Molecular Science

Review

Molecular mechanisms of neurodegenerative disease (NDD)

Ashok Chakraborty[1],* and Anil Diwan[2]

[1] Department of Cell Biology, Allexcel, Inc., Shelton, CT, USA
[2] Department of Chemistry, Allexcel, Inc., Shelton, CT, USA

* **Correspondence:** Email: ashok.chakraborty@allexcel.com; Tel: +12036409433.

Abstract: Degenerative nerve diseases affect body's balance, movement, speech, breathing and heart function. Classification of neurodegenerative disorders can be done on the basis of their molecular cause, like abnormal protein aggregation, involved cell death or loss of function of involved cell. Parkinson's disease (PD) is associated with aggregation of α-synuclein, while Alzheimer disease (AD) is associated with *tau*, amyloid-β42 protein aggregation. TDP-43 aggregation was found in Amyloidosis. Besides, Argyrophilic grain disease (AGD); Amyotrophic lateral sclerosis (ALS); Astrocyte plaque (AP); ALS and Parkinsonism-Dementia Complex (*APDC*); Aging-related tau astrogliopathy (*ARTAG*); Ballooned neuron (BN); Cerebral age-related TDP-43 with sclerosis (*CARTS*); Corticobasal degeneration (*CBD*); Chronic traumatic encephalopathy (*CTE*); Dementia with Lewy bodies (*DLB*); Dystrophic neuritis (*DN*); Facial onset sensory and motor neuronopathy (*FOSMN*); Glial cytoplasmic inclusions (GCI); globular glial tauopathy (*GGT*); Guadeloupean Parkinsonism (GP); idiopathic REM sleep behavior disorder (*iRBD*); Limbic-predominant age-related TDP-43 encephalopathy (*LATE*); Lewy bodies (*LB*); Lewy body diseases (*LBD*); Lewy neuritis (*LN*); muscle cells (*MC*); multiple system atrophy (*MSA*); multisystem proteinopathy (*MSP*); Neuronal cytoplasmic inclusions (*NCI*); neurofibrillary tangles (*NFT*); neuronal intranuclear inclusions (*NII*); neuropil threads (*NPT*); Nodding Syndrome (*NS*); oligodendroglial coiled bodies (*OCB*); oligodendroglial Pick's body-like inclusions (*OPiBLI*); pure autonomic failure (*PAF*); primary age-related tauopathy (*PART*); Pick's bodies (*PiB*); Pick's disease (*PiD*); Primary lateral sclerosis (*PLS*); Progressive muscular atrophy (*PMA*); progressive supranuclear palsy (*PSP*); pretangles (*PT*); tufted astrocyte (*TA*), are several neurodegenerative diseases name according to their involved protein factor(s).

The cause may be genetic, may also be sporadic. Alcoholism, pesticides, a tumor, or a stroke are sometimes noticed in the disease background. Sometimes the cause remains totally unknown. Neurodegeneration, till date, cannot be cured. Only some palliative treatments may relieve some of

the symptoms but temporarily. Further, some types of NDD could also be fatal.

Our focus, in this review, is mainly on AD and PD since they vastly affect millions of people in the world, and occurs when nerve cells lose functional ability and/or die over time. AD and PD, the likelihood of developing the issues rise dramatically with age. Unfortunately, there is no cure at present for them except some palliative measure to give some comfort to the victims. Improvement of our understanding about the cause(s) of neurodegenerative diseases may help to design the new approaches for treatment and prevention of the ailments. In recent days, high-throughput technologies like RNA sequencing, network biology, and Omics data provide insights of all neurodegenerative disease.

Graphical abstract:
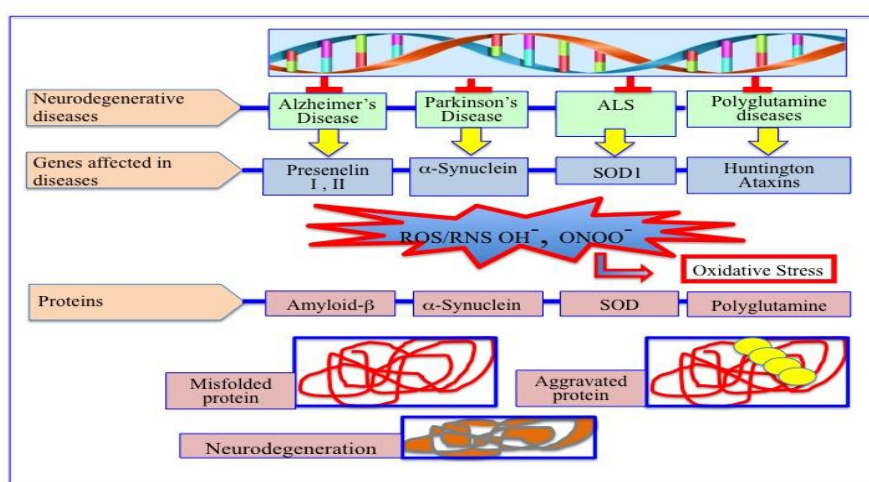
Keywords: Alzheimer's disease; Parkinson's disease; motor neuron diseases; radicals/reactive oxygen species; neurodegenerative diseases; molecular mechanism

