Review Article

Signalling Pathways involved in Neurodegenerative Disorder

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ABSTRACT

Neurodegenerative disorder mainly includes Alzheimer's Disease, Parkinson's and Dementia. Alzheimer's disease (AD) is characterized by the progressive loss of cholinergic neurons leading to dementia, extracellular amyloid deposits, intracellular neurofibrillary tangles, cholinergic deficits, synaptic loss, inflammation and extensive oxidative stress. The changes are accompanied by significant behavioural, motor and cognitive impairment leading to accelerated mortality. Parkinson's disease (PD) is characterized by a preferential loss of the dopaminergic neurons of the *substantia nigra pars compacta.* Major factors responsible for this disease include: - 1) Environmental toxins including MPTP, paraquat and rotenone which increase the risk of PD in humans. 2) Mitochondrial complex I inhibition - derangements in complex I cause α-synuclein aggregation, which contributes to the demise of dopamine neurons, Dysfunction of parkin and DJ-1 could also contribute to these deficits. 3) Aging (with inter-related factors). The elucidation of the protein building blocks of these organelles as well advances in understanding how these proteins become altered in AD and PD will provide insights into the molecular basis of this disorder. This review aims to highlight the involvement of various signalling pathway in AD and PD.

Keywords: Neurodegenerative, Alzheimer's disease, Parkinson disease, signalling pathways.

INTRODUCTION

The term Neurodegeneration is a combination of two words "Neuro" referring to nerve cells and "degeneration" referring to progressive damage. The term Neurodegeneration can be applied to several conditions that result in loss of nerve structure and function. Alzheimer's disease is characterized by the progressive loss of cholinergic neurons leading to dementia. Patients with impairment of cognitive functions[1] loose their ability to encode new memories.

Neurons are chief type of cells destroyed by Alzheimer's disease. Signals that form memories and thoughts move through an individual nerve cell as a tiny electrical charge.[2]

Nerve cells connect to one another at synapses when a charge reaches a synapse. It may trigger release of tiny burst of chemicals called Neurotransmitter. The Neurotransmitter travel across the synapse, carrying signals to other cells. Alzheimer's disease disrupts both the way electrical charges travel within the cells and the activity of neurotransmitter.

On the other hand, Parkinson's disease is a neurodegenerative movement disorder which leads to severe motor symptoms[11] including uncontrollable tremor, postural imbalance, slowness of movement and rigidity[14]. Additionally catecholaminergic neuronal systems, are also affected, but less severely. The first neurodegenerative change that occurs in these disorders is loss of striatal terminals accompanied by cytoplasmic aggregate proteins called Lewy Bodies[12].

Most PD cases are sporadic; however, rare familial forms have been identified[13]. Range of factors that are responsible for pathogenesis of sporadic PD are also associated with mutations in familial Parkinson's genes such as mitochondrial and lysosomal dysfunction, oxidative stress, excitotoxicity, proteasomal stress, neuroinflammation, and protein aggregation[12].

Understanding these signalling processes that leads to neurodegeneration has provided the field with numerous targets that may be therapeutically useful for the development of disease-modifying treatments.

Alzheimer's disease

Signalling Pathways Involved in Ad

Extracellular amyloid beta plaques and intracellular neurofibrillary tangles containing hyper phosphorylated tau, are frequently present in the brain of patients with senile dementia, plaques and tangles.[3]

The Amyloid Cascade Hypothesis

1. The cascade is initiated by the generation of amyloid-β42 (Aβ42). Aβ42 is overproduced owing to pathogenic mutations. In sporadic AD, various factors can contribute to an increased load of Aβ42 oligomers and aggregates. Amyloid-β oligomers might directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes. Tau pathology, which contributes substantially to the disease process through hyperphosphorylated tau and tangles, is triggered by Aβ42.

