68. Diebold L, Chandel NS. Mitochondrial ROS regulation of proliferating cells. *Free Radic Biol Med* 2016;100:86-93. doi: 10.1016/j.freeradbiomed.2016.04.198

69. Rabinovitch RC, Samborska B, Faubert B, Ma EH, Gravel SP, Andrzejewski S, et al. AMPK Maintains

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

Cellular Metabolic Homeostasis through Regulation of Mitochondrial Reactive Oxygen Species. *Cell Rep* 2017;21(1):1-9. doi: 10.1016/j.celrep.2017.09.026

70. Dias V, Junn E, Mouradian MM. The Role of Oxidative Stress in Parkinson's Disease. *J Parkinsons Dis* 2013;3(4):461-91. doi: 10.3233/JPD-130230

71. Wei Z, Li X, Li X, Liu Q, Cheng Y. Oxidative Stress in Parkinson's Disease: A Systematic Review and Meta-Analysis. *Front Mol Neurosci* 2018;11. doi: 10.3389/fnmol.2018.00236

72. Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR. Oxidative stress and Parkinson's disease. *Front Neuroanat* 2015;9. doi: 10.3389/fnana.2015.00091

73. Guo J, Zhao X, Li Y, Li G, Liu X. Damage to dopaminergic neurons by oxidative stress in Parkinson's disease (Review). *Int J Mol Med* 2018;41(4):1817-25. doi: 10.3892/ijmm.2018.3406

74. Greenamyre JT, Cannon JR, Drolet R, Mastroberardino PG. Lessons from the rotenone model of Parkinson's disease. *Trends Pharmacol Sci* 2010;31(4):141-2. doi: 10.1016/j.tips.2009.12.006

75. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Front Neuroanat* 2014;8. doi: 10.3389/fnana.2014.00155

76. Stott SRW, Barker RA. Time course of dopamine neuron loss and glial response in the 6-<scp>OHDA</scp> striatal mouse model of <scp>P</scp> arkinson's disease. *Eur J Neurosci* 2014;39(6):1042-56. doi: 10.1111/ejn.12459

77. Zimmermann K, Baldinger J, Mayerhofer B, Atanasov AG, Dirsch VM, Heiss EH. Activated AMPK boosts the Nrf2/HO-1 signaling axis—A role for the unfolded protein response. *Free Radic Biol Med* 2015;88:417-26. doi: 10.1016/j.freeradbiomed.2015.03.030

78. Tebay LE, Robertson H, Durant ST, Vitale SR, Penning TM, Dinkova-Kostova AT, et al. Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease. *Free Radic Biol Med* 2015;88:108-46. doi: 10.1016/j.freeradbiomed.2015.06.021

79. Lynch-Day MA, Mao K, Wang K, Zhao M, Klionsky DJ. The Role of Autophagy in Parkinson's Disease. *Cold Spring Harb Perspect Med* 2012;2(4):a009357-a009357. doi: 10.1101/cshperspect.a009357

80. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J ichi, Tanida I, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* 2006;441(7095):880-4. doi: 10.1038/nature04723

81. Wang X, Hu W, Qu L, Wang J, Wu A, Lo HH, et al. Tricin promoted ATG-7 dependent autophagic degradation of α-synuclein and dopamine release for improving cognitive and motor deficits in Parkinson's disease. *Pharmacol Res* 2023;196:106874. doi: 10.1016/j.phrs.2023.106874

82. Vogiatzi T, Xilouri M, Vekrellis K, Stefanis L. Wild Type α-Synuclein Is Degraded by Chaperone-mediated Autophagy and Macroautophagy in Neuronal Cells. *J Biol Chem* 2008;283(35):23542-56. doi: 10.1074/jbc.M801992200

83. Cuervo AM. Impaired Degradation of Mutant -Synuclein by Chaperone-Mediated Autophagy. *Science (80-)* 2004;305(5688):1292-5. doi: 10.1126/science.1101738

84. Ciechanover A, Kwon YT a. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. *Exp Mol Med* 2015;47(3):e147-e147. doi: 10.1038/emm.2014.117

