Open Access

OBM Geriatrics

LIDSEN Publishing Inc.

Review

Emerging Roles of Signal Transduction Pathways in Neurodegenerative Diseases. Hunting New Possible Therapeutic Molecular Targets

Vincenza Rita Lo Vasco *

Department of Biomedical, Metabolic and Neural Sciences-Human Morphology Section, University of Modena and Reggio Emilia, Istituti Anatomici, Ed. M30, Policlinico Universitario di Modena, Largo del Pozzo, 71-41121, Modena, Italy; E-Mail: ritalovasco@hotmail.it

* **Correspondence:** Vincenza Rita Lo Vasco; E-Mail: ritalovasco@hotmail.it

Academic Editor: P. Hemachandra Reddy

Special Issue: Research in Neurodegenerative Diseases II

OBM Geriatrics
2023, volume 7, issue 2
doi:10.21926/obm.geriatr.2302234

Received: January 27, 2023
Accepted: April 26, 2023
Published: May 05, 2023

Abstract

Illnesses following the degeneration of the nervous system can occur due to aging or genetic mutations and represent a clinical concern. In neurodegenerative diseases, loss of neuronal structure and functions mainly causes cognitive impairment, representing an increasing social burden. In neurodegenerative diseases, the progressive loss of vulnerable populations of neurons in specific regions of the central nervous system was traced to different pathological events, such as misfolded proteins' accumulation, abnormalities in proteasomes or phagosomes, as well as anomalies in lysosomes or mitochondria. Many research efforts identified important events involved in neurodegeneration, but the complex pathogenesis of neurodegenerative diseases is far from being fully elucidated. More recently, insights into the signal transduction pathways acting in the nervous system contributed to unveiling some molecular mechanisms triggering neurodegeneration. Abnormalities in the intra- or inter-cellular signaling were described to be involved in the pathogenesis of neurodegenerative disease. Understanding the signal transduction pathways that impact the nervous system homeostasis can offer a wide panel of potential targets for modulating therapeutic

approaches. The present review will discuss the main signal transduction pathways involved in neurodegenerative disorders.

Keywords
Neurodegenerative diseases; signal transduction pathways; TGF β; WnT; Sirtuins; Nerf2; STING; MAPK; PI3K; cell cycle

1. Introduction

Neurodegenerative diseases (NDs) comprise different pathologies, which cause mortality and morbidity worldwide, especially in the elderly. NDs are heterogeneous in clinical manifestations, etiology and pathogenesis, but they may bear overlapping features, mainly neurodegeneration. In neurodegeneration, the number of neurons progressively and massively decreases, and neurons lose their peculiar structure and function [1], resulting in synapse dysfunction, abnormalities in the neural network, and deposition of abnormal variant proteins in the brain [2-5]. In many NDs, abnormal accumulation of misfolded peptides or proteins occurs in the central nervous system (CNS). These insoluble deposits accumulate with time, and especially affect aged neurons. The accumulation of abnormal protein deposits, including Aβ1–42 peptide, hyperphosphorylated Tau protein or α-synuclein, affects the complex neuronal and glial intracellular signal transduction pathways [1-4]. That results in abnormalities of the mitochondrial and lysosomal regulation, and of the stress response, as well as in autophagy, neuroinflammation, synaptic toxicity, or maladaptive innate immune response [3, 4]. However, the final cause of neuronal death is still unknown, and many risk factors were implicated. Although it is widely accepted that NDs are multifactorial diseases, dysregulation of selected signal transduction pathways and/or the cascade dysregulation of several interconnecting signaling pathways are emerging as common features of different NDs, offering new possible therapeutic targets. Several research reports suggested that NDs are multifactorial diseases. Over the years, several causes of etiology and/or events in the progression of the pathogenesis have been gradually attributed to NDs, including the hypothesis of the amyloid cascade, the role of Tau and neurofibrillary tangles (NFT), protein misfolding, predisposing genetic mutations, impaired neurotransmission and neurotrophic, neurotoxicity, neuroinflammation, mitochondria and endoplasmic reticulum dysfunctions, oxidative stress, proteasome or lysosome dysfunction and related autophagy, insulin and lipid metabolism abnormalities and related leptin neuroprotective effect, the role of the blood brain barrier (BBB), the involvement of the gut microbiota [6]. Interestingly, these factors often overlap and require several signal transduction pathways to be involved in all these events. The same is true for all these signal transduction pathways: overlap and interconnections can be identified and a large network of pathways is progressively recruited from the onset and during disease progression.

Aging is considered the main risk factor for developing ND. The worldwide incidence of NDs is progressively and inexorably increasing. Recent findings suggested that genetic predisposition and environmental factors contribute equally to increased risk of developing NDs. Moreover, in genetically predisposed people, the timing and extent of neurodegeneration depend on the environment [7-9]. Although different NDs share commonly identified disease mechanisms,

including abnormal protein aggregation and clearance, axonal degeneration, and altered immune response, no curative therapies have been developed. Most NDs usually progress without remission.

The diagnosis of ND is often difficult, especially when early symptoms occur. Moreover, the management of ND represents an increasing social and economic burden [10, 11], the personalized prognosis may be uncertain, and treatment is not effective [12]. Depending on the loss of specific neurons, NDs are featured by the progressive impairment of cognitive function, defective motor coordination, and increased pain sensitivity [13]. An ND can often be life-threatening, depending on the type and stage of the disease. Multiple aspects of daily activities and behavior can be affected, and basic tasks, such as speech, movement, stability, and balance are impaired. Also complicated tasks, such as cognitive abilities or bladder and bowel functions can be dramatically affected [1].

Most pharmacological treatments currently approved for managing NDs act upon the associated symptoms. The presence of the blood-brain barrier (BBB) affects the therapeutic approach. The BBB represents an efficient barrier protecting the brain from about 99% of foreign substances and towards selected putative successful management of ND [14]. Although successful treatment approaches with surgery and highly evasive techniques have limited clinical acceptance due to possible concerns about their long-term benefits for potential brain damage [14].

NDs such as Alzheimer's disease (AD), Parkinson's disease (PD) and dementia have increasingly become a clinical concern in older people [15, 16].

2. The Signal Transduction in Neurodegenerative Diseases

The neural stem cells (NSC) produce the majority of neurons during childhood, while the number of neurons progressively decreases in adulthood [17]. Neurodegeneration characterizes different illnesses, including AD, PD, prion disease, amyotrophic lateral sclerosis (ALS), motor neuron disease (MND), Huntington's disease, spinal muscular atrophies (SMA), and spinocerebellar ataxia (SCA) [18-22]. Several different pathologies may underline a single ND [23-26].

Although the hallmarks of some NDs, such as AD and PD, have been partially identified, the underlying mechanisms of disease development are far from fully elucidated. Several stimuli were demonstrated to trigger neurodegeneration, such as cell cycle activation, altered oxidative stress, and inflammation [27-30]. Specific genetic mutations have been identified in a few cases of familial AD and PD, as well as in genetically determined NDs, such as Huntington's disease, SCA and SMA [31-36].

Many research efforts identified important events involved in neurodegeneration, but the complex pathogenesis of NDs is far from being fully elucidated. Recently, a growing body of evidence has drawn attention to the response of neurons to control signal transducers, which may be abnormal due to molecular alterations in specific proteins/genes associated with signaling pathways. Signaling molecules are connected and form an intricate network, so alterations following abnormal protein production can disrupt the cascade of interactions in one or more pathways. Molecules belonging to the signaling pathways acting in neurons seem to play crucial functions in the appearance of features of NDs. Identifying or defining intra or inter-cellular signal transduction pathways are crucial to understand almost all biological processes, including cell growth, differentiation and migration, tissue organization, immune response, cancer initiation and development. Recent technological advancements improved the study of signal transduction in

measuring and manipulating signal transduction molecules, and in single-cell resolution modeling. Analyses of the crosstalk between the signaling molecules might lead to identifying molecular therapeutic targets, paving the way to promising new therapy approaches also for NDs.

The present review aims to provide a partial list of the main signaling pathways that could underlie NDs and briefly touch on the state of the art of their involvement and interconnections, in both *in vitro* and *in vivo* experimental models, as well as in affected patients. Some signal transduction pathways, the possible involvement in features of NDs, relationship with aging and misfolded proteins will be discussed, including TLRs, TGF β and neuroinflammation; Sirtuins, Nrf2, p53 and oxidative stress; STING–TBK1–IRF axis, PI3K/AKT/mTOR axis and autophagy; MAPK, Wnt, Notch and nervous development; the cell cycle pathway, Myc, Hippo pathway, Rho and cell cycle regulation.

3. TLRs

Toll-like receptors (TLRs) represent the converging point of the innate and adaptive immune system, and act as the immunity compartment in the nervous system, which can provide an immune response, unlike the absolute immunological privilege of the brain, as long since [37]. TLRs are expressed in neurons and macrophages resident in the nervous tissue [37]. In the CNS of both mice and humans, neurons and microglia express similarly the TLRs, but the expression differs in astrocytes, and oligodendrocytes [38, 39]. In the peripheral nervous system of both mice and humans, neurons and resident macrophages similarly express the TLRs. However, the expression differs in Schwann cells, which produce myelin as the oligodendrocytes [40].

TLRs can be activated in the absence of microbial infection [41] and contribute to the regulation of neurogenesis [42]. The transcription of TLR-codifying genes changes with aging [43]. Although not be completely reliable in the case of TLRs, the experimental models offered some interesting insights. Studies in murine models of AD, PD, ALS, Pick's disease, and olivopontocerebellar atrophy suggested the possible involvement of the TLR pathway, demonstrating high expression levels or upregulation of selected TLRs [43, 44].

In AD, glial activation of the innate immune response is an important event, and inflammatory response is concentrated around the sites of Aβ plaques deposition, where increased levels of pro-inflammatory cytokines, complement components and proteases are delivered probably by the activated astrocytes and microglia surrounding the plaque [44, 45]. Long-term treatment with non-steroidal anti-inflammatory drugs seems to reduce AD risk and to delay the clinical progression. Accordingly, in AD brains, the expression of TLRs is upregulated, both in experimental murine models and in AD patients [43, 46]. Moreover, activated glia expressing high TLR4 and TLR2 were observed to surround Aβ plaques [46].

In APP transgenic mice overexpressing the amyloid precursor protein (APP), a significant increase in the transcription of TLR4 was described [46]. Treatment of APP mice for 12 weeks with the inflammatory stimulus (lipopolysaccharide-LPS, which binds TLR4) induced high numbers of activated microglia and astrocytes in the neocortex and hippocampus and accumulation of aggregated amyloid-β (Aβ) in neurons neighboring the activated microglia [47]. Promising studies suggested that neurons expressing TLR4 are very sensitive to Aβ accumulation in AD [47].

Other reports suggested that activation of TLR4 and/or TLR 9 might be required for clearance of Aβ in AD [48-53]. It seems that Aβ can activate TLRs and mediate the activation of the microglia to

produce nitric oxide and TNF-α [54]. Accordingly, in mice bearing a mutation in TLR4, the stimulation of microglia and related production of cytokines by Aβ decreased, suggesting a functional role of TLR4 [46, 55].

The mechanism leading the TLR activation to determine Aβ clearance is not elucidated, nor is it clear whether Aβ-induced TLR activation promotes or inhibits AD progression. Clarifying this controversial point would be extremely useful, as the TLR signaling pathways represent a promising therapeutic target.

4. TGF β

The transforming growth factor β (TGF β) superfamily comprises of growth factors (GFs) including TGF β, activins, and bone morphogenetic proteins (BMPs). The complex TGF β pathway is involved in the regulation of pleiotropic physiological functions in cells [56]. In the early stages of cancer, TGF β induces apoptosis and cell-cycle arrest, acting *de facto* as a tumor suppressor. By contrast, in advanced stages of cancer, TGF β acts as a tumor promoter [57-59].

In the nervous tissue, the TGF β superfamily members are poorly expressed, although involved in the inflammation and repair after brain injury [60]. Astrocytes represent the main source of TGF β, while selected neurons express TGF β receptors [61]. Recent reports directly and indirectly suggested the involvement of TGF β in aging-related processes, including a gradual decline in physiological functions, impaired adaptability, and endurance of tissues and organs in a lifetime [62-64].

As a matter of fact, during aging the expression of TGF β-related molecules in the brain increases [65]. However, the role of the TGF β signaling is not fully understood and controversial observations were reported.