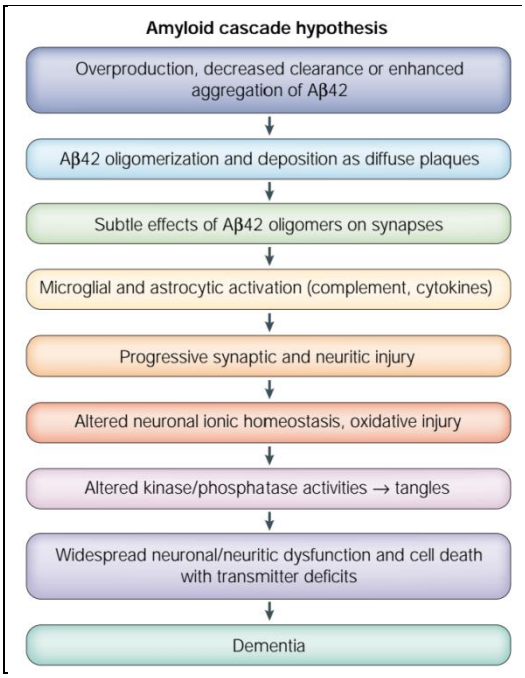

Figure 1: Amyloid cascade hypothesis[4]

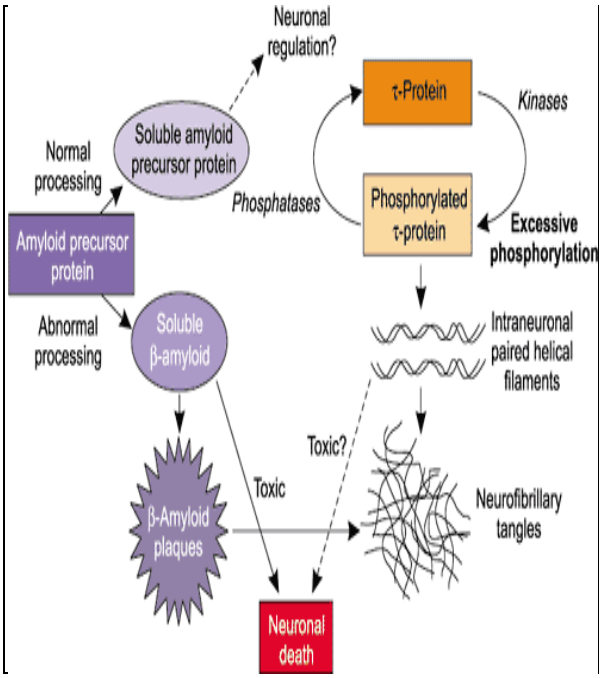

Figure 2: Steps involved in Neuronal death

2. Increase of ROS production, Amyloid Beta –induced mitochondrial dysfunction, and apoptosis due to impairment of mitochondrial calcium handling ability, altered calcium homeostasis, increased mitochondrial permeability transition pore opening, and promotion of cytochrome c release. Amyloid beta inhibits protein import inside the mitochondria. Mitochondrial DNA mutations and DNA damage are also involved in the pathogenesis of AD, and are associated with synaptic and neuronal loss, Amyloid plaques, and NFTs.
3. Perturbed cerebral energy metabolism plays a central role in multiple pathogenic cascades of AD. Particularly related to low levels of glucose.
4. Deficits in mitochondrial function and increased Aβ accumulation in synapses lead to reduced synaptic activity and consequent neuronal damage.
5. Synaptic alteration and mitochondrial dysfunction have been observed in many neurodegenerative disorders including AD.
6. Neurofibrillary tangles consist of aberrantly phosphorylated fibrillary proteins aggregated within the neuronal cytoplasm. Their presence signifies the failure of the neuron to properly maintain its cytoskeleton, which is required to support the extraordinarily complex branching shape of its numerous processes[5]. A small number of neurofibrillary tangles are a universal consequence of aging. The development of tangles is a major and possibly the main mechanism of neuronal death in AD.[6]