85. Xilouri M, Stefanis L. Autophagic pathways in Parkinson disease and related disorders. *Expert Rev Mol Med* 2011;13:e8. doi: 10.1017/S1462399411001803

86. Decressac M, Mattsson B, Weikop P, Lundblad M, Jakobsson J, Bjorklund A. TFEB-mediated autophagy rescues midbrain dopamine neurons from α-synuclein toxicity. *Proc Natl Acad Sci* 2013;110(19):E1817-26. doi: 10.1073/pnas.1305623110

87. Spencer B, Potkar R, Trejo M, Rockenstein E, Patrick C, Gindi R, et al. Beclin 1 Gene Transfer Activates Autophagy and Ameliorates the Neurodegenerative Pathology in -Synuclein Models of Parkinson's and Lewy Body Diseases. *J Neurosci* 2009;29(43):13578-88. doi: 10.1523/JNEUROSCI.4390-09.2009

88. Egan DF, Chun MGH, Vamos M, Zou H, Rong J, Miller CJ, et al. Small Molecule Inhibition of the Autophagy Kinase ULK1 and Identification of ULK1 Substrates. *Mol Cell* 2015;59(2):285-97. doi: 10.1016/j.molcel.2015.05.031

89. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 2011;13(2):132-41. doi: 10.1038/ncb2152

90. Russell RC, Tian Y, Yuan H, Park HW, Chang YY, Kim J, et al. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. *Nat Cell Biol* 2013;15(7):741-50. doi: 10.1038/ncb2757

91. Wang S, Li H, Yuan M, Fan H, Cai Z. Role of AMPK in autophagy. *Front Physiol* 2022;13. doi: 10.3389/fphys.2022.1015500

92. Phillipson OT. Alpha-synuclein, epigenetics, mitochondria, metabolism, calcium traffic, & circadian

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

dysfunction in Parkinson's disease. An integrated strategy for management. *Ageing Res Rev* 2017;40:149-67. doi: 10.1016/j.arr.2017.09.006

93.   Segatto M, Rosso P, Fioramonti M, Fracassi A, Marangoni M, Taglietti V, et al. AMPK in the central nervous system: physiological roles and pathological implications. *Res Rep Biol* Published online January 2016:1. doi: 10.2147/RRB.S90858

94.   Moors TE, Hoozemans JJM, Ingrassia A, Beccari T, Parnetti L, Chartier-Harlin MC, et al. Therapeutic potential of autophagy-enhancing agents in Parkinson's disease. *Mol Neurodegener* 2017;12(1):11. doi: 10.1186/s13024-017-0154-3

95.   El-Ghaiesh SH, Bahr HI, Ibrahiem AT, Ghorab D, Alomar SY, Farag NE, et al. Metformin Protects From Rotenone–Induced Nigrostriatal Neuronal Death in Adult Mice by Activating AMPK-FOXO3 Signaling and Mitigation of Angiogenesis. *Front Mol Neurosci* 2020;13:84. doi: 10.3389/fnmol.2020.00084

96.   Ng CH, Guan MSH, Koh C, Ouyang X, Yu F, Tan EK, et al. AMP Kinase Activation Mitigates Dopaminergic Dysfunction and Mitochondrial Abnormalities in Drosophila Models of Parkinson's Disease. *J Neurosci* 2012;32(41):14311-7. doi: 10.1523/JNEUROSCI.0499-12.2012

97.   Wu Y, Li X, Zhu JX, Xie W, Le W, Fan Z, et al. Resveratrol-Activated AMPK/SIRT1/Autophagy in Cellular Models of Parkinson's Disease. *Neurosignals* 2011;19(3):163-74. doi: 10.1159/000328516

98.   Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, et al. Effect of resveratrol on mitochondrial function: Implications in parkin-associated familiar Parkinson's disease. *Biochim Biophys Acta - Mol Basis Dis* 2014;1842(7):902-15. doi: 10.1016/j.bbadis.2014.02.010