Some studies reported that TGF β a beneficial role in the onset of AD, PD, and other diseases, while other reports described detrimental effects. One might speculate that, similarly to cancer, TGF β could play a dual role depending on the context [60]. Abnormalities in the TGF β pathway were described in patients affected with neurodegenerative disorders. In the plasma of AD patients, TGF β was reduced, while in the cerebrospinal fluid it was increased [65-69].

Controversial reports were available in patients affected with Huntington's disease, as some investigations identified an increase in the plasmatic levels of TGF β [70]. In contrast, others reported a decrease in blood levels [68].

In AD brains, the TGF β pathway is co-expressed with Tau in neurons and tangles, promoting amyloid deposition [71].

In cortical and hippocampal neurons of transgenic TβRIIΔk-Fib mouse model of systemic sclerosis expressing the truncated TGF β type II receptor (TβRII) form, the overall activity of the pathway, triggering the neurodegenerative process, accounts for a reduced number of neurons, but a higher number of astrocytes [61].

Breeding of TβRIIΔk mice to AD mouse models enhanced the presence of Aβ plaques, due to increased levels of APP, thus corroborating the role of the TGF β pathway in AD.

Controversial reports could not highlight the role of TGF β. Administration of TGF β reduced plaque formation, and rescued the Aβ-induced cognitive impairment [72]. By contrast, the overexpression of TGF β induced the onset of amyloid deposition [73, 74]. In PD patients, TGF β seemed to have different implications, as it was increased in the brain [75]. The number of

dopaminergic cells was significantly reduced in transgenic mouse models lacking TGF β signaling [76].

Although controversial investigations reported opposite effects of TGF β, probably reduction/loss of this pathway in neurons is likely to affect age-related memory and cognitive impairment.

5. Sirtuins

Components of the silent mating-type information regulation proteins (sirtuins, SIRT) family are involved in many cell activities, including transcription, apoptosis, response activities to various stress stimuli from inflammation to low-calorie feeding conditions, and aging [77].

The Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and the NAD+-dependent deacetylase SIRT1 contribute to the mitochondrial biogenesis regulating the transcription of nucleus-encoded mitochondrial genes [78]. The PGC/SIRT signaling might belong to a more complex neural pathway regulated by micro-nutrients. SIRT1 responds to nutrient-sensitive changes in basal NAD+ levels [79]. Resveratrol, a SIRT1 activator, induces mitochondrial biogenesis and protects against metabolic decline [79]. In neurons, intracellular NAD+ levels play a crucial role in viability under chronic oxidative stress, and mitochondrial dysfunction by promoting oxidative phosphorylation (ATP production) [80-82]. In hippocampal AD neurons and in subcutaneous adipose mesenchymal M17 cells from APP mice, the levels of PGC-1α, nuclear respiratory factor (NRF) 1, and NRF2 were reported to be significantly reduced [83-85]. That suggested prolonged overexpression of PGC-1α was cytotoxic for dopaminergic neurons, and might be involved in neurodegeneration [86].

6. Nrf2

The Nuclear factor-erythroid factor 2-related factor 2 (Nrf2) covers different physiological cell functions in homeostasis maintenance and during proliferation. The Nrf2 signal transduction pathway is involved in the regulation of redox balance and antioxidant-related activities [87], in the metabolic reprogramming [88], in triggering proteasome degradation [89], and participates in the transcription of detoxification, antioxidant, metabolism, or proliferative genes [90, 91]. Abnormalities in Nrf2 were described in cancer progression and chemoresistance, in different tumor types [92-94].

The oxidative stress often underlies the pathogenic mechanisms in NDs [95-97]. The possible role of Nrf2 in neurodegeneration is becoming increasingly evident, since the oxidative damage response was described in the early stages of AD and PD [98-100]. Great interest arose in the antioxidant effects of Nrf2, as it was proposed as a possible therapeutic target. An interesting clue is represented by the different Nrf2 subcellular locations in the brains of AD-affected patients compared to the brains of PD patients. In hippocampal neurons from AD brains, Nrf2 staining was mainly cytoplasmic. By contrast, in PD dopaminergic cells, Nrf2 was mainly nuclear [98]. That suggested that in neurons under enhanced oxidative stress, Nrf2 translated to the nucleus, to induce the transcription of genes involved in the antioxidant response [98]. In AD brains, the cytoplasmic location of Nrf2 might indicate failure of neurons' acclimation to oxidative stress. In PD patients, dead dopaminergic cells did not show Nrf2 staining, but alive neurons probably maintain proper functions and Nrf2 remains in the nucleus [98].

In the hippocampus and cortex of experimental double transgenic APP/PS1 mouse models, which overexpress APP and presenilin 1 (PS1) gene mutation, the defective expression of Nrf2 and its downstream targets was observed contemporarily to the increase of Aβ aggregates [101-103]. Conversely, the overexpression of Nrf2 in APP/PS1 mice's hippocampus reduced the soluble Aβ and rescued or ameliorated the learning deficits [102]. Accordingly, in other AD murine models, loss of Nrf2 induced the same effects upon Aβ deposition, spatial learning, and memory [103].

Besides the oxidative stress, the involvement of Nrf2 in the progression of neurodegenerative disorders was linked to inflammation and autophagy, due to the interconnection with the p62 autophagy receptor, a multifunctional protein located throughout the cell, involved in proteasome degradation of ubiquitinated proteins [103, 104]. Interaction between p62 and Nrf2 acts as a positive feedback loop, as defective autophagy promotes the oxidative stress response and autophagy [105]. The imbalance of this complex homeostasis seems to be involved in the progression of neurodegeneration. Interestingly, a connection between TLR4 and Nrf2 was demonstrated, as Nrf2 regulates TLR4 innate responses in mouse liver ischemia/reperfusion injury via Akt/FOXO1 signaling network [105, 106]. Interesting perspectives were offered by the studies which analyze the Nrf2/TLR4/NF-κB signaling in an Aβ mouse model [106].

7. STING–TBK1–IRF

The stimulator of interferon genes (STING)-mediated type-I interferon/Tumor necrosis factor receptor-associated factor NF-κB activator-binding kinase 1 (TBK1)/Interferon regulatory factor-3 (IRF33) signal transduction pathway was recently involved in neurodegeneration. STING activates the type-I interferons (IFNs), pleiotropic cytokines involved in different nervous diseases [107-109]. Although controversial data were reported, STING is involved in triggering the innate immune response following microbial infections. The activity of STING is related to oxidative stress conditions, as during inflammatory activation of the nervous tissue, which can be involved in neurodegeneration.

In transgenic STING$^{-/-}$ mouse embryonic fibroblast (MEF) SV40 immortalized cells, activating the STING pathway induced by using H_2O_2 can play a protective role against cell death compared to the wild type. Lack of STING prevents the increase in autophagy flux probably due to impairment at the autophagosome-lysosomal fusion step [110]. That suggested a putative role for STING in the autophagy flux maintenance and protection from H_2O_2-induced cell death. The STING signal transduction pathway might play a complex role in the cellular mechanisms underlying to the pathogenesis of NDs related to the response to oxidative stress. Recently, the STING signaling pathway was suggested to represent a critical molecular link, predominantly in microglia, that might be involved in the pathogenesis of AD [111].

8. PI3K/AKT/mTOR

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway is involved in different cell activities, including survival, metabolism, differentiation, motility, and proliferation [112], and is actively studied in cancer [113-115]. Components of the PI3K pathway were described to be altered in NDs [116, 117].

Activation of the PI3K/AKT/mTOR signal transduction was described in AD and PD. In AD neurons, activation of AKT (phosphorylated AKT, pAKT) was observed, and upregulation, as well as peculiar

perinuclear location was described with no changes in total AKT levels [118]. By contrast, decreased PI3K/AKT pathway activation in AD brains was reported [119].

In PD brains, the activity of AKT decreased [120-123], and overexpression of AKT had a protective role in PD experimental mouse models [124-126].

Involvement of the AKT targets mTOR and Glycogen synthase kinase-3 beta (GSK3β) in autophagy, amyloid aggregation, and Tau phosphorylation was reported during the development of NDs [127]. The activated pAKT promotes the phosphorylation of either target, thus activating mTOR and repressing GSK3β [127]. In very early stages AD brains and in AD experimental models, mTOR increase occurs concurrently with a reduction of autophagy markers' expression, suggesting that abnormalities in autophagy are related to the PI3K/AKT/mTOR signaling [127]. In AD brains, GSK3β is crucial for the phosphorylation and consequent acitvation of Tau (pTau) [127, 128]. Increased Akt reduced the phosphorylation of Tau, but pTau levels are increased in the diseased brain, thus suggesting the involvement of components belonging to this signal transduction pathway in Tau pathologies [127].

9. MAPK

The complex mitogen-activated protein kinase (MAPK) superfamily comprises signaling families activated by receptor tyrosine kinases (TRKs), including MAPK/extracellular signal-regulated kinase (ERK), Big MAP kinase-1 (BMK-1), c-Jun N-terminal kinase (JNK), and protein 38 (p38) signaling families [129, 130]. MAPK overall represents the point of convergence of key molecules/pathways involved in cell proliferation, growth, and survival [131]. Due to the wide network in which the MAPK pathway is involved, it is frequently altered in cancer [132].

The complex MAPK signaling plays an important role in the nervous system. In the brain, MAPK is directly or indirectly involved in the genesis of both neurons and glial cells, and in synaptic transmission, thus affecting the cognitive processes [133]. ERK, p38, and JNK are involved in striatal dopaminergic neurons's survival and the overall dopaminergic signaling [134].

Abnormalities of one branch of MAPK promote changes in cognition and learning [135]. In the brains of AD and PD patients, the levels of phosphorylated MAPK1 and phosphorylated ERK were higher compared to normal controls [136-139]. Also in AD or PD experimental models, different components of the MAPK signaling pathways were upregulated [140]. In early-stage AD, phosphorylated p38 was upregulated [141, 142]. JNKs increased in AD brains and CSF, and were suggested to be involved in the dopaminergic cell loss featuring PD [143]. In AD brains, selected members of MAPK signaling co-expressed in neurofibrillary tangles (NFTs), aggregates of hyperphosphorylated Tau protein, and senile plaques. In experimental AD models, the pharmacological or transgenic ablation of pERK, p38 and JNK rescued the cognitive impairment associated with reducing Aβ levels [144-147].

The expression of APP was related to the activity of MAPK. In fact, in an AD model, the deposition of Aβ was reduced when loss of p38 occurs associated with reduced β-secretase activity [146]. Also the inhibition of JNK is associated with the reduction of plaques in the cortex and hippocampus, decrease of secretase activity, and expression of phosphorylated APP, thus ameliorating the working memory [146].

In experimental pharmacological models of PD, abnormal expression of the most important MAPK pathways was described [134, 146]. Ablation of JNK2 had a protective role against the 1-

methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model, [134], and pharmacological blocking of JNK3 mitigates the MPTP-induced dopaminergic cell loss [143]. In glial cells, the presence of α-synuclein induced the expression of p38, ERK, and JNK [148]. Damaged neurons released α-synuclein, triggering the microglia's pro-inflammatory response [149].

In experimental models of Huntington's disease, increased levels of phosphorylated p38 and JNK were described in the striatum, and mutations in the huntingtin gene (HTT) affected MAPK and activated this pathway [150, 151].

10. Wnt

The Wingless-related integration site (Wnt)/β-catenin pathway regulates crucial events including gene stability, cell differentiation, proliferation, apoptosis, migration, and stem cell renewal [152-154].

The 19 mammalian Wnt proteins bind to frizzled receptors and lipoprotein receptor-related protein (LRP) co-receptors. The binding of Wnt to its receptors suppresses the β-catenin destruction complex, composed of adenomatous polyposis coli (APC), Axin, casein kinase 1α (CK1α), GSK3β, and free β-catenin. The nuclear translation of β-catenin promotes the transcription of proliferation-related genes [155-157]. Cytoplasmic β-catenin might form a complex with adherent junctions, promoting cell adhesion. Abnormalities in the Wnt/β-catenin pathway were described in all the stages of cancer transformation, including initiation, progression, metastasis spread, and cancer stem cell activation [153, 158-161].

The Wnt signal transduction pathway acts during brain development. Wnt proteins are involved in neurogenesis, and synapse development and activity [162]. The Wnt pathway is interconnected with several downstream signaling pathways, indirectly acting upon gene transcription and cytoskeleton modifications [162]. The role of the Wnt pathway in the mature brain is not fully highlighted [163, 164]. However, several reports demonstrated that components of this pathway might be altered in age-related disorders and linked to aggregates deposition in NDs, including AD [165].