Some group of neurons are preferentially affected by tangles in AD. For example, neurofibrillary tangles frequently occur in areas of the hippocampus that are involved in processing experiences prior to storage as permanent memories. This correlates with the clinical deficits observed in the early stages of AD in learning and in the creation of new memories, as well as with the relative preservation of established memories. The neurons at the basal forebrain that provide most of the cholinergic innervation to the cortex are also prominently affected; the resulting cholinergic neurotransmitter deficits are often treated with cholinesterase inhibitors. Donepezil, a piperdine-based acetylcholinesterase inhibitor and currently the only approved symptomatic treatment for AD in Canada, has been shown to have consistent mild-to-moderate treatment effects in clinical trial.[7, 8]

Amyloid precursor protein (APP) and its metabolites

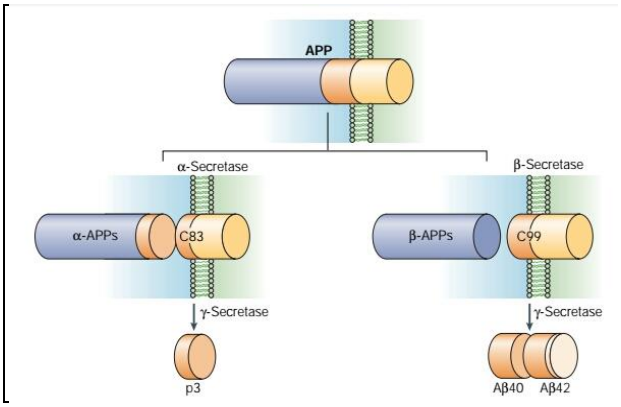

Figure 3: Amyloid precursor protein (APP) and its metabolites.[9]

The protein sequences are not drawn to scale. The transmembrane protein APP can be processed along two main pathways, the α-secretase pathway and the amyloid-forming βsecretase pathway. In the α-secretase pathway, α-secretase cleaves in the middle of the amyloid β region to release a large soluble APP-fragment, α-APPs. The carboxy (C) terminal C83 peptide is metabolized to p3

by γ-secretase. In the amyloid-forming β-secretase pathway, β-secretase releases a large soluble fragment, β-APPs. The C-terminal C99 peptide is then cleaved by γ-secretase at several positions, leading to the formation of amyloidβ40 (Aβ40) and the pathogenic amyloid-β42 (Aβ42). γ-Secretase cleavage also releases the APP intracellular domain (AICD), which could have a role in transcriptional regulation[10]. The effects of βand γ-secretase inhibitors can be distinguished in secondary assays: both inhibitor classes block the formation of pathogenic Aβ42, but β-secretase inhibitors also block the formation of β-APPs and C99, whereas γ-secretase inhibitors also block the formation of p3 and the APP C-terminal fragment, leading to accumulation of C99 and C83.

Parkinson's disease

Neurodegeneration In Parkinson's Disease Arises From Dysregulation Of Interlinked Signalling Pathways[15,16]