99.   Klein C, Westenberger A. Genetics of Parkinson's Disease. *Cold Spring Harb Perspect Med* 2012;2(1):a008888-a008888. doi: 10.1101/cshperspect.a008888

100.   Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, et al. Alpha-Synuclein Aggregation in Parkinson's Disease. *Front Med* 2021;8. doi: 10.3389/fmed.2021.736978

101.   Kalia L V., Lang AE. Parkinson's disease. *Lancet* 2015;386(9996):896-912. doi: 10.1016/S0140-6736(14)61393-3

102.   Phillipson OT. Alpha-synuclein, epigenetics, mitochondria, metabolism, calcium traffic, & circadian dysfunction in Parkinson's disease. An integrated strategy for management. *Ageing Res Rev* Published online 2017. doi: 10.1016/j.arr.2017.09.006

103.   Deeg S, Gralle M, Sroka K, Bähr M, Wouters FS, Kermer P. BAG1 restores formation of functional DJ-1 L166P dimers and DJ-1 chaperone activity. *J Cell Biol* 2010;188(4):505-13. doi: 10.1083/jcb.200904103

104.   Cookson MR. DJ-1, PINK1, and their effects on mitochondrial pathways. *Mov Disord* 2010;25(S1):S44-8. doi: 10.1002/mds.22713

105.   Heremans IP, Caligiore F, Gerin I, Bury M, Lutz M, Graff J, et al. Parkinson's disease protein PARK7 prevents metabolite and protein damage caused by a glycolytic metabolite. *Proc Natl Acad Sci* 2022;119(4). doi: 10.1073/pnas.2111338119

106.   Meulener M, Whitworth AJ, Armstrong-Gold CE, Rizzu P, Heutink P, Wes PD, et al. Drosophila DJ-1 Mutants Are Selectively Sensitive to Environmental Toxins Associated with Parkinson's Disease. *Curr Biol* 2005;15(17):1572-7. doi: 10.1016/j.cub.2005.07.064

107.   Murata H, Takamatsu H, Liu S, Kataoka K, Huh N ho, Sakaguchi M. NRF2 Regulates PINK1 Expression under Oxidative Stress Conditions. Tsuji Y, editor. *PLoS One* 2015;10(11):e0142438. doi: 10.1371/journal.pone.0142438

108.   Moon HE, Paek SH. Mitochondrial Dysfunction in Parkinson's Disease. *Exp Neurobiol* 2015;24(2):103-16. doi: 10.5607/en.2015.24.2.103

109.   Cookson MR. Parkinsonism Due to Mutations in PINK1, Parkin, and DJ-1 and Oxidative Stress and Mitochondrial Pathways. *Cold Spring Harb Perspect Med* 2012;2(9):a009415-a009415. doi: 10.1101/cshperspect.a009415

110.   Li X, Geng J, Liu J. Adiponectin offers protection against L166P mutant DJ-1-induced neuronal cytotoxicity mediated by APPL1-dependent AMPK activation. *Int J Neurosci* 2014;124(5):350-61. doi: 10.3109/00207454.2013.846340

111.   Gundersen V. Parkinson's Disease: Can Targeting Inflammation Be an Effective Neuroprotective Strategy? *Front Neurosci* 2021;14. doi: 10.3389/fnins.2020.580311

112.   Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 2011;26(S1):1-58. doi: 10.1007/s10654-011-9581-6

113.   O'Neill LAJ, Hardie DG. Metabolism of inflammation limited by AMPK and pseudo-starvation. *Nature* 2013;493(7432):346-55. doi: 10.1038/nature11862

114.   Yin J, Valin KL, Dixon ML, Leavenworth JW. The Role of Microglia and Macrophages in CNS Homeostasis, Autoimmunity, and Cancer. *J Immunol Res* 2017;2017:1-12. doi: 10.1155/2017/5150678

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

115. Kofler J, Wiley CA. Microglia: key innate immune cells of the brain. *Toxicol Pathol* 2011;39(1):103-14. doi: 10.1177/0192623310387619

116. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology* 1988;38(8):1285-1285. doi: 10.1212/WNL.38.8.1285