The extracellular ligand of Wnt receptors, Dickkopf-1 (DKK1), a negative regulator of the pathway, is highly expressed in cortical neurons of the diseased brain [166, 167]. The co-receptor LRP6 was demonstrated to be downregulated in the temporal cortex of AD brains. This downregulation occurs contemporarily to a decrease in the expression of β-catenin, and to a less efficient translocation to the nucleus [168].

In different experimental animal models of amyloid deposition and tau pathology, increased expression of DKK1 was identified, accompanied by reduced levels of β-catenin. Impairment of the Wnt signal transduction pathway enhances amyloid deposition [167].

Dysregulation of genes regulated by the Wnt pathway was also described in PD brains [167, 169], and the effects upon the dopaminergic cell loss might be linked to the role of Wnt in synapse formation and cell regeneration.

Interestingly, controversial literature data reported that the non-canonical Wnt signal transduction might play an opposite role, protecting mitochondria from fission-fusion alterations occurring in AD [170], an especially critical event for the crucial energy metabolism in neurons. In NDs, abnormalities of mitochondria morphology and functions were described, including structure alterations, deregulation of enzymatic activities, increased oxidative stress, and rising levels of Aβ.

That suggested a new approach, supporting the hypothesis that the mitochondria and related signaling pathways might represent a possible therapeutic target for NDs, probably during the disease's initiation and progression [170].

11. Notch

The Notch pathway involves several physiological events, including cell proliferation, differentiation, and angiogenesis [171-173]. Notch acts depending on the context [174, 175], and was described as involved in tumors [176-179]. Notch signaling regulates neurogenesis, neural maturation, and synaptic plasticity [180].

In the nervous tissue, Notch and related ligands were suggested to be also involved in NDs [181, 182], with special regard to AD. Notch was demonstrated to play a role in forming Aβ plaques [183, 184]. Notch was abnormally expressed in the brains of AD patients [185, 186], and colocalized with PSs [187, 188]. In the brains of AD patients, the expression of Notch increased due to the aggregation in plaque-like structures [189], probably involving the pro-inflammatory response. The Notch- and Aβ-positive plaques were invaded by microglia and astrocytes, suggesting that the delocalization of Notch might activate the pro-inflammatory response [189].

The accumulation of Notch in plaque-like structure in the brain parenchyma probably reduced the filtration to the cerebrospinal fluid [184]. In fact, in the cerebrospinal fluid of patients affected with AD, the Notch expression was lower than normal controls [184].

12. Cell Cycle Pathway

The complex process that governs the duplication of the genetic material and cell division through the cell lifetime is governed by the peculiar cell cycle pathway [190], which is highly regulated to avoid the transmission of genetic abnormalities to daughter cell clones.

Accurate checkpoints regulate the ordered progression of the cell cycle, arresting the cycle, when required, promoting DNA repair or, in case of unrepairable damage, leading to cell death.

The progression through the four phases of the cell cycle is strictly regulated by the alternate phosphorylation/dephosphorylation of cyclin-dependent kinases (CDKs) and cyclin proteins, which are actively studied in cancer [190-192].

Neurons usually do not undergo mitosis, but abnormal regulation of the cell cycle pathway was described in degenerated neurons [191, 193, 194]. Abnormal DNA replication allows neurons to re-enter the cell cycle, but the failure to divide can promote the development or progression of neurological disorders.

In the brains of patients affected with NDs, including AD, PD, Huntington’s disease and ALS, abnormal expression has been described in different cell cycle components, such as cyclins, CDKs, and related genes [195].

Depending on the brain region, some cell cycle components were upregulated in AD, such as proliferating cell nuclear antigen (PCNA), cyclin B, CDK4, CDK5 and related CDK activators [195-197].

In the hippocampus of both AD patients and murine AD models, the expression of an S/G2/M marker was increased [194]. Induction of Aβ accumulation in the brain of experimental AD models promoted gene expression in the cell cycle re-entry [194].

The rapid re-entering into the cell cycle seemed to gain protective effects against amyloid-induced neuronal death [194]. Moreover, cell cycle components are indirectly involved in the

hyperphosphorylation of Tau, which is implicated in the dysregulation of the cell cycle in AD [198]. As an interesting perspective, the dysregulation of the cell cycle was studied as a possible therapeutic target for AD. The pharmacological inhibition of cell cycle-related genes, such as the modulation of the abnormal activity of CDK5, rescued symptoms in AD murine models [197].

In PD, PCNA, retinoblastoma protein (Rb), CDK2 and CDK5 were abnormally expressed [199]. In Huntington's disease, increased levels of cyclin D1 [199], inducing the expression of the normal Htt gene in YAC-18 experimental models of Huntington's disease, lead to the re-entry of neurons in the cell cycle, and induced reactive neuroblastomas [200].

In experimental PD models, neurons also present the cell cycle pathway dysregulation. In dopaminergic PD neurons, treatment with MPTP induces the expression and activity of CDK5, while pharmacological inhibition attenuates the MPTP-induced dopamine cell loss. Also the expression of cyclin B is enhanced by overexpression of α-synuclein [201, 202].

13. Myc

The Myc family comprises regulator genes and proto-oncogenes, consisting of three related paralog human genes, namely c-MYC, n-MYC and l-MYC [203, 204]. The overall structure and organization of the Myc family members are very similar. The MYC family member c-Myc [205] is a transcription factor crucial to many cell functions, including cell growth and metabolism, proliferation, and apoptosis. The activity of c-Myc is tightly related to other pathways, including the Ras/Phosphoinositide 3-kinase (PI3K)/AKT/GSK3, Ras/Raf/ERK, and Wnt pathways [206-210]. Dysregulation of Myc was described in the tumorigenesis or progression of different cancers [211-216].

In NDs, the possible role of Myc was related to cell cycle re-entry in both the onset and development of AD and other NDs [217]. Dysregulation of Myc members was described in the brains of AD and Huntington's disease patients [218, 219].

Interestingly, the expression of n-Myc was reduced in AD brains [218], while in Huntington's disease c-Myc expression was affected [219]. In PD brains no differences in the expression pattern of Myc members were observed [219].

In the AD hippocampus, no differences were reported in total c-Myc expression, while the phosphorylation state was abnormal [219]. In AD, Pick's disease, and other NDs, phosphorylated c-Myc was detected in neurons positive for NFTs and around senile plaques [219]. In both the human AD brain and in the brain of the murine tg-arcswe AD model, which overexpresses human APP and featured by perivascular and neuropil-confined plaques, the transcript levels of the gene encoding for c-Myc were enhanced [220].

By using the CaMKII-Myc transgenic mouse, conditionally expressing c-Myc in neurons, the increased expression of c-Myc induced neuronal loss in the hippocampus and memory impairment [221]. In the hippocampus of AD patients, the Neuregulin 2, codified by the n-Myc downstream-regulated *NDRG2* gene (OMIM * 603818), a cell stress response gene primarily expressed in astrocytes, were increased compared to normal controls [222].

In pharmacological and genetic murine models of AD, knockout of *Ndgr2* worsened the AD-like phenotype [223], and induced downregulation of the proteasome activity. Moreover, enhanced expression levels of *NRG2* were related to the increased APP, triggering the presence of Aβ plaques [223].

14. p53

The protein p53 is mainly involved in the cell response to stress, including DNA damage, ribosomal stress, telomere erosion, hypoxia, and oxidative stress [224, 225], and its role as a tumor suppressor is well known.

In NDs, the levels of p53 are not altered, but the protein's location differs [226-230].

In AD and PD brains, p53 and its phosphorylated form (p-p53) are located in the cytoplasm, while in control brains both are located in the nucleus [230]. Probably, abnormal neuronal cytoplasm-nucleus transport depends on the presence of p53 aggregates, and destabilization of the organization of cytoskeletal microtubules in the perinuclear area occurs. The abnormal cytoplasmic location of p53 in NDs' neurons was related to both tau and amyloid pathologies, as p53 interacts with Tau and PS1.

In AD experimental models, APP, Tau, and PS1 expression can modulate the levels of p53. In the brains of PS- or βAPP-deficient mice, lack of PS1 or APP reduced the expression of p53 [231]. In AD, p53 correlated to the transcription of *PSEN1* (OMIM *104311), the gene which codifies for PS1, while in PD reduced the transcription of genes codifying for Parkin (*PRKN*; OMIM *602544) and α-synuclein, (*SNCA*; OMIM *163890) probably with a reciprocal regulatory loop [232, 233].

In the brains of patients affected with Huntington's disease, p53 levels were high, and its expression positively correlated with the severity of clinical manifestations [234]. As p53 binds huntingtin, in experimental $Hdh^{Q140/Q140}$ mouse models, overexpressing mutant forms of the gene which codifies for huntingtin (*Htt*; MGI 96067), the deletion of p53 seemed to rescue the neurodegeneration and behavioral abnormalities [234, 235].

In DAT-p53KO mouse PD experimental models, deleting p53 in dopaminergic neurons had a protective role from the MPTP-induced neurodegeneration, ameliorating motor coordination [236].

15. Hippo

Hippo signaling (or Salvador-Warts-Hippo-SWH pathway) is an evolutionarily highly conserved pathway, identified as a regulator of organ size. Organ growth relies on several processes, including division and apoptosis. The name derives from the protein kinase Hippo (Hpo), a key signaling component of the pathway in Drosophila. Mutations in the *hop* (FlyBase CG11228), a gene that codifies for Hpo, result in tumor tissue overgrowth (hippopotamus-like phenotype) [237]. Hippo signaling involved many processes, including cell differentiation, tissue regeneration, and mechanic transduction [238-240].

The Hippo pathway activates the mammalian sterile 20-like kinases 1 and 2 (MST1/2), which in turn phosphorylates the complex formed by Yes-associated protein (YAP) and Trascriptional Coactivator with PDZ-bindin Coactivator with PDZ-binding motif (TAZ), involved in different regulating mechanisms, including those regulating the angiogenesis [241]. The transcriptional co-activators YAP/TAZ are activated by modifications of the subcellular localization and of the structure stability by phosphorylating upstream kinases, such as Large tumor suppressor 1 (LATS1) and 2 kinases (LATS2) [242]. Phosphorylated YAP remains in the cytoplasm, marked for proteasome degradation. Non-phosphorylated YAP translates to the nucleus, where it interacts with different transcription factors triggering the transcription of different genes involved in cell proliferation and survival [239, 243].

Both inactivation of the Hippo pathway and/or constitutive activation of YAP leading to YAP overexpression and nuclear location have been reported. Also the aberrant location of YAP promotes the transcription, especially of genes involved in metastasis spreading, in favoring the maintenance of the tumor microenvironment, or anti-apoptosis genes [244, 245].

The Hippo pathway-related genes were down-regulated in different regions of the brains of patients affected with AD [246, 247]. In AD experimental models, the transcription of YAP is downregulated early. The intracellular localization of YAP was abnormal in the brains of patients both affected with AD and presenting with mild cognitive impairment (MCI) [248]. In cortical neurons, the Aβ complex sequestrates YAP, increasing the cytoplasmic levels and contemporarily reducing the nuclear levels.

In experimental AD models, YAP was identified in the cytoplasm even before the onset of symptoms [248]. Moreover, overexpression of YAP increased the levels of nuclear YAP, reducing extracellular Aβ plaques, and ameliorating some behavioral parameters in experimental models [248].

Although the greatest interest arose about the role of the Hippo pathway in cancer, it has been well-studied in the developing brain and, more recently, in the adult brain for the possible involvement in neurodegeneration [249, 250].

Changes in YAP location were detected in the brains of patients affected with Huntington's disease [251]. In cortical neurons from Huntington's disease brain, YAP is mainly localized in the cytoplasm. In experimental $Hdh^{Q111/Q111}$ murine models of Huntington's disease, high levels of total YAP and phosphorylated YAP, the inactive form, were detected in the striatum and cortex [251].

The cytoplasmic localization of YAP in the neurons of AD and of Huntington's disease patients seems to be related to the so-called TEA domain (TEAD)-YAP dependent necrosis (TRIAD), described in different experimental models of NDs [252]. TRIAD is characterized by enlargement (ballooning) of the endoplasmic reticulum (ER), probably driven by the presence of YAP in the cytoplasm. The morphology of the ER can be reversed by YAP overexpression [248].

Also further components belonging to the Hippo pathway, such as MST1 and LATS1/2, were suggested to be involved in the progression of NDs [253, 254].

Abnormally high levels of phospho-MST1 were reported in the motor neurons of the spinal cord of ALS patients and in experimental models [171]. In PD, MST1 is involved in the loss of dopaminergic neurons.