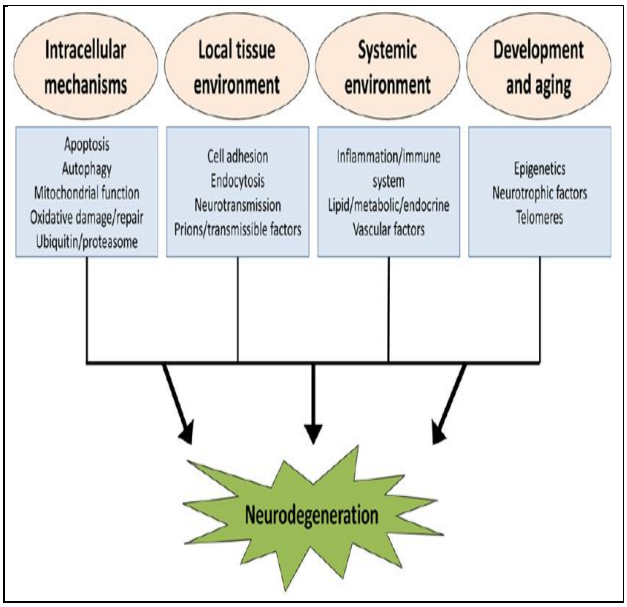

Figure 4: Signalling pathways in Neurodegeneration

Intracellular Mechanisms

Apoptosis

In human PD brains, molecular markers of apoptosis are abundant in the substantia nigra , which contains mostly dopaminergic neurons and is the primary site of atrophy and pathology in the disease . The hallmark pathological feature of PD is the presence of intracellular inclusions known as Lewy bodies, which are mainly composed of insoluble aggregates of α-synuclein. α-synuclein is associated with both early- and late-onset PD and accumulation of it in cultured dopaminergic neurons results in apoptosis.

Other PD-related genes with potential roles in apoptosis include LRRK2 (leucine-rich repeat kinase 2), MAPT (microtubule-associated protein tau), and PARK2 (parkinson protein 2, E3 ubiquitin protein ligase).

Autophagy

Autophagy is a mechanism for degradation of unnecessary or dysfunctional cellular components. Controlled activation of autophagy may provide a strategy for clearance of long-lived, aggregated, or dysfunctional proteins which contribute to neurodegeneration.

Mitochondrial Dysfunction

Mitochondria are primarily useful for cellular energy production through catabolism of sugars, fats, and proteins. The underlying mechanisms for these processes yield metabolites which have the potential to promote neurodegenerative oxidative stress and DNA damage.

However, mitochondria also play important roles in other functions that can modulate neurodegeneration, such as apoptosis and endocytosis, and several key PD-related proteins are localized to mitochondria or at the interface between the mitochondria and endoplasmic reticulum. The intersection of multiple pathways with mitochondrial function makes this organelle an important target for strategies to combat neurodegeneration.

In PD models alpha gene overexpression leads to the excess α-synuclein associating with the mitochondrial membrane and inducing cytochrome c release and oxidative stress. Two other genes associated with both early- and late-onset PD, PARK2 and PINK1 (PTEN induced putative kinase 1), codes for proteins that regulate axonal transport of healthy mitochondria and autophagy of old or dysfunctional mitochondria (also known as mitophagy).

Another cause of early-onset PD, PARK7 (Parkinson protein 7; also known as DJ1), appears to work in concert with PARK2 and PINK1 as a sensor of oxidative stress and a regulator of mitophagy.

Interestingly, two compounds exert their toxic effects in mitochondria. Exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was initially proposed as an environmental cause of PD. In the brain, the MAO-B (monoamine oxidase B) enzyme converts MPTP into MPP+ (1-methyl4-phenylpyridinium), which interferes with complex I of the mitochondrial electron transport chain to fatally deplete ATP levels and cause neuronal death. The pesticide rotenone similarly interferes with electron transport chain function.

Oxidative DNA Damage and Repair

Oxidative stress refers to an imbalance between levels of toxic reactive oxygen species (ROS) and the activity of mechanisms – such as the glutathione system and DNA repair pathways – to detoxify ROS to less reactive intermediates or to reverse ROS-induced cellular damage.