117. Sanchez-Guajardo V, Febbraro F, Kirik D, Romero-Ramos M. Microglia Acquire Distinct Activation Profiles Depending on the Degree of α-Synuclein Neuropathology in a rAAV Based Model of Parkinson's Disease. Cookson MR, editor. *PLoS One* 2010;5(1):e8784. doi: 10.1371/journal.pone.0008784

118. Chung CY, Koprich JB, Siddiqi H, Isacson O. Dynamic Changes in Presynaptic and Axonal Transport Proteins Combined with Striatal Neuroinflammation Precede Dopaminergic Neuronal Loss in a Rat Model of AAV α-Synucleinopathy. *J Neurosci* 2009;29(11):3365-73. doi: 10.1523/JNEUROSCI.5427-08.2009

119. Sanchez-Guajardo V, Tentillier N, Romero-Ramos M. The relation between α-synuclein and microglia in Parkinson's disease: Recent developments. *Neuroscience* 2015;302:47-58. doi: 10.1016/j.neuroscience.2015.02.008

120. Dzamko N, Gysbers A, Perera G, Bahar A, Shankar A, Gao J, et al. Toll-like receptor 2 is increased in neurons in Parkinson's disease brain and may contribute to alpha-synuclein pathology. *Acta Neuropathol* 2017;133(2):303-19. doi: 10.1007/s00401-016-1648-8

121. Pajares M, I. Rojo A, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells* 2020;9(7):1687. doi: 10.3390/cells9071687

122. Na SJ, DiLella AG, Lis E V., Jones K, Levine DM, Stone DJ, et al. Molecular Profiling of a 6-Hydroxydopamine Model of Parkinson's Disease. *Neurochem Res* 2010;35(5):761-72. doi: 10.1007/s11064-010-0133-3

123. Singh S Sen, Rai SN, Birla H, Zahra W, Rathore AS, Singh SP. NF-κB-Mediated Neuroinflammation in Parkinson's Disease and Potential Therapeutic Effect of Polyphenols. *Neurotox Res* 2020;37(3):491-507. doi: 10.1007/s12640-019-00147-2

124. Li Y, Xia Y, Yin S, Wan F, Hu J, Kou L, et al. Targeting Microglial α-Synuclein/TLRs/NF-kappaB/NLRP3 Inflammasome Axis in Parkinson's Disease. *Front Immunol* 2021;12. doi: 10.3389/fimmu.2021.719807

125. Al-Nusaif M, Yang Y, Li S, Cheng C, Le W. The role of NURR1 in metabolic abnormalities of Parkinson's disease. *Mol Neurodegener* 2022;17(1):46. doi: 10.1186/s13024-022-00544-w

126. Yang X xing, Yang R, Zhang F. Role of Nrf2 in Parkinson's Disease: Toward New Perspectives. *Front Pharmacol* 2022;13. doi: 10.3389/fphar.2022.919233

127. Parga JA, Rodriguez-Perez AI, Garcia-Garrote M, Rodriguez-Pallares J, Labandeira-Garcia JL. NRF2 Activation and Downstream Effects: Focus on Parkinson's Disease and Brain Angiotensin. *Antioxidants* 2021;10(11):1649. doi: 10.3390/antiox10111649

128. Salminen A, Hyttinen JMT, Kaarniranta K. AMP-activated protein kinase inhibits NF-κB signaling and inflammation: impact on healthspan and lifespan. *J Mol Med* 2011;89(7):667-76. doi: 10.1007/s00109-011-0748-0

129. Chu X, Cao L, Yu Z, Xin D, Li T, Ma W, et al. Hydrogen-rich saline promotes microglia M2 polarization and complement-mediated synapse loss to restore behavioral deficits following hypoxia-ischemic in neonatal mice via AMPK activation. *J Neuroinflammation* 2019;16(1):104. doi: 10.1186/s12974-019-1488-2

130. Salama A, Elgohary R. L-carnitine and Co Q10 ameliorate potassium dichromate -induced acute brain injury in rats targeting AMPK/AKT/NF-κβ. *Int Immunopharmacol* 2021;101:107867. doi: 10.1016/j.intimp.2021.107867