The Activated MST1 acts upon the Uncoordinated 5 Homolog B receptor (UNC5B), a pro-apoptotic netrin family receptor, inducing motor dysfunctions and reduction of dopaminergic cell number in the *substantia nigra* [253]. Also MST1 was overexpressed in the brains of patients with Huntington's disease [248].

16. Rho

The small GTPase of the Rho family Ras homolog gene family member A (RhoA) and related downstream effector proteins regulate multiple signal transduction pathways in many cellular functions. The RhoA complex is abundantly expressed in the nervous system, and recent evidence suggested the involvement of aberrant RhoA signaling in NDs [255].

In the substantia nigra of mice treated with MPTP, upregulation of RhoA and Rho-associated protein kinase (ROCK) was observed [256]. In both neurons' cultures and murine models, the

inhibition of ROCK seems to play a neuroprotective effect from the MPTP-induced dopaminergic cell death [256, 257], probably due to the inhibition of the MPTP-induced microglial inflammatory response [258, 259].

The RhoA pathway is increased in human stem cell-derived neurons bearing mutations in the Parkinson's disease 2 (*PARK2*; OMIM #600116*)* gene. In PARK2 knockout neurons, an increase in the activity of RhoA modified the migration and reduced the formation of neurites, rescued by using the RhoA inhibitor Rhosin [260]. Also in cultured neurons both hippocampal and dopaminergic treated with the neurotoxic pesticide rotenone, the activity of RhoA was increased and associated with reduced neurite outgrowth, rescued by using the ROCK inhibitor Y27632 [261]. In primary mouse mesencephalic cultures, rotenone increased the activity of RhoA. By contrast, the inhibition of RhoA using C3 transferase or Simvastatin protected the dopaminergic neurons against the effects of rotenone [262]. In this perspective, RhoA signaling represents a promising target for the therapy of neuritic and axonal degeneration, one of the earliest features of PD [263].

In MN9D dopaminergic neurons, derived by the fusion of embryonic ventral mesencephalic and neuroblastoma cells, the inhibition of RhoA reduced the expression of α-synuclein by reducing the Serum response factor (SRF), a ubiquitous nuclear transcription factor [264]. In dopaminergic neurons and in PC12 pheochromocytoma-derived cells, the inhibition of RhoA by using the microRNA miR-133b, which is involved in the maturation and function of midbrain dopaminergic neurons within a negative feedback loop, attenuated MPTP-induced upregulation of α-synuclein, reducing the axon degeneration [265]. In vivo experiments in a transgenic murine model expressing human α-synuclein bearing the missense A53T mutation associated with PD, the inhibition of ROCK mediated by the ROCK inhibitor Fasudil reduced the aggregation of α-synuclein, ameliorating motor and cognitive functions [266]. In SH-SY5Y neuroblastoma-derived cells overexpressing A53T, Fasudil induced α-synuclein clearance by activating autophagy via the JNK/Bcl-2/Beclin 1/Vps34 pathway [267]. In the microglia, integrin CD11b mediates α-synuclein-induced production of reactive oxygen species (ROS) through a Rho-dependent pathway involving the nicotinamide adenine dinucleotide phosphate [NADPH] oxidase (NOX) [268].

In MPTP-treated PC12 cells and in an MPTP murine model, the treatment with Y27632 rescued the aberrant mitochondrial fission and apoptosis mediated by Dynamin-related protein 1 (Drp1) [269].

Recent evidence demonstrated that inhibition of ROCK enhanced Parkin recruitment to damaged mitochondria, promoting the removal of damaged mitochondria from the cells [269-274].

In the substantia nigra and striatum of 6-hydroxydopamine lesioned rats with a dyskinesia rat model of PD, RhoA and ROCK increased. At the same time, Fasudil prevented L-DOPA-induced dyskinesia or inhibited the already established dyskinesia, thus affecting the therapeutic effect of L-DOPA [275]. Also in PD, the pathway of RhoA might represent a possible target for a new therapeutic approach for more advanced stages of the disease.

17. Conclusions

The cognitive and physical decline of patients with NDs represents an economic and social burden, as well as an enormous psychological burden for the patients' families. Many research efforts identified important events involved in neurodegeneration, but the complex pathogenesis of NDs is far from being fully elucidated. The death of neurons is the main feature of NDs. Two large

and ambitious lines of research have emerged: the first aims at avoiding neuronal death, and the second aims at neurogenesis.

Concerning the first objective, unraveling the numerous and complex intracellular mechanisms that lead to the death of neurons could slow down or, very optimistically, block this event. More recently, insights into the signal transduction pathways acting in the nervous system contributed to unveiling molecular mechanisms triggering neurodegeneration. Intra- or inter-cellular signaling was indicated as a crucial player in the pathogenesis of NDs, whose ever-growing list needs continuous updates. Effectors and/or components of the signaling pathways were identified to be involved in the progression, and probably also in the initiation, of NDs. The extensive and complex cross-talk among the signal transduction pathways acting in the nervous system and the alterations/dysregulation occurring at the onset or during the progression of NDs make it difficult to understand the mechanisms underlying physiological and pathological events. Although many efforts have been made to obtain an overall and global view of the pathogenesis of NDs, this is still far from being achieved. Surely the recent advances in signal transduction in the nervous system, both normal and pathological, have increased the knowledge in the field. Identifying all signal transduction pathways recruited in the nervous system and of the crossing points could represent a promising starting point for a better understanding of the mechanisms underlying the pathogenesis of NDs.

Currently, the signaling pathways underlying or contributing to NDs were not fully identified, and the signal transduction events perturbed in NDs have not been fully recognized. Understanding the complex signal transduction pathways and cascade interconnections that impact the nervous system homeostasis might improve our understanding of nervous system development. Likewise, in-depth and complete knowledge of alterations of signal transduction molecules occurring in NDs might offer promising insights for the understanding of the mechanisms related to the initiation and/or progression of neurodegeneration and, as far as one can see, might pave the way for a wide panel of putative targets for the modulation of therapeutic approach, improving current therapies.

Acknowledgments

The author wishes to thank Dr Filip Hoibakk for English language editing.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

References

1. Przedborski S, Vila M, Jackson-Lewis V. Series introduction: Neurodegeneration: What is it and where are we? J Clin Investig. 2003; 111: 3-10.
2. Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK, et al. Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron. 2010; 68: 1067-1081.

3. Milnerwood AJ, Raymond LA. Early synaptic pathophysiology in neurodegeneration: Insights from Huntington's disease. Trends Neurosci. 2010; 33: 513-523.
4. Scott DA, Tabarean I, Tang Y, Cartier A, Masliah E, Roy S. A pathologic cascade leading to synaptic dysfunction in α-synuclein-induced neurodegeneration. J Neurosci. 2010; 30: 8083-8095.
5. Kovacs GG. Molecular pathology of neurodegenerative diseases: Principles and practice. J Clin Pathol. 2019; 72: 725-735.
6. Gadhave K, Kumar D, Uversky VN, Giri R. A multitude of signaling pathways associated with Alzheimer's disease and their roles in AD pathogenesis and therapy. Med Res Rev. 2021; 41: 2689-2745.
7. Jain V, Baitharu I, Barhwal K, Prasad D, Singh SB, Ilavazhagan G. Enriched environment prevents hypobaric hypoxia induced neurodegeneration and is independent of antioxidant signaling. Cell Mol Neurobiol. 2012; 32: 599-611.
8. Jain N, Chen-Plotkin AS. Genetic modifiers in neurodegeneration. Curr Genet Med Rep. 2018; 6: 11-19.
9. Liu H, Hu Y, Zhang Y, Zhang H, Gao S, Wang L, et al. Mendelian randomization highlights significant difference and genetic heterogeneity in clinically diagnosed Alzheimer's disease GWAS and self-report proxy phenotype GWAX. Alzheimer's Res Ther. 2022; 14: 17.
10. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurosci. 2019; 15: 565-581.
11. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol. 2019; 18: 459-480.
12. Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2018; 10: a033118.
13. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2017; 9: a028035.
14. Lamptey RN, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A review of the common neurodegenerative disorders: Current therapeutic approaches and the potential role of nanotherapeutics. Int J Mol Sci. 2022; 23: 1851.
15. Choonara YE, Pillay V, Du Toit LC, Modi G, Naidoo D, Ndesendo VM, et al. Trends in the molecular pathogenesis and clinical therapeutics of common neurodegenerative disorders. Int J Mol Sci. 2009; 10: 2510-2557.
16. Rapp T, Chauvin P, Costa N, Molinier L. Health economic considerations in neurodegenerative disorders. In: Imaging in neurodegenerative disorders. Oxford: Oxford University Press; 2015. p. 42.
17. Ganat YM, Silbereis J, Cave C, Ngu H, Anderson GM, Ohkubo Y, et al. Early postnatal astroglial cells produce multilineage precursors and neural stem cells in vivo. J Neurosci. 2006; 26: 8609-8621.
18. Martin JB. Molecular basis of the neurodegenerative disorders. N Engl J Med. 1999; 340: 1970-1980.
19. Mattson MP. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol. 2000; 1: 120-130.

20. Hague S, Klaffke S, Bandmann O. Neurodegenerative disorders: Parkinson's disease and Huntington's disease. J Neurol Neurosurg Psychiatry. 2005; 76: 1058-1063.
21. Harding BN, Kariya S, Monani UR, Chung WK, Benton M, Yum SW, et al. Spectrum of neuropathophysiology in spinal muscular atrophy type I. J Neuropathol Exp Neurol. 2015; 74: 15-24.
22. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers. 2019; 5: 24.
23. Esch T, Stefano GB, Fricchione GL, Benson H. The role of stress in neurodegenerative diseases and mental disorders. Neuro Endocrinol Lett. 2002; 23: 199-208.
24. Brouwer-DudokdeWit AC, Savenije A, Zoeteweij MW, Maat-Kievit A, Tibben A. A hereditary disorder in the family and the family life cycle: Huntington disease as a paradigm. Fam Process. 2002; 41: 677-692.
25. Allan SM, Rothwell NJ. Inflammation in central nervous system injury. Philos Trans R Soc B. 2003; 358: 1669-1677.
26. Liu Z, Zhou T, Ziegler AC, Dimitrion P, Zuo L. Oxidative stress in neurodegenerative diseases: From molecular mechanisms to clinical applications. Oxid Med Cell Longev. 2017; 2017: 2525967.
27. Klein JA, Ackerman SL. Oxidative stress, cell cycle, and neurodegeneration. J Clin Investig. 2003; 111: 785-793.
28. Antony PM, Diederich NJ, Krüger R, Balling R. The hallmarks of Parkinson's disease. FEBS J. 2013; 280: 5981-5993.
29. Bloom G. Amyloid-β and tau: The trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 2014; 71: 505-508.
30. Gkekas I, Gioran A, Boziki MK, Grigoriadis N, Chondrogianni N, Petrakis S. Oxidative stress and neurodegeneration: Interconnected processes in polyQ diseases. Antioxidants. 2021; 10: 1450.
31. Bates GP. The molecular genetics of Huntington disease-a history. Nat Rev Genet. 2005; 6: 766-773.
32. Kiernan M, Vucic S, Cheah B, Turner M, Eisen A, Hardiman O, et al. Amyotrophic lateral sclerosis. Lancet. 2011; 377: 942-955.
33. Tanzi RE. The genetics of alzheimer disease. Cold Spring Harb Perspect Med. 2012; 2: a006296.
34. Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. Nat Neurosci. 2014; 17: 17-23.
35. Bocchetta M, Iglesias JE, Cash DM, Warren JD, Rohrer JD. Amygdala subnuclei are differentially affected in the different genetic and pathological forms of frontotemporal dementia. Alzheimers Dement. 2019; 11: 136-141.
36. Aasly JO. Long-term outcomes of genetic parkinson's disease. J Mov Disord. 2020; 13: 81-96.
37. Kawasaki T, Kawai T. Toll-like receptor signaling pathways. Front Immunol. 2014; 5: 461.
38. Goethals S, Ydens E, Timmerman V, Janssens S. Toll-like receptor expression in the peripheral nerve. Glia. 2010; 58: 1701-1709.
39. Barajon I, Serrao G, Arnaboldi F, Opizzi E, Ripamonti G, Balsari A, et al. Toll-like receptors 3, 4, and 7 are expressed in the enteric nervous system and dorsal root ganglia. J Histochem Cytochem. 2009; 57: 1013-1023.
40. McKimmie CS, Fazakerley JK. In response to pathogens, glial cells dynamically and differentially regulate Toll-like receptor gene expression. J Neuroimmunol. 2005; 169: 116-125.