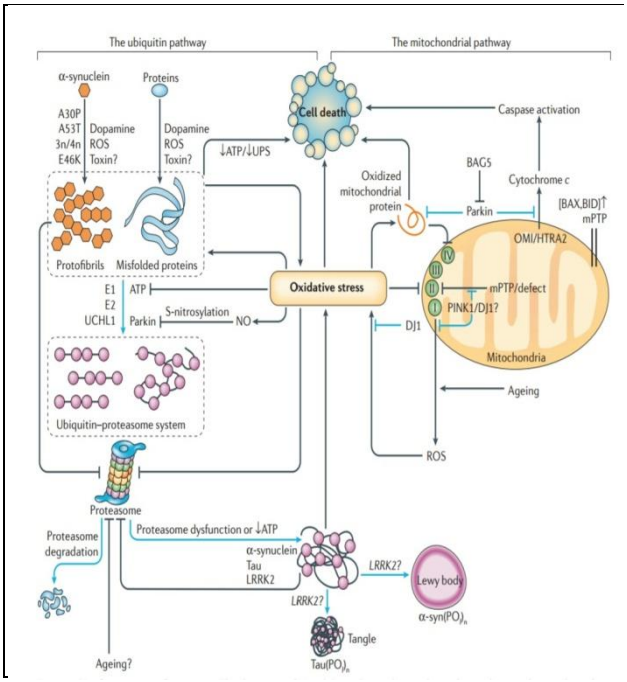

Figure 5: The ubiquitin and mitochondrial pathway responsible for parkinsonism[17].

Mitochondria are the major cellular source of ROS, and therefore dysfunction of mitochondrial components is a significant contributor to oxidative stress and its downstream effects on the structures of DNA, proteins, and lipids. For example, oxidative damage to α-synuclein can change the protein's targeting sequence to affect its cellular localization and can promote its aggregation.

As a result, there is significant interest in whether genetic variation that modulates oxidative stress and its responses might affect susceptibility to neurodegeneration.

The PD-associated genes PARK2, PARK7, and PINK1 may represent one molecular axis contributing to disease risk through regulation of oxidative stress.

Ubiquitin-Proteasome System

The ubiquitin-proteasome system is responsible for targeted degradation of misfolded, aggregated, or abnormal proteins.

The first step in activating this pathway involves ubiquitin labelling of a protein to direct it to cylindrical proteasomes in the nucleus, endoplasmic reticulum, and other compartments, which recognize this ubiquitin-labelled proteins and directs protease enzymes for protein degradation. In contrast to autophagy, which can also degrade proteins in addition to whole organelles, ubiquitin-mediated proteasomal degradation is thought to be highly selective.

For PD, and other neurodegenerative diseases marked by accumulation and aggregation of specific abnormal proteins, ubiquitin proteasome pathways represent natural candidates for modulating pathology. Ubiquitin positive inclusions in neurons and glial cells are also frequently identified in PD and other neurodegenerative disorders. And this may be a sequelae of dysfunction in proteasomal pathways due to variation in genes including GRN (progranulin) and MAPT.

More broadly, ubiquitin-mediated protein degradation may be neuroprotective in modest quantities but may stimulate bulk autophagy or BCL-2-dependent apoptosis at overwhelming or chronic levels.

Local tissue environment

Cell Adhesion

Cell adhesion involves the binding of a cell to another cell or to an extracellular surface. In healthy brains, cell adhesion pathways are important for maintenance of synaptic contacts and blood-brain barrier integrity as well as efficient neurotransmission and intracellular signalling. Altered expression of cell adhesion genes is a consistent finding in PD.

Endocytosis

The process known as endocytosis, where extracellular molecules are engulfed into membrane-bound vesicles for internalization is important for gathering nutrients, facilitating molecular interactions and protein degradation in a protected environment, and recycling ligands and receptors. PD-associated genes have central roles in endocytic pathways. In PD, LRRK2 similarly regulates the recycling and/or degradation of α-synuclein and is a key influence on the endocytic formation of synaptic vesicles containing neurotransmitters .

Targeting of endocytic pathways may also be a viable approach to combat PD. The PD-asso- ciated gene GAK (cyclin G associated kinase) is a key mediator of endocytic vesicle trafficking by regulating interactions with adaptor proteins and later driving disassembly of the vesicle clathrin coat. The closely related gene AAK1 (AP-2 associated kinase 1) has also been associated with age of PD onset.

Neurotransmission

The loss of dopaminergic neurons from the substantia nigra that dysfunctions dopaminergic neurotransmission was a primary cause of PD. As a result, modulation of dopaminergic neurotransmission forms the basis of several symptomatic therapies for PD.