131. Li YQ, Chen Y, Jiang SQ, Shi YY, Jiang XL, Wu SS, et al. An Inhibitor of NF-κB and an Agonist of AMPK: Network Prediction and Multi-Omics Integration to Derive Signaling Pathways for Acteoside Against Alzheimer's Disease. *Front Cell Dev Biol* 2021;9. doi: 10.3389/fcell.2021.652310

132. Cao B, Zhang Y, Chen J, Wu P, Dong Y, Wang Y. Neuroprotective effects of liraglutide against inflammation through the AMPK/NF-κB pathway in a mouse model of Parkinson's disease. *Metab Brain Dis* 2022;37(2):451-62. doi: 10.1007/s11011-021-00879-1

133. Mohamad KA, El-Naga RN, Wahdan SA. Neuroprotective effects of indole-3-carbinol on the rotenone rat model of Parkinson's disease: Impact of the SIRT1-AMPK signaling pathway. *Toxicol Appl Pharmacol* 2022;435:115853. doi: 10.1016/j.taap.2021.115853

134. Skonieczna M, Hejmo T, Poterala-Hejmo A, Cieslar-Pobuda A, Buldak RJ. NADPH Oxidases: Insights into Selected Functions and Mechanisms of Action in Cancer and Stem Cells. *Oxid Med Cell Longev* 2017;2017:1-15. doi: 10.1155/2017/9420539

135. Balteau M, Van Steenbergen A, Timmermans AD, Dessy C, Behets-Wydemans G, Tajeddine N, et al. AMPK activation by glucagon-like peptide-1 prevents NADPH oxidase activation induced by hyperglycemia in adult cardiomyocytes. *Am J Physiol Circ Physiol* 2014;307(8):H1120-33. doi: 10.1152/ajpheart.00210.2014

136. Pilon G, Dallaire P, Marette A. Inhibition of Inducible Nitric-oxide Synthase by Activators of AMP-activated Protein Kinase. *J Biol Chem* 2004;279(20):20767-74. doi: 10.1074/jbc.M401390200

137. Guma M, Wang Y, Viollet B, Liu-Bryan R. AMPK Activation by A-769662 Controls IL-6 Expression in Inflammatory Arthritis. Bertrand L, editor. *PLoS One* 2015;10(10):e0140452. doi: 10.1371/journal.pone.0140452

138. Zhang Q, Zhang P, Qi GJ, Zhang Z, He F, Lv ZX, et al. Cdk5 suppression blocks SIRT1 degradation via the ubiquitin-proteasome pathway in Parkinson's disease models. *Biochim Biophys Acta - Gen Subj* 2018;1862(6):1443-51. doi: 10.1016/j.bbagen.2018.03.021

139. Rodriguez L, Marano MM, Tandon A. Import and Export of Misfolded α-Synuclein. *Front Neurosci* 2018;12. doi: 10.3389/fnins.2018.00344

140. Batiha GES, Al-kuraishy HM, Al-Gareeb AI, Elekhnawy E. SIRT1 pathway in Parkinson's disease: a faraway snapshot but so close. *Inflammopharmacology* 2023;31(1):37-56. doi: 10.1007/s10787-022-01125-5

141. Li X, Feng Y, Wang XX, Truong D, Wu YC. The Critical Role of SIRT1 in Parkinson's Disease: Mechanism and Therapeutic Considerations. *Aging Dis* 2020;11(6):1608. doi: 10.14336/AD.2020.0216

142. Xu H, Shen J, Xiao J, Chen F, Wang M. Neuroprotective effect of cajaninstilbene acid against cerebral ischemia and reperfusion damages by activating AMPK/Nrf2 pathway. *J Adv Res* 2021;34:199-210. doi: 10.1016/j.jare.2020.07.011

143. Erekat NS. Apoptosis and its Role in Parkinson's Disease. In: *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications; 2018. P. 65-82. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch4