41. Zhang Z, Schluesener H. Mammalian toll-like receptors: From endogenous ligands to tissue regeneration. Cell Mol Life Sci. 2006; 63: 2901-2907.
42. Rolls A, Shechter R, London A, Ziv Y, Ronen A, Levy R, et al. Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol. 2007; 9: 1081-1088.
43. Bsibsi M, Ravid R, Gveric D, van Noort JM. Broad expression of Toll-like receptors in the human central nervous system. J Neuropathol Exp Neurol. 2002; 61: 1013-1021.
44. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000; 21: 383-421.
45. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology. 1997; 48: 626-632.
46. Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, et al. Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. Cell Physiol Biochem. 2007; 20: 947-956.
47. Sheng JG, Bora SH, Xu G, Borchelt DR, Price DL, Koliatsos VE. Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid β peptide in APPswe transgenic mice. Neurobiol Dis. 2003; 14: 133-145.
48. DiCarlo G, Wilcock D, Henderson D, Gordon M, Morgan D. Intrahippocampal LPS injections reduce Aβ load in APP + PS1 transgenic mice. Neurobiol Aging. 2001; 22: 1007-1012.
49. Herber DL, Mercer M, Roth LM, Symmonds K, Maloney J, Wilson N, et al. Microglial activation is required for Aβ clearance after intracranial injection of lipopolysaccharide in APP transgenic mice. J Neuroimmune Pharmacol. 2007; 2: 222-231.
50. Tahara K, Kim H, Jin J, Maxwell J, Li L, Fukuchi K. Role of Toll-like receptor signalling in Aβ uptake and clearance. Brain. 2006; 129: 3006-3019.
51. Chen K, Iribarren P, Hu J, Chen J, Gong W, Cho EH, et al. Activation of Toll-like receptor 2 on microglia promotes cell uptake of Alzheimer disease-associated amyloid β peptide. J Biol Chem. 2006; 281: 3651-3659.
52. Prat A, Antel J. Pathogenesis of multiple sclerosis. Curr Opin Neurobiol. 2005; 18: 225-230.
53. Prinz M, Garbe F, Schmidt H, Mildner A, Gutcher I, Wolter K, et al. Innate immunity mediated by TLR9 modulates pathogenicity in an animal model of multiple sclerosis. J Clin Investig. 2006; 116: 456-464.
54. Lotz M, Ebert S, Esselmann H, Iliev AI, Prinz M, Wiazewicz N, et al. Amyloid beta peptide 1–40 enhances the action of Toll-like receptor-2 and-4 agonists but antagonizes Toll-like receptor-9-induced inflammation in primary mouse microglial cell cultures. J Neurochem. 2005; 94: 289-298.
55. Jin JJ, Kim HD, Maxwell JA, Li L, Fukuchi Ki. Toll-like receptor 4-dependent upregulation of cytokines in a transgenic mouse model of Alzheimer's disease. J Neuroinflammation. 2008; 5: 23.
56. David CJ, Massagué J. Contextual determinants of TGFβ action in development, immunity and cancer. Nat Rev Mol Cell Biol. 2018; 19: 419-435.
57. Wakefield LM, Roberts AB. TGF-β signaling: Positive and negative effects on tumorigenesis. Curr Opin Genet Dev. 2002; 12: 22-29.
58. Tang B, Vu M, Booker T, Santner SJ, Miller FR, Anver MR, et al. TGF-β switches from tumor suppressor to prometastatic factor in a model of breast cancer progression. J Clin Investig. 2003; 112: 1116-1124.

59. Ikushima H, Miyazono K. TGFβ signalling: A complex web in cancer progression. Nat Rev Cancer. 2010; 10: 415-424.
60. Kashima R, Hata A. The role of TGF-β superfamily signaling in neurological disorders. Acta Biochim Biophys Sin. 2018; 50: 106-120.
61. Tesseur I, Zou K, Esposito L, Bard F, Berber E, Van Can J, et al. Deficiency in neuronal TGF-β signaling promotes neurodegeneration and Alzheimer's pathology. J Clin Investig. 2006; 116: 3060-3069.
62. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153: 1194-1217.
63. He S, Sharpless NE. Senescence in health and disease. Cell. 2017; 169: 1000-1011.
64. Tominaga K, Suzuki HI. TGF-β signaling in cellular senescence and aging-related pathology. Int J Mol Sci. 2019; 20: 5002.
65. Von Bernhardi R, Cornejo F, Parada G, Eugenin J. Role of TGFβ signaling in the pathogenesis of Alzheimer's disease. Front Cell Neurosci. 2015; 9: 426.
66. Burton T, Liang B, Dibrov A, Amara F. Transforming growth factor-β-induced transcription of the Alzheimer β-amyloid precursor protein gene involves interaction between the CTCF-complex and Smads. Biochem Biophys Res Commun. 2002; 295: 713-723.
67. Colangelo V, Schurr J, Ball MJ, Pelaez RP, Bazan NG, Lukiw WJ. Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: Transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. J Neurosci Res. 2002; 70: 462-473.
68. Mocali A, Cedrola S, Della Malva N, Bontempelli M, Mitidieri V, Bavazzano A, et al. Increased plasma levels of soluble CD40, together with the decrease of TGFβ1, as possible differential markers of Alzheimer disease. Exp Gerontol. 2004; 39: 1555-1561.
69. Juraskova B, Andrys C, Holmerova I, Solichova D, Hrnciarikova D, Vankova H, et al. Transforming growth factor beta and soluble endoglin in the healthy senior and in Alzheimer's disease patients. J Nutr Health Aging. 2010; 14: 758-761.
70. Chang KH, Wu YR, Chen YC, Chen CM. Plasma inflammatory biomarkers for Huntington's disease patients and mouse model. Brain Behav Immun. 2015; 44: 121-127.
71. Chalmers KA, Love S. Neurofibrillary tangles may interfere with Smad 2/3 signaling in neurons. J Neuropathol Exp Neurol. 2007; 66: 158-167.
72. Chen JH, Ke KF, Lu JH, Qiu YH, Peng YP. Protection of TGF-β1 against neuroinflammation and neurodegeneration in Aβ1–42-induced Alzheimer's disease model rats. PLoS One. 2015; 10: e0116549.
73. Wyss-Coray T, Feng L, Masliah E, Ruppe MD, Lee HS, Toggas SM, et al. Increased central nervous system production of extracellular matrix components and development of hydrocephalus in transgenic mice overexpressing transforming growth factor-beta 1. Am J Pathol. 1995; 147: 53-67.
74. Lifshitz V, Weiss R, Levy H, Frenkel D. Scavenger receptor A deficiency accelerates cerebrovascular amyloidosis in an animal model. J Mol Neurosci. 2013; 50: 198-203.
75. Vawter MP, Dillon-Carter O, Tourtellotte W, Carvey P, Freed WJ. TGFβ1 and TGFβ2 concentrations are elevated in Parkinson's disease in ventricular cerebrospinal fluid. Exp Neurol. 1996; 142: 313-322.

76. Tesseur I, Nguyen A, Chang B, Li L, Woodling NS, Wyss-Coray T, et al. Deficiency in neuronal TGF-β signaling leads to nigrostriatal degeneration and activation of TGF-β signaling protects against MPTP neurotoxicity in mice. J Neurosci. 2017; 37: 4584-4592.
77. Chandramowlishwaran P, Vijay A, Abraham D, Li G, Mwangi SM, Srinivasan S. Role of sirtuins in modulating neurodegeneration of the enteric nervous system and central nervous system. Front Neurosci. 2020; 14: 614331.
78. Aquilano K, Vigilanza P, Baldelli S, Pagliei B, Rotilio G, Ciriolo MR. Peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) and sirtuin 1 (SIRT1) reside in mitochondria: Possible direct function in mitochondrial biogenesis. J Biol Chem. 2010; 285: 21590-21599.
79. Majeed Y, Halabi N, Madani AY, Engelke R, Bhagwat AM, Abdesselem H, et al. SIRT1 promotes lipid metabolism and mitochondrial biogenesis in adipocytes and coordinates adipogenesis by targeting key enzymatic pathways. Sci Rep. 2021; 11: 8177.
80. Di Lisa F, Ziegler M. Pathophysiological relevance of mitochondria in NAD^+ metabolism. FEBS Lett. 2001; 492: 4-8.
81. Wang H, Shimoji M, YU SW, Dawson TM, Dawson VL. Apoptosis inducing factor and PARP-mediated injury in the MPTP mouse model of Parkinson's disease. Ann NY Acad Sci. 2003; 991: 132-139.
82. Massudi H, Grant R, Guillemin GJ, Braidy N. NAD^+ metabolism and oxidative stress: The golden nucleotide on a crown of thorns. Redox Rep. 2012; 17: 28-46.
83. Wareski P, Vaarmann A, Choubey V, Safiulina D, Liiv J, Kuum M, et al. PGC-1α and PGC-1β regulate mitochondrial density in neurons. J Biol Chem. 2009; 284: 21379-21385.
84. Meyer R, Meyer-Ficca M, Jacobsen E, Jacobsen M. Enzymes in poly(ADP-ribose) metabolism. New York: Springer-Landes Bioscience; 2006.
85. Alano CC, Ying W, Swanson RA. Poly (ADP-ribose) polymerase-1-mediated cell death in astrocytes requires NAD^+ depletion and mitochondrial permeability transition. J Biol Chem. 2004; 279: 18895-18902.
86. Nemoto S, Fergusson MM, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α. J Biol Chem. 2005; 280: 16456-16460.
87. Ma Q. Role of nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013; 53: 401-426.
88. Zhao J, Lin X, Meng D, Zeng L, Zhuang R, Huang S, et al. Nrf2 mediates metabolic reprogramming in non-small cell lung cancer. Front Oncol. 2020; 10: 578315.
89. Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD, et al. Keap1 represses nuclear activation of antioxidant responsive elements by nrf2 through binding to the amino-terminal neh2 domain. Genes Dev. 1999; 13: 76-86.
90. Sporn MB, Liby KT. NRF2 and cancer: The good, the bad and the importance of context. Nat Rev Cancer. 2012; 12: 564-571.
91. Baird L, Llères D, Swift S, Dinkova-Kostova AT. Regulatory flexibility in the Nrf2-mediated stress response is conferred by conformational cycling of the Keap1-Nrf2 protein complex. Proc Natl Acad Sci. 2013; 110: 15259-15264.
92. Satoh H, Moriguchi T, Takai J, Ebina M, Yamamoto M. Nrf2 prevents initiation but accelerates progression through the Kras signaling pathway during lung carcinogenesis. Cancer Res. 2013; 73: 4158-4168.

93. Tao S, de la Vega MR, Chapman E, Ooi A, Zhang DD. The effects of NRF2 modulation on the initiation and progression of chemically and genetically induced lung cancer. Mol Carcinog. 2018; 57: 182-192.
94. Kitamura H, Motohashi H. NRF2 addiction in cancer cells. Cancer Sci. 2018; 109: 900-911.
95. Saha S, Buttari B, Profumo E, Tucci P, Saso L. A perspective on Nrf2 signaling pathway for neuroinflammation: A potential therapeutic target in Alzheimer's and Parkinson's diseases. Front Cell Neurosci. 2022; 15: 787258.
96. Zgorzynska E, Dziedzic B, Walczewska A. An overview of the Nrf2/ARE pathway and its role in neurodegenerative diseases. Int J Mol Sci. 2021; 22: 9592.
97. Zhang W, Feng C, Jiang H. Novel target for treating Alzheimer's diseases: Crosstalk between the Nrf2 pathway and autophagy. Ageing Res Rev. 2021; 65: 101207.
98. Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, et al. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol. 2007; 66: 75-85.
99. Kersten S, Mandard S, Tan NS, Escher P, Metzger D, Chambon P, et al. Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene. J Biol Chem. 2000; 275: 28488-28493.
100. Delaidelli A, Richner M, Jiang L, van der Laan A, Bergholdt Jul Christiansen I, Ferreira N, et al. α-Synuclein pathology in Parkinson disease activates homeostatic NRF2 anti-oxidant response. Acta Neuropathol Commun. 2021; 9: 105.
101. Kanninen K, Malm TM, Jyrkkänen HK, Goldsteins G, Keksa-Goldsteine V, Tanila H, et al. Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. Mol Cell Neurosci. 2008; 39: 302-313.
102. Kanninen K, Heikkinen R, Malm T, Rolova T, Kuhmonen S, Leinonen H, et al. Intrahippocampal injection of a lentiviral vector expressing Nrf2 improves spatial learning in a mouse model of Alzheimer's disease. Proc Natl Acad Sci. 2009; 106: 16505-16510.
103. Ren P, Chen J, Li B, Zhang M, Yang B, Guo X, et al. Nrf2 ablation promotes Alzheimer's disease-like pathology in APP/PS1 transgenic mice: The role of neuroinflammation and oxidative stress. Oxid Med Cell Longev. 2020; 2020: 3050971.
104. Pajares M, Jiménez-Moreno N, García-Yagüe ÁJ, Escoll M, de Ceballos ML, Van Leuven F, et al. Transcription factor NFE2L2/NRF2 is a regulator of macroautophagy genes. Autophagy. 2016; 12: 1902-1916.
105. Tanji K, Maruyama A, Odagiri S, Mori F, Itoh K, Kakita A, et al. Keap1 is localized in neuronal and glial cytoplasmic inclusions in various neurodegenerative diseases. J Neuropathol Exp Neurol. 2013; 72: 18-28.
106. Ikram M, Muhammad T, Rehman SU, Khan A, Jo MG, Ali T, et al. Hesperetin confers neuroprotection by regulating Nrf2/TLR4/NF-κB signaling in an Aβ mouse model. Mol Neurobiol. 2019; 56: 6293-6309.
107. Vitner EB, Farfel-Becker T, Ferreira NS, Leshkowitz D, Sharma P, Lang KS, et al. Induction of the type I interferon response in neurological forms of Gaucher disease. J Neuroinflammation. 2016; 13: 104.
108. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. Nat Rev Immunol. 2015; 15: 429-440.