Genetic and molecular studies support a role for neurotransmitter mechanisms in neurodegenerative disease. Pathways related to calcium signalling, which are important for presynaptic neurotransmitter release and postsynaptic signal transduction involving cyclic AMP (cAMP), protein kinase A (PKA), and cAMP response element binding protein (CREB), have displayed association to PD. The gene COMT (catechol-O-methyltransferase) encodes an enzyme that degrades dopamine and other catecholamine neurotransmitters, and COMT variants have been associated with dopamine levels in early PD. Further, in addition to its effects on

mitochondria, MPP+ gains entry to cells via the dopamine transporter and inhibits synthesis of dopamine and other catecholamines. Variation in multiple genes also contributes to elevated glutamate levels in multiple sclerosis (MS), which is classically marked by demyelination and neuroinflammation.

Prions and Transmissible Factors

Prion protein is a membrane-associated, protease-sensitive glycoprotein that is typically enriched in lipid rafts consisting of tightly packed signalling and trafficking molecules. As with other misfolded proteins, misfolded prion protein is normally susceptible to proteasome-mediated and other forms of protein degradation. However, accumulation of misfolded prion protein through inhibition of protein degradation pathways has been proposed to lead to the formation of protease-resistant, aggregated, infectious (i.e., transmissible) particles which can be released to neighbouring cells and promote misfolded protein states in those cells. This mechanism is thought to underlie the development of fatal degenerative transmissible spongiform encephalopathies such as Creutzfeld-Jakob disease (CJD).

Systemic Environment

Inflammation and Immune Dysfunction

Studies of microglia, the resident immune system macrophages in the brain and CSF, provide some clues for resolving these issues. Post-mortem tissue analyses as well as newer in vivo PET imaging methods have identified an abundance of activated microglia in PD brains. α-synuclein is known to activate microglia, stimulating the release of inflammatory cytokines and activation of inflammation-mediating enzymes such as matrix metalloproteinases (MMPs). Activated microglia also express NLRP3 (nucleotide-binding domain and leucine-rich repeat family, pyrin domain containing 3), a component of larger structures known as inflammasomes which promote several inflammatory processes including the maturation of IL-1β (interleukin 1, beta). In animal models, IL-1β exacerbates PD progression.

Genetic associations in inflammation- and immune-related pathways may have similar implications. Variants in IL1B (interleukin 1, beta) and TNFA (tumor necrosis factor, alpha) have been associated PD and may contribute to altered cytokine levels and inflammatory signalling .

Other genes appear to bridge inflammation and innate immune responses. For example, the PD- and Crohn's disease-associated gene LRRK2 both mediates microglial-induced inflammation and is a target of IFN-γ (interferon gamma), suggesting an additional role in the immune response to pathogens.

Lipid, Metabolic and Endocrine Factors

Loss of lipid homeostasis can prominently contribute to neurodegeneration. Importantly, neuronal membranes contain substantial amounts of cholesterol and other lipids, and disturbances in lipid pathways have been frequently proposed to impact synaptic signalling and neuronal plasticity and degeneration.

Among PD-related genes, both PARK2 and LRRK2 code for proteins which regulate cellular uptake of lipid-rich structures.

Vascular Changes

Vascular pathology, including increases in vessel wall stiffness, changes in endothelial cell adhesion and metabolism, and dysfunction of the blood-brain barrier, can promote neurodegeneration through yielding chronic, low perfusion.

Neurodevelopment and Biological Aging

Epigenetic Changes

Epigenetic factors provide mechanisms for genetic control that do not involve modifications to an individual's DNA sequence. These heritable changes, including RNA-associated silencing and methylation or acetylation of DNA or histones, can dynamically respond to environmental stimuli and also appear to increase in frequency with aging. Several PD-related genes are regulators or targets of epigenetic mechanisms. For example, nuclear α-synuclein accumulation inhibits histone acetylation and promotes apoptosis in cell culture. While PD-related SNCA mutations potentiate this effect, inhibition of SIRT2 (sirtuin 2) deacetylase activity may reverse SNCA-induced toxicity.