144. Hartmann A, Michel PP, Troadec JD, Mouatt-Prigent A, Faucheux BA, Ruberg M, et al. Is Bax a mitochondrial mediator in apoptotic death of dopaminergic neurons in Parkinson's disease? *J Neurochem* 2001;76(6):1785-93. doi: 10.1046/j.1471-4159.2001.00160.x

145. Chang KH, Chen CM. The Role of Oxidative Stress in Parkinson's Disease. *Antioxidants* 2020;9(7):597. doi: 10.3390/antiox9070597

146. Villanueva-Paz M, Cotán D, Garrido-Maraver J, Oropesa-Ávila M, de la Mata M, Delgado-Pavón A, et al. AMPK Regulation of Cell Growth, Apoptosis, Autophagy, and Bioenergetics. In: *EXS*. 2016. P. 45-71. doi: 10.1007/978-3-319-43589-3_3

147. Bonini MG, Gantner BN. The multifaceted activities of AMPK in tumor progression-why the "one size fits all" definition does not fit at all? *IUBMB Life* 2013;65(11):889-96. doi: 10.1002/iub.1213

148. Dyck JRB, Lopaschuk GD. AMPK alterations in cardiac physiology and pathology: enemy or ally? *J Physiol* 2006;574(1):95-112. doi: 10.1113/jphysiol.2006.109389

149. Meisse D, Van de Casteele M, Beauloye C, Hainault I, Kefas BA, Rider MH, et al. Sustained activation of AMP- activated protein kinase induces c- Jun N- terminal kinase activation and apoptosis in liver cells. *FEBS Lett* 2002;526(1-3):38-42. doi: 10.1016/S0014-5793(02)03110-1

150. Kefas B, Cai Y, Ling Z, Heimberg H, Hue L, Pipeleers D, et al. AMP-activated protein kinase can induce apoptosis of insulin-producing MIN6 cells through stimulation of c-Jun-N-terminal kinase. *J Mol Endocrinol* 2003;30(2):151-61. doi: 10.1677/jme.0.0300151

151. Stefanelli C, Stanic' I, Bonavita F, Flamigni F, Pignatti C, Guarnieri C, et al. Inhibition of Glucocorticoid-Induced Apoptosis with 5-Aminoimidazole-4-carboxamide Ribonucleoside, a Cell-Permeable Activator of AMP-Activated Protein Kinase. *Biochem Biophys Res Commun* 1998;243(3):821-6. doi: 10.1006/bbrc.1998.8154

152. Culmsee C, Monnig J, Kemp BE, Mattson MP. AMP-Activated Protein Kinase is Highly Expressed in Neurons in the Developing Rat Brain and Promotes Neuronal Survival Following Glucose Deprivation. *J Mol Neurosci* 2001;17(1):45-58. doi: 10.1385/JMN:17:1:45

153. Russell RR, Li J, Coven DL, Pypaert M, Zechner C, Palmeri M, et al. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. *J Clin Invest* 2004;114(4):495-503. doi: 10.1172/JCI19297

154. Kim J, Park YJ, Jang Y, Kwon YH. AMPK activation inhibits apoptosis and tau hyperphosphorylation mediated by palmitate in SH-SY5Y cells. *Brain Res* 2011;1418:42-51. doi: 10.1016/j.brainres.2011.08.059

155. Shaw MM, Gurr WK, McCrimmon RJ, Schorderet DF, Sherwin RS. 5'AMP-activated protein kinase ? deficiency enhances stress-induced apoptosis in BHK and PC12 cells. *J Cell Mol Med* 2007;11(2):286-

Accepted Manuscript (unedited)

The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form.