109. Nazmi A, Field RH, Griffin EW, Haugh O, Hennessy E, Cox D, et al. Chronic neurodegeneration induces type I interferon synthesis via STING, shaping microglial phenotype and accelerating disease progression. Glia. 2019; 67: 1254-1276.
110. Abdullah A, Mobilio F, Crack PJ, Taylor JM. STING-mediated autophagy is protective against H_2O_2-induced cell death. Int J Mol Sci. 2020; 21: 7059.
111. Chen K, Lai C, Su Y, Bao WD, Yang LN, Xu PP, et al. cGAS-STING-mediated IFN-I response in host defense and neuroinflammatory diseases. Curr Neuropharmacol. 2022; 20: 362-371.
112. Thorpe LM, Yuzugullu H, Zhao JJ. Pi3k in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015; 15: 7-24.
113. Janku F. Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: From laboratory to patients. Cancer Treat Rev. 2017; 59: 93-101.
114. Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: Are we making headway? Nat Rev Clin Oncol. 2018; 15: 273-291.
115. Zhang Y, Ng PKS, Kucherlapati M, Chen F, Liu Y, Tsang YH, et al. A pan-cancer proteogenomic atlas of PI3K/AKT/mTOR pathway alterations. Cancer Cell. 2017; 31: 820-832.
116. Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, Pedraza-Chaverri J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cell Signal. 2014; 26: 2694-2701.
117. Long HZ, Cheng Y, Zhou ZW, Luo HY, Wen DD, Gao LC. PI3K/AKT signal pathway: A target of natural products in the prevention and treatment of Alzheimer's disease and Parkinson's disease. Front Pharmacol. 2021; 12: 648636.
118. Griffin RJ, Moloney A, Kelliher M, Johnston JA, Ravid R, Dockery P, et al. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. J Neurochem. 2005; 93: 105-117.
119. Curtis D, Bandyopadhyay S. Mini-review: Role of the PI3K/Akt pathway and tyrosine phosphatases in Alzheimer's disease susceptibility. Ann Hum Genet. 2021; 85: 1-6.
120. Malagelada C, Jin ZH, Greene LA. RTP801 is induced in Parkinson's disease and mediates neuron death by inhibiting Akt phosphorylation/activation. J Neurosci. 2008; 28: 14363-14371.
121. Timmons S, Coakley MF, Moloney AM, O'Neill C. Akt signal transduction dysfunction in Parkinson's disease. Neurosci Lett. 2009; 467: 30-35.
122. Greene LA, Levy O, Malagelada C. Akt as a victim, villain and potential hero in Parkinson's disease pathophysiology and treatment. Cell Mol Neurobiol. 2011; 31: 969-978.
123. Luo S, Kang SS, Wang Z-H, Liu X, Day JX, Wu Z, et al. Akt phosphorylates NQO1 and triggers its degradation, abolishing its antioxidative activities in Parkinson's disease. J Neurosci. 2019; 39: 7291-7305.
124. Ries V, Henchcliffe C, Kareva T, Rzhetskaya M, Bland R, During MJ, et al. Oncoprotein Akt/PKB induces trophic effects in murine models of Parkinson's disease. Proc Natl Acad Sci. 2006; 103: 18757-18762.
125. Aleyasin H, Rousseaux MW, Marcogliese PC, Hewitt SJ, Irrcher I, Joselin AP, et al. DJ-1 protects the nigrostriatal axis from the neurotoxin MPTP by modulation of the AKT pathway. Proc Natl Acad Sci. 2010; 107: 3186-3191.
126. Hu M, Li F, Wang W. Vitexin protects dopaminergic neurons in MPTP-induced Parkinson's disease through PI3K/Akt signaling pathway. Drug Des Devel Ther. 2018; 12: 565-573.

127. Tramutola A, Triplett JC, Di Domenico F, Niedowicz DM, Murphy MP, Coccia R, et al. Alteration of mTOR signaling occurs early in the progression of Alzheimer disease (AD): Analysis of brain from subjects with pre-clinical AD, amnestic mild cognitive impairment and late-stage AD. J Neurochem. 2015; 133: 739-749.
128. Kitagishi Y, Nakanishi A, Ogura Y, Matsuda S. Dietary regulation of PI3K/AKT/GSK-3β pathway in Alzheimer's disease. Alzheimer's Res Ther. 2014; 6: 35.
129. Cargnello M, Roux PP. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011; 75: 50-83.
130. Lavoie H, Therrien M. Regulation of RAF protein kinases in ERK signalling. Nat Rev Mol Cell Biol. 2015; 16: 281-298.
131. Braicu C, Buse M, Busuioc C, Drula R, Gulei D, Raduly L, et al. A comprehensive review on MAPK: A promising therapeutic target in cancer. Cancers. 2019; 11: 1618.
132. Sanchez-Vega F, Mina M, Armenia J, Chatila W, Luna A, La K, et al. Oncogenic signaling pathways in The Cancer Genome Atlas. Cell. 2018; 173: 321-337.
133. Asih PR, Prikas E, Stefanoska K, Tan AR, Ahel HI, Ittner A. Functions of p38 MAP kinases in the central nervous system. Front Mol Neurosci. 2020; 13: 570586.
134. Bohush A, Niewiadomska G, Filipek A. Role of mitogen activated protein kinase signaling in Parkinson's disease. Int J Mol Sci. 2018; 19: 2973.
135. Kim EK, Choi EJ. Pathological roles of mapk signaling pathways in human diseases. Biochim Biophys Acta. 2010; 1802: 396-405.
136. Pei JJ, Braak H, An WL, Winblad B, Cowburn RF, Iqbal K, et al. Up-regulation of mitogen-activated protein kinases ERK1/2 and MEK1/2 is associated with the progression of neurofibrillary degeneration in Alzheimer's disease. Mol Brain Res. 2002; 109: 45-55.
137. Russo C, Dolcini V, Salis S, Venezia V, Zambrano N, Russo T, et al. Signal transduction through tyrosine-phosphorylated C-terminal fragments of amyloid precursor protein via an enhanced interaction with Shc/Grb2 adaptor proteins in reactive astrocytes of Alzheimer's disease brain. J Biol Chem. 2002; 277: 35282-35288.
138. Zhu JH, Kulich SM, Oury TD, Chu CT. Cytoplasmic aggregates of phosphorylated extracellular signal-regulated protein kinases in Lewy body diseases. Am J Pathol. 2002; 161: 2087-2098.
139. Kirouac L, Rajic AJ, Cribbs DH, Padmanabhan J. Activation of Ras-ERK signaling and GSK-3 by amyloid precursor protein and amyloid beta facilitates neurodegeneration in Alzheimer's disease. Eneuro. 2017; 4. doi: 10.1523/ENEURO.0149-1516.2017.
140. Schnöder L, Hao W, Qin Y, Liu S, Tomic I, Liu X, et al. Deficiency of neuronal p38α MAPK attenuates amyloid pathology in Alzheimer disease mouse and cell models through facilitating lysosomal degradation of BACE1. J Biol Chem. 2016; 291: 2067-2079.
141. Hensley K, Floyd RA, Zheng NY, Nael R, Robinson KA, Nguyen X, et al. p38 kinase is activated in the Alzheimer's disease brain. J Neurochem. 1999; 72: 2053-2058.
142. Sun A, Liu M, Nguyen XV, Bing G. P38 MAP kinase is activated at early stages in Alzheimer's disease brain. Exp Neurol. 2003; 183: 394-405.
143. Pan J, Xiao Q, Sheng CY, Hong Z, Yang HQ, Wang G, et al. Blockade of the translocation and activation of c-Jun N-terminal kinase 3 (JNK3) attenuates dopaminergic neuronal damage in mouse model of Parkinson's disease. Neurochem Int. 2009; 54: 418-425.
144. Munoz L, Ranaivo HR, Roy SM, Hu W, Craft JM, McNamara LK, et al. A novel p38α MAPK inhibitor suppresses brain proinflammatory cytokine up-regulation and attenuates synaptic

dysfunction and behavioral deficits in an Alzheimer's disease mouse model. J Neuroinflammation. 2007; 4: 21.
145. Sclip A, Tozzi A, Abaza A, Cardinetti D, Colombo I, Calabresi P, et al. c-Jun N-terminal kinase has a key role in Alzheimer disease synaptic dysfunction in vivo. Cell Death Dis. 2014; 5: e1019.
146. Zhou Q, Wang M, Du Y, Zhang W, Bai M, Zhang Z, et al. Inhibition of c-J un N-terminal kinase activation reverses Alzheimer disease phenotypes in APPswe/PS1dE9 mice. Ann Neurol. 2015; 77: 637-654.
147. Du Y, Du Y, Zhang Y, Huang Z, Fu M, Li J, et al. MKP-1 reduces Aβ generation and alleviates cognitive impairments in Alzheimer's disease models. Signal Transduct Target Ther. 2019; 4: 58.
148. Rai SN, Dilnashin H, Birla H, Singh SS, Zahra W, Rathore AS, et al. The role of PI3K/Akt and ERK in neurodegenerative disorders. Neurotox Res. 2019; 35: 775-795.
149. Corrêa SA, Eales KL. The role of p38 MAPK and its substrates in neuronal plasticity and neurodegenerative disease. J Signal Transduct. 2012; 2012: 649079.
150. Fan J, Gladding CM, Wang L, Zhang LY, Kaufman AM, Milnerwood AJ, et al. P38 MAPK is involved in enhanced NMDA receptor-dependent excitotoxicity in YAC transgenic mouse model of Huntington disease. Neurobiol Dis. 2012; 45: 999-1009.
151. Apostol BL, Illes K, Pallos J, Bodai L, Wu J, Strand A, et al. Mutant huntingtin alters MAPK signaling pathways in PC12 and striatal cells: ERK1/2 protects against mutant huntingtin-associated toxicity. Hum Mol Genet. 2006; 15: 273-285.
152. Clevers H, Nusse R. Wnt/β-catenin signaling and disease. Cell. 2012; 149: 1192-1205.
153. Pai SG, Carneiro BA, Mota JM, Costa R, Leite CA, Barroso-Sousa R, et al. Wnt/beta-catenin pathway: Modulating anticancer immune response. J Hematol Oncol. 2017; 10: 101.
154. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017; 169: 985-999.
155. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, Da Costa LT, et al. Identification of c-MYC as a target of the APC pathway. Science. 1998; 281: 1509-1512.
156. Ben-Ze'ev A, Shtutman M, Zhurinsky J, Simcha I, Albanese C, D'Amico M, et al. The cyclin D1 gene is a target of the β-catenin/LEF-1 pathway. Proc Natl Acad Sci USA. 1999; 96: 5522-5527.
157. Gan XQ, Wang JY, Xi Y, Wu Zl, Li YP, Li L. Nuclear Dvl, c-Jun, β-catenin, and TCF form a complex leading to stabiLization of β-catenin–TCF interaction. J Cell Biol. 2008; 180: 1087-1100.
158. Kristensen B, Priesterbach-Ackley L, Petersen J, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol. 2019; 30: 1265-1278.
159. Lee Y, Lee JK, Ahn SH, Lee J, Nam DH. WNT signaling in glioblastoma and therapeutic opportunities. Lab Invest. 2016; 96: 137-150.
160. Zurawel RH, Chiappa SA, Allen C, Raffel C. Sporadic medulloblastomas contain oncogenic β-catenin mutations. Cancer Res. 1998; 58: 896-899.
161. Silva RD, Marie SK, Uno M, Matushita H, Wakamatsu A, Rosemberg S, et al. CTNNB1, AXIN1 and APC expression analysis of different medulloblastoma variants. Clinics. 2013; 68: 167-172.
162. Mulligan KA, Cheyette BN. Wnt signaling in vertebrate neural development and function. J Neuroimmune Pharmacol. 2012; 7: 774-787.
163. Inestrosa NC, Varela-Nallar L. Wnt signaling in the nervous system and in Alzheimer's disease. J Mol Cell Biol. 2014; 6: 64-74.
164. Palomer E, Buechler J, Salinas PC. Wnt signaling deregulation in the aging and Alzheimer's brain. Front Cell Neurosci. 2019; 13: 227.