Neurotrophic Factors

Neurotrophic factors (neurotrophins) are secreted growth factors that promote the development, functioning, and survival of neurons through regulation of gene transcription. Neurotrophins typically affect transcription through binding receptors at neuron terminals to stimulate second messenger signalling cascades or to promote their internalization and direct transport along the axon to the nucleus. Diminished signalling and axonal transport of BDNF and NGF (nerve growth factor) have been identified in age of onset in familial PD, and age-related changes in brain structure and cognitive function in individuals without frank disease, suggesting a primary role for neurotrophin signalling in susceptibility to neurodegeneration.

CONCLUSION

As the world's ageing population continues to increase and age appears to be a prominent risk factor for most neurodegenerative diseases, novel therapeutic regimens which delay the onset of age-related disorders are highly desirable. Today, neurodegenerative research is usually focused to unveil limited areas of the disease with unsuccessful results when challenged in real patients, we believe that through renewed insight on the cellular and molecular mechanisms responsible for cellular and mitochondrial abnormalities reported in

neurodegeneration, efficient and safe translation of these signalling pathways into novel therapeutic alternatives against neuronal degeneration may shorten the gap between basic science and clinical research.

REFERENCES

1. Dennis J. Selkoe, Alzheimer's disease is a Synaptic Failure, Science DOI: 10.1126/science. 1074069, 789, 2002, 298.
2. http://www.alz.org/braintour/plaques tangles.asp
3. Juan A Godoy, Signaling pathway cross talk in Alzheimer's disease, Godoy et al. Cell Communication and Signaling 2014.
4. Mattson M: Pathways towards and away from Alzheimer's disease. Nature 430, 2004, 631–639.
5. David G. Munoz, Feldman, causes of Alzheimer's disease, Cmag 162 (1), Jan 11, 2000.
6. Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol 41, 1997, 17-24.
7. Rogers SL, Farlow MR, Mohs R, Freidhoff LT, Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 50, 1998, 136-45.
8. Rogers SL, Fried off LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre randomized, doubleblind, placebo-controlled trial. The donepezil study group. Dementia 7, 1996, 293-303.
9. Martin Citron, Strategies for disease modification in Alzheimer's Disease, Nature Reviews, Nature science, volume 5, September 2004.
10. DeStrooper, B. Aph-1, Pen-2, and Nicastrin with Presenilin generate an active γ-secretase complex. Neuron 38, 2003, 9–12.
11. Laura Scott, Valina L. Dawson, Ted M. Dawson, Trumping neurodegeneration: Targeting common pathway sregulated by autosomal recessive Parkinson's disease genes. Exp Neurol. 2017.
12. Georgia S. Gaki, Athanasios G. Papavassiliou . Oxidative Stress-Induced Signaling Pathways Implicatedin the Pathogenesis of Parkinson's disease. Neuromol Med. June Volume 16, Issue 2, 2014, pp 217–230.
13. Zhao J, Yu S, Zheng Y, Yang H, Zhang J.Oxidative Modification and Its Implicationsfor the Neurodegeneration of Parkinson's Disease. Mol Neurobiol. 54(2), 2017 Mar.
14. Lotharius J, Brundin P. Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha-synuclein. Nat Rev Neurosci. 3(12), 2002 Dec, 932-42.
15. Kazuhiro A. Fujita. Integrating Pathways of Parkinson's disease in a Molecular Interaction Map. Molecular Neurobiology, February Volume 49, Issue 1, 2014, pp 88–10
16. Vijay K Ramanan, Andrew J Saykin . Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson'sdisease, and related disorders. Am J Neurodegener Dis 2(3), 2013, 145-175.
17. Patrick M. Abou-Sleiman, Miratul M. K. Muqit and Nicholas W. Wood. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nature Reviews Neuroscience 7, March 2006, 207-219.

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