98. doi: 10.1111/j.1582-4934.2007.00023.x

156. Eid AA, Ford BM, Block K, Kasinath BS, Gorin Y, Ghosh-Choudhury G, et al. AMP-activated Protein Kinase (AMPK) Negatively Regulates Nox4-dependent Activation of p53 and Epithelial Cell Apoptosis in Diabetes. *J Biol Chem* 2010;285(48):37503-12. doi: 10.1074/jbc.M110.136796

157. Liu L, Liu C, Fang L. AMPK‑SIRT1 pathway dysfunction contributes to neuron apoptosis and cognitive impairment induced by sevoflurane. *Mol Med Rep* 2020;23(1):56. doi: 10.3892/mmr.2020.11694

158. Wang Y, Tian M, Tan J, Pei X, Lu C, Xin Y, et al. Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin αVβ5/AMPK signaling pathway after intracerebral hemorrhage in mice. *J Neuroinflammation* 2022;19(1):82. doi: 10.1186/s12974-022-02438-6

159. Park JS, Choe K, Lee HJ, Park TJ, Kim MO. Neuroprotective effects of osmotin in Parkinson's disease-associated pathology via the AdipoR1/MAPK/AMPK/mTOR signaling pathways. *J Biomed Sci* 2023;30(1):66. doi: 10.1186/s12929-023-00961-z

160. Su J, Zhang J, Bao R, Xia C, Zhang Y, Zhu Z, et al. Mitochondrial dysfunction and apoptosis are attenuated through activation of AMPK/GSK-3β/PP2A pathway in Parkinson's disease. *Eur J Pharmacol* 2021;907:174202. doi: 10.1016/j.ejphar.2021.174202

161. Peixoto CA, Oliveira WH de, Araújo SM da R, Nunes AKS. AMPK activation: Role in the signaling pathways of neuroinflammation and neurodegeneration. *Exp Neurol* 2017;298:31-41. doi: 10.1016/j.expneurol.2017.08.013

162. Chen P, Wang Y, Chen L, Song N, Xie J. Apelin-13 Protects Dopaminergic Neurons against Rotenone—Induced Neurotoxicity through the AMPK/mTOR/ULK-1 Mediated Autophagy Activation. *Int J Mol Sci* 2020;21(21):8376. doi: 10.3390/ijms21218376

163. Chen M, Peng L, Gong P, Zheng X, Sun T, Zhang X, et al. Baicalein Induces Mitochondrial Autophagy to Prevent Parkinson's Disease in Rats via miR-30b and the SIRT1/AMPK/mTOR Pathway. *Front Neurol* 2022;12. doi: 10.3389/fneur.2021.646817

164. Wang H, Dou S, Zhu J, Shao Z, Wang C, Xu X, et al. Ghrelin protects against rotenone-induced cytotoxicity: Involvement of mitophagy and the AMPK/SIRT1/PGC1α pathway. *Neuropeptides* 2021;87:102134. doi: 10.1016/j.npep.2021.102134

165. Huang Y, Wu H, Hu Y, Zhou C, Wu J, Wu Y, et al. Puerarin Attenuates Oxidative Stress and Ferroptosis via AMPK/PGC1α/Nrf2 Pathway after Subarachnoid Hemorrhage in Rats. *Antioxidants* 2022;11(7):1259. doi: 10.3390/antiox11071259

166. de Gregorio E, Colell A, Morales A, Marí M. Relevance of SIRT1-NF-κB Axis as Therapeutic Target to Ameliorate Inflammation in Liver Disease. *Int J Mol Sci* 2020;21(11):3858. doi: 10.3390/ijms21113858

167. Yu J, Wang W na, Matei N, Li X, Pang J wei, Mo J, et al. Ezetimibe Attenuates Oxidative Stress and Neuroinflammation via the AMPK/Nrf2/TXNIP Pathway after MCAO in Rats. *Oxid Med Cell Longev* 2020;2020:1-14. doi: 10.1155/2020/4717258

168. Li J, Chen L, Qin Q, Wang D, Zhao J, Gao H, et al. Upregulated hexokinase 2 expression induces the apoptosis of dopaminergic neurons by promoting lactate production in Parkinson's disease. *Neurobiol Dis* 2022;163:105605. doi: 10.1016/j.nbd.2021.105605

169. Park JS, Choe K, Lee HJ, Park TJ, Kim MO. Neuroprotective effects of osmotin in Parkinson's disease-associated pathology via the AdipoR1/MAPK/AMPK/mTOR signaling pathways. *J Biomed Sci* 2023;30(1):66. doi: 10.1186/s12929-023-00961-z