165. Folke J, Pakkenberg B, Brudek T. Impaired Wnt signaling in the prefrontal cortex of Alzheimer's disease. Mol Neurobiol. 2019; 56: 873-891.
166. Caricasole A, Copani A, Caraci F, Aronica E, Rozemuller AJ, Caruso A, et al. Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. J Neurosci. 2004; 24: 6021-6027.
167. Rosi MC, Luccarini I, Grossi C, Fiorentini A, Spillantini MG, Prisco A, et al. Increased Dickkopf-1 expression in transgenic mouse models of neurodegenerative disease. J Neurochem. 2010; 112: 1539-1551.
168. Liu CC, Tsai CW, Deak F, Rogers J, Penuliar M, Sung YM, et al. Deficiency in LRP6-mediated Wnt signaling contributes to synaptic abnormalities and amyloid pathology in Alzheimer's disease. Neuron. 2014; 84: 63-77.
169. Zhang L, Deng J, Pan Q, Zhan Y, Fan JB, Zhang K, et al. Targeted methylation sequencing reveals dysregulated Wnt signaling in Parkinson disease. J Genet Genomics. 2016; 43: 587-592.
170. Arrázola MS, Silva-Alvarez C, Inestrosa NC. How the Wnt signaling pathway protects from neurodegeneration: The mitochondrial scenario. Front Cell Neurosci. 2015; 9: 166.
171. Kovall RA, Gebelein B, Sprinzak D, Kopan R. The canonical Notch signaling pathway: Structural and biochemical insights into shape, sugar, and force. Dev Cell. 2017; 41: 228-241.
172. Sjöqvist M, Andersson ER. Do as I say, Not(ch) as I do: Lateral control of cell fate. Dev Biol. 2019; 447: 58-70.
173. Kopan R, Ilagan MXG. The canonical Notch signaling pathway: Unfolding the activation mechanism. Cell. 2009; 137: 216-233.
174. Schwanbeck R, Martini S, Bernoth K, Just U. The Notch signaling pathway: Molecular basis of cell context dependency. Eur J Cell Biol. 2011; 90: 572-581.
175. Bray SJ. Notch signalling in context. Nat Rev Mol Cell Biol. 2016; 17: 722-735.
176. Reedijk M, Odorcic S, Chang L, Zhang H, Miller N, McCready DR, et al. High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res. 2005; 65: 8530-8537.
177. Ranganathan P, Weaver KL, Capobianco AJ. Notch signalling in solid tumours: A little bit of everything but not all the time. Nat Rev Cancer. 2011; 11: 338-351.
178. Tosello V, Ferrando AA. The NOTCH signaling pathway: Role in the pathogenesis of T-cell acute lymphoblastic leukemia and implication for therapy. Ther Adv Hematol. 2013; 4: 199-210.
179. Ferrarotto R, Mitani Y, Diao L, Guijarro I, Wang J, Zweidler-McKay P, et al. Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to Notch1 inhibitors. J Clin Oncol. 2017; 35: 352-360.
180. Basak O, Giachino C, Fiorini E, MacDonald HR, Taylor V. Neurogenic subventricular zone stem/progenitor cells are Notch1-dependent in their active but not quiescent state. J Neurosci. 2012; 32: 5654-5666.
181. Fischer DF, van Dijk R, Sluijs JA, Nair SM, Racchi M, Levelt CN, et al. Activation of the Notch pathway in Down syndrome: Cross-talk of Notch and APP. FASEB J. 2005; 19: 1451-1458.
182. Imai Y, Kobayashi Y, Inoshita T, Meng H, Arano T, Uemura K, et al. The Parkinson's disease-associated protein kinase LRRK2 modulates notch signaling through the endosomal pathway. PLoS Genet. 2015; 11: e1005503.

183. Woo HN, Park JS, Gwon AR, Arumugam TV, Jo DG. Alzheimer's disease and Notch signaling. Biochem Biophys Res Commun. 2009; 390: 1093-1097.
184. Cho SJ, Yun SM, Jo C, Jeong J, Park MH, Han C, et al. Altered expression of Notch1 in Alzheimer's disease. PLoS One. 2019; 14: e0224941.
185. Berezovska O, Xia M, Hyman B. Notch is expressed in adult brain, is coexpressed with presenilin-1, and is altered in Alzheimer disease. J Neuropathol Exp Neurol. 1998; 57: 738-745.
186. Nagarsheth MH, Viehman A, Lippa SM, Lippa CF. Notch-1 immunoexpression is increased in Alzheimer's and Pick's disease. J Neurol Sci. 2006; 244: 111-116.
187. Moehlmann T, Winkler E, Xia X, Edbauer D, Murrell J, Capell A, et al. Presenilin-1 mutations of leucine 166 equally affect the generation of the Notch and APP intracellular domains independent of their effect on Aβ42 production. Proc Natl Acad Sci. 2002; 99: 8025-8030.
188. Chávez-Gutiérrez L, Bammens L, Benilova I, Vandersteen A, Benurwar M, Borgers M, et al. The mechanism of γ-secretase dysfunction in familial Alzheimer disease. EMBO J. 2012; 31: 2261-2274.
189. Brai E, Alina Raio N, Alberi L. Notch1 hallmarks fibrillary depositions in sporadic Alzheimer's disease. Acta Neuropathol Commun. 2016; 4: 64.
190. Otto T, Sicinski P. Cell cycle proteins as promising targets in cancer therapy. Nat Rev Cancer. 2017; 17: 93-115.
191. van Leeuwen LA, Hoozemans JJ. Physiological and pathophysiological functions of cell cycle proteins in post-mitotic neurons: Implications for Alzheimer's disease. Acta Neuropathol. 2015; 129: 511-525.
192. Xiao Y, Dong J. The hippo signaling pathway in cancer: A cell cycle perspective. Cancers. 2021; 13: 6214.
193. Sharma R, Kumar D, Jha NK, Jha SK, Ambasta RK, Kumar P. Re-expression of cell cycle markers in aged neurons and muscles: Whether cells should divide or die? Biochim Biophys Acta Mol Basis Dis. 2017; 1863: 324-336.
194. Ippati S, Deng Y, Van Der Hoven J, Heu C, Van Hummel A, Chua SW, et al. Rapid initiation of cell cycle reentry processes protects neurons from amyloid-β toxicity. Proc Natl Acad Sci. 2021; 118: e2011876118.
195. Joseph C, Mangani AS, Gupta V, Chitranshi N, Shen T, Dheer Y, et al. Cell cycle deficits in neurodegenerative disorders: Uncovering molecular mechanisms to drive innovative therapeutic development. Aging Dis. 2020; 11: 946-966.
196. Yang Y, Mufson EJ, Herrup K. Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. J Neurosci. 2003; 23: 2557-2563.
197. Crews L, Patrick C, Adame A, Rockenstein E, Masliah E. Modulation of aberrant CDK5 signaling rescues impaired neurogenesis in models of Alzheimer's disease. Cell Death Dis. 2011; 2: e120.
198. Park KH, Hallows JL, Chakrabarty P, Davies P, Vincent I. Conditional neuronal simian virus 40 T antigen expression induces Alzheimer-like tau and amyloid pathology in mice. J Neurosci. 2007; 27: 2969-2978.
199. Pelegrí C, Duran-Vilaregut J, del Valle J, Crespo-Biel N, Ferrer I, Pallàs M, et al. Cell cycle activation in striatal neurons from Huntington's disease patients and rats treated with 3-nitropropionic acid. Int J Dev Neurosci. 2008; 26: 665-671.

200. Manickam N, Radhakrishnan RK, Andrews JFV, Selvaraj DB, Kandasamy M. Cell cycle re-entry of neurons and reactive neuroblastosis in Huntington's disease: Possibilities for neural-glial transition in the brain. Life Sci. 2020; 263: 118569.
201. Stefanis L. Alpha-synuclein in parkinson's disease. Cold Spring Harb Perspect Med. 2012; 2: a009399.
202. Lee S, Kim Y, Junn E, Lee G, Park KH, Tanaka M, et al. Cell cycle aberrations by α-synuclein over-expression and cyclin B immunoreactivity in Lewy bodies. Neurobiol Aging. 2003; 24: 687-696.
203. DePinho R, Mitsock L, Hatton K, Ferrier P, Zimmerman K, Legouy E, et al. Myc family of cellular oncogenes. J Cell Biochem. 1987; 33: 257-266.
204. Duffy MJ, O'Grady S, Tang M, Crown J. MYC as a target for cancer treatment. Cancer Treat Rev. 2021; 94: 102154.
205. Malynn BA, de Alboran IM, O'Hagan RC, Bronson R, Davidson L, DePinho RA, Alt FW. N-myc can functionally replace c-myc in murine development, cellular growth, and differentiation. Genes Dev. 2000; 14: 1390-1399.
206. Hsieh AL, Dang CV. Myc, metabolic synthetic lethality, and cancer. Recent Results Cancer Res. 2016; 207: 73-91.
207. Kress TR, Sabò A, Amati B. MYC: Connecting selective transcriptional control to global RNA production. Nat Rev Cancer. 2015; 15: 593-607.
208. Chang TC, Zeitels LR, Hwang HW, Chivukula RR, Wentzel EA, Dews M, et al. Lin-28B transactivation is necessary for Myc-mediated let-7 repression and proliferation. Proc Natl Acad Sci. 2009; 106: 3384-3389.
209. Ji H, Wu G, Zhan X, Nolan A, Koh C, De Marzo A, et al. Cell-type independent MYC target genes reveal a primordial signature involved in biomass accumulation. PLoS One. 2011; 6: e26057.
210. Koh CM, Gurel B, Sutcliffe S, Aryee MJ, Schultz D, Iwata T, et al. Alterations in nucleolar structure and gene expression programs in prostatic neoplasia are driven by the MYC oncogene. Am J Pathol. 2011; 178: 1824-1834.
211. Pelengaris S, Khan M, Evan G. c-MYC: More than just a matter of life and death. Nat Rev Cancer. 2002; 2: 764-776.
212. Shachaf CM, Kopelman AM, Arvanitis C, Karlsson Å, Beer S, Mandl S, et al. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. Nature. 2004; 431: 1112-1117.
213. Vita M, Henriksson M. The Myc oncoprotein as a therapeutic target for human cancer. Semin Cancer Biol. 2006; 16: 318-330.
214. Mossafa H, Damotte D, Jenabian A, Delarue R, Vincenneau A, Amouroux I, et al. Non-Hodgkin's lymphomas with Burkitt-like cells are associated with c-Myc amplification and poor prognosis. Leuk Lymphoma. 2006; 47: 1885-1893.
215. Ben-David E, Bester AC, Shifman S, Kerem B. Transcriptional dynamics in colorectal carcinogenesis: New insights into the role of c-Myc and miR17 in benign to cancer transformation. Cancer Res. 2014; 74: 5532-5540.
216. Korangath P, Teo WW, Sadik H, Han L, Mori N, Huijts CM, et al. Targeting glutamine metabolism in breast cancer with aminooxyacetate. Clin Cancer Res. 2015; 21: 3263-3273.
217. Marinkovic T, Marinkovic D. Obscure involvement of MYC in neurodegenerative diseases and neuronal repair. Mol Neurobiol. 2021; 58: 4169-4177.

218. Ferrer I, Blanco R. N-myc and c-myc expression in Alzheimer disease, Huntington disease and Parkinson disease. Mol Brain Res. 2000; 77: 270-276.
219. Ferrer I, Blanco R, Carmona M, Puig B. Phosphorylated c-MYC expression in Alzheimer disease, Pick's disease, progressive supranuclear palsy and corticobasal degeneration. Neuropathol Appl Neurobiol. 2001; 27: 343-351.
220. Blom ES, Wang Y, Skoglund L, Hansson AC, Ubaldi M, Lourdusamy A, et al. Increased mRNA levels of TCF7L2 and MYC of the Wnt pathway in Tg-ArcSwe mice and Alzheimer's disease brain. Int J Alzheimers Dis. 2010; 2011: 936580.
221. Lee HG, Casadesus G, Nunomura A, Zhu X, Castellani RJ, Richardson SL, et al. The neuronal expression of MYC causes a neurodegenerative phenotype in a novel transgenic mouse. Am J Pathol. 2009; 174: 891-897.
222. Ichikawa T, Nakahata S, Tamura T, Manachai N, Morishita K. The loss of NDRG2 expression improves depressive behavior through increased phosphorylation of GSK3β. Cell Signal. 2015; 27: 2087-2098.
223. Tao L, Zhu Y, Wang R, Han J, Ma Y, Guo H, et al. N-myc downstream-regulated gene 2 deficiency aggravates memory impairment in Alzheimer's disease. Behav Brain Res. 2020; 379: 112384.
224. Lane DP. p53, guardian of the genome. Nature. 1992; 358: 15-16.
225. D'Orazi G, Cirone M. Mutant p53 and cellular stress pathways: A criminal alliance that promotes cancer progression. Cancers. 2019; 11: 614.
226. Kitamura Y, Shimohama S, Kamoshima W, Matsuoka Y, Nomura Y, Taniguchi T. Changes of p53 in the brains of patients with Alzheimer's disease. Biochem Biophys Res Commun. 1997; 232: 418-421.
227. Tatton NA. Increased caspase 3 and Bax immunoreactivity accompany nuclear GAPDH translocation and neuronal apoptosis in Parkinson's disease. Exp Neurol. 2000; 166: 29-43.
228. Chang JR, Ghafouri M, Mukerjee R, Bagashev A, Chabrashvili T, Sawaya BE. Role of p53 in neurodegenerative diseases. Neurodegener Dis. 2012; 9: 68-80.
229. Szybińska A, Leśniak W. P53 dysfunction in neurodegenerative diseases-the cause or effect of pathological changes? Aging Dis. 2017; 8: 506-518.
230. Farmer KM, Ghag G, Puangmalai N, Montalbano M, Bhatt N, Kayed R. P53 aggregation, interactions with tau, and impaired DNA damage response in Alzheimer's disease. Acta Neuropathol Commun. 2020; 8: 132.
231. da Costa CA, Sunyach C, Pardossi-Piquard R, Sévalle J, Vincent B, Boyer N, et al. Presenilin-dependent γ-secretase-mediated control of p53-associated cell death in Alzheimer's disease. J Neurosci. 2006; 26: 6377-6385.
232. Checler F, Da Costa CA. Interplay between parkin and p53 governs a physiological homeostasis that is disrupted in Parkinson's disease and cerebral cancer. Neurodegener Dis. 2014; 13: 118-121.
233. da Costa CA, Duplan E, Checler F. α-synuclein and p53 functional interplay in physiopathological contexts. Oncotarget. 2017; 8: 9001-9002.
234. Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, et al. P53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. Neuron. 2005; 47: 29-41.
235. Ryan AB, Zeitlin SO, Scrable H. Genetic interaction between expanded murine Hdh alleles and p53 reveal deleterious effects of p53 on Huntington's disease pathogenesis. Neurobiol Dis. 2006; 24: 419-427.

236. Qi X, Davis B, Chiang YH, Filichia E, Barnett A, Greig NH, et al. Dopaminergic neuron-specific deletion of p53 gene is neuroprotective in an experimental Parkinson's disease model. J Neurochem. 2016; 138: 746-757.
237. Xu T, Wang W, Zhang S, Stewart RA, Yu W. Identifying tumor suppressors in genetic mosaics: The Drosophila lats gene encodes a putative protein kinase. Development. 1995; 121: 1053-1063.
238. Halder G, Johnson RL. Hippo signaling: Growth control and beyond. Development. 2011; 138: 9-22.
239. Zhang L. Control of growth and beyond: A special issue on Hippo signaling. Acta Biochim Biophys Sin. 2015; 47. doi: 10.1093/abbs/gmu113.
240. Zheng Y, Pan D. The Hippo signaling pathway in development and disease. Dev Cell. 2019; 50: 264-282.
241. Boopathy G, Hong W. Role of Hippo pathway-YAP/TAZ signaling in angiogenesis. Front Cell Dev Biol. 2019; 7: 49.
242. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev. 2007; 21: 2747-2761.
243. Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat Rev Cancer. 2013; 13: 246-257.
244. Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee SJ, Anders RA, et al. Genetic and pharmacological disruption of the TEAD–YAP complex suppresses the oncogenic activity of YAP. Genes Dev. 2012; 26: 1300-1305.
245. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the roots of cancer. Cancer Cell. 2016; 29: 783-803.
246. Xu J, Patassini S, Rustogi N, Riba-Garcia I, Hale BD, Phillips AM, et al. Regional protein expression in human Alzheimer's brain correlates with disease severity. Commun Biol. 2019; 2: 43.
247. Yamanishi E, Hasegawa K, Fujita K, Ichinose S, Yagishita S, Murata M, et al. A novel form of necrosis, TRIAD, occurs in human Huntington's disease. Acta Neuropathol Commun. 2017; 5: 19.
248. Tanaka H, Homma H, Fujita K, Kondo K, Yamada S, Jin X, et al. YAP-dependent necrosis occurs in early stages of Alzheimer's disease and regulates mouse model pathology. Nat Commun. 2020; 11: 507.
249. Sahu MR, Mondal AC. The emerging role of Hippo signaling in neurodegeneration. J Neurosci Res. 2020; 98: 796-814.
250. Sahu MR, Mondal AC. Neuronal Hippo signaling: From development to diseases. Dev Neurobiol. 2021; 81: 92-109.
251. Mueller KA, Glajch KE, Huizenga MN, Wilson RA, Granucci EJ, Dios AM, et al. Hippo signaling pathway dysregulation in human Huntington's disease brain and neuronal stem cells. Sci Rep. 2018; 8: 11355.
252. Mao Y, Chen X, Xu M, Fujita K, Motoki K, Sasabe T, et al. Targeting TEAD/YAP-transcription-dependent necrosis, TRIAD, ameliorates Huntington's disease pathology. Hum Mol Genet. 2016; 25: 4749-4770.

253. Ahn EH, Kang SS, Qi Q, Liu X, Ye K. Netrin1 deficiency activates MST1 via UNC5B receptor, promoting dopaminergic apoptosis in Parkinson's disease. Proc Natl Acad Sci. 2020; 117: 24503-24513.
254. Lee JK, Shin JH, Hwang SG, Gwag BJ, McKee AC, Lee J, et al. Mst1 functions as a key modulator of neurodegeneration in a mouse model of als. Proc Natl Acad Sci USA. 2013; 110: 12066-12071.
255. Schmidt SI, Blaabjerg M, Freude K, Meyer M. RhoA signaling in neurodegenerative diseases. Cells. 2022; 11: 1520.
256. Villar-Cheda B, Dominguez-Meijide A, Joglar B, Rodriguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. Involvement of microglial RhoA/Rho-Kinase pathway activation in the dopaminergic neuron death. Role of angiotensin via angiotensin type 1 receptors. Neurobiol Dis. 2012; 47: 268-279.
257. Tönges L, Frank T, Tatenhorst L, Saal KA, Koch JC, Szegő ÉM, et al. Inhibition of rho kinase enhances survival of dopaminergic neurons and attenuates axonal loss in a mouse model of Parkinson's disease. Brain. 2012; 135: 3355-3370.
258. Barcia C, Ros CM, Annese V, Carrillo-de Sauvage MA, Ros-Bernal F, Gómez A, et al. ROCK/Cdc42-mediated microglial motility and gliapse formation lead to phagocytosis of degenerating dopaminergic neurons in vivo. Sci Rep. 2012; 2: 809.
259. Borrajo A, Rodriguez-Perez AI, Villar-Cheda B, Guerra MJ, Labandeira-Garcia JL. Inhibition of the microglial response is essential for the neuroprotective effects of Rho-kinase inhibitors on MPTP-induced dopaminergic cell death. Neuropharmacology. 2014; 85: 1-8.
260. Bogetofte H, Jensen P, Okarmus J, Schmidt SI, Agger M, Ryding M, et al. Perturbations in RhoA signalling cause altered migration and impaired neuritogenesis in human iPSC-derived neural cells with PARK2 mutation. Neurobiol Dis. 2019; 132: 104581.
261. Sanchez M, Gastaldi L, Remedi M, Cáceres A, Landa C. Rotenone-induced toxicity is mediated by Rho-GTPases in hippocampal neurons. Toxicol Sci. 2008; 104: 352-361.
262. Mattii L, Pardini C, Ippolito C, Bianchi F, Sabbatini ARM, Vaglini F. Rho-inhibition and neuroprotective effect on rotenone-treated dopaminergic neurons in vitro. Neurotoxicology. 2019; 72: 51-60.
263. Gcwensa NZ, Russell DL, Cowell RM, Volpicelli-Daley LA. Molecular mechanisms underlying synaptic and axon degeneration in Parkinson's disease. Front Cell Neurosci. 2021; 15: 626128.
264. Zhou Z, Kim J, Insolera R, Peng X, Fink DJ, Mata M. Rho GTPase regulation of α-synuclein and VMAT2: Implications for pathogenesis of Parkinson's disease. Mol Cell Neurosci. 2011; 48: 29-37.
265. Kim J, Inoue K, Ishii J, Vanti WB, Voronov SV, Murchison E, et al. A MicroRNA feedback circuit in midbrain dopamine neurons. Science. 2007; 317: 1220-1224.
266. Tatenhorst L, Eckermann K, Dambeck V, Fonseca-Ornelas L, Walle H, Lopes da Fonseca T, et al. Fasudil attenuates aggregation of α-synuclein in models of Parkinson's disease. Acta Neuropathol Commun. 2016; 4: 39.
267. Liu FT, Yang YJ, Wu JJ, Li S, Tang YL, Zhao J, et al. Fasudil, a Rho kinase inhibitor, promotes the autophagic degradation of A53T α-synuclein by activating the JNK 1/Bcl-2/beclin 1 pathway. Brain Res. 2016; 1632: 9-18.
268. Hou L, Bao X, Zang C, Yang H, Sun F, Che Y, et al. Integrin CD11b mediates α-synuclein-induced activation of NADPH oxidase through a Rho-dependent pathway. Redox Biol. 2018; 14: 600-608.

269. Zhang Q, Hu C, Huang J, Liu W, Lai W, Leng F, et al. ROCK1 induces dopaminergic nerve cell apoptosis via the activation of Drp1-mediated aberrant mitochondrial fission in Parkinson's disease. Exp Mol Med. 2019; 51: 1-13.
270. Minin AA, Kulik AV, Gyoeva FK, Li Y, Goshima G, Gelfand VI. Regulation of mitochondria distribution by RhoA and formins. J Cell Sci. 2006; 119: 659-670.
271. Cereghetti G, Stangherlin A, De Brito OM, Chang C, Blackstone C, Bernardi P, et al. Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria. Proc Natl Acad Sci. 2008; 105: 15803-15808.
272. Schwarz TL. Mitochondrial trafficking in neurons. Cold Spring Harb Perspect Biol. 2013; 5: a011304.
273. McCoy MK, Kaganovich A, Rudenko IN, Ding J, Cookson MR. Hexokinase activity is required for recruitment of parkin to depolarized mitochondria. Hum Mol Genet. 2014; 23: 145-156.
274. Moskal N, Riccio V, Bashkurov M, Taddese R, Datti A, Lewis PN, et al. ROCK inhibitors upregulate the neuroprotective Parkin-mediated mitophagy pathway. Nat Commun. 2020; 11: 88.
275. Lopez-Lopez A, Labandeira CM, Labandeira-Garcia JL, Muñoz A. Rho kinase inhibitor fasudil reduces l-DOPA-induced dyskinesia in a rat model of Parkinson's disease. Br J Pharmacol. 2020; 177: 5622-5641.