1. Introduction

1.1. What is neurodegenerative disease

Neurodegenerative diseases (NDDs) result from selective dysfunction and/or loss of neurons due to the pathological deposition of misfolded proteins in the human neural circuits [1]. These proteins and/or their genes can be used as the disease biomarkers and can be targeted for therapy, also. The most common NDDs include AD, PD, prion disease, ALS, MND, HD, spinal muscular atrophy, and spinocerebellar ataxia [2–5]. The most ND diseases are generally named by the name of the discoverer, and/or described by their symptoms. Like AD is known as irreversible forgetfulness [6], and PD is known as shaking palsy [7]. However, lately they got the different names according to their molecular cause, like AD is also known as *taupathies*, as the *tau* protein agglutination caused the damage of the neural circuit. Similarly, agglutination of α-synuclein, a presynaptic neural protein, was found in PD, hence it is also called as α-synucleinopathies [8].

NDDs affect millions of people worldwide. The risk factors, besides the individual's genetic make up, are their immediate environment, and age, also [9–15].

1.2. Classification of neurodegenerative diseases in relation to their molecular and cellular mechanisms

- Misfolding of protein, improper degradation, proteasomal dysfunction.
- Oxidative stress (OS) due to the formation of free radicals and reactive oxygen species (ROS) [16].
- Genetic linkage, ageing, stress, pesticides, fungicides/insecticides and SUMOylation process are also considered as causative factors for the onset of NDDs like PD, AD, HD, and ALS [17].
- Several chemicals used in industry or consumer products including metals (e.g., arsenic, lead, manganese), air pollution, and bacteria-made endotoxins are also believed to cause NDDs.
- Besides, some dietary factors (e.g., caffeine, tobacco, dietary antioxidants), as well as lifestyle are linked with the appearance of the disease like AD, PD, at least [1].
- In addition, many stress response proteins and chaperones may result energetic dysregulation, abnormalities of ion homeostasis, molecular damage, and metabolic changes [18].

1.3. Molecular mechanisms of neurodegenerative disease

It was demonstrated that different neurodegeneration-related proteins are misfolded, and their defective degradation causes deposition in the brain results the clinical symptoms of the diseases [16], such as:
- amyloid-beta (Aβ), tau for AD
- prion protein for prion disease
- synuclein for PD
- TAR DNA-binding protein 43 (TDP-43) cause ALS
- Fused sarcoma protein (FUS) cause ALS

1.4. Cellular mechanisms of neurodegeneration

- L-glutamate and/or L-aspartate can cause acute excitotoxicity in the brain, resulting long-term neurodegenerative processes like ALS, AD, and HD, cerebral ischemia or epilepsy, even though their molecular basis might be distinct for each disease [16,19]
- Dysfunction of mitochondria is also a cause of PD [6].
  In brief, oxidative stress, impaired bioenergetic capacity of the nervous system are responsible for the pathogenesis of many neurodegenerative diseases (NDD) [20].

2. Descriptions of some prevalent NDDs

A. Motor neuron diseases (MNDs)

The feature of most MNDs include, recurrent chest infections, sleep apnea, memory loss, confusion, morning headaches, etc. These are due to insufficient oxygen intake capabilities by lungs that ultimately results breathlessness [21].

B. Amyloidosis

Amyloidosis (am-uh-loi-DO-sis) results when amyloid protein buildup and organs like heart, kidneys, liver, spleen, nervous system and digestive tract cannot work properly. This disease is recognized by its signs and symptoms those includes:

- Severe fatigue and weakness
- Shortness of breath
- Numbness, tingling, or pain in the hands or feet
- Swelling of the ankles and legs
- Diarrhea, possibly with blood, or constipation
- An enlarged tongue, which sometimes looks rippled around its edge
- Skin changes, such as thickening or easy bruising, and purplish patches around the eyes occurs when a protein called amyloid builds up in organs.
  There are many different types of amyloidosis, like:
- AL amyloidosis which is a primary one, usually affects the heart, kidneys, liver and nerves.
- AA amyloidosis is called as a secondary amyloidosis, usually associated with an inflammatory disease, such as rheumatoid arthritis. It commonly affects the kidneys, liver and spleen.
- Hereditary amyloidosis (familial amyloidosis). This is an inherited disorder where the transthyretin (TTR) protein forms by liver is abnormal, and that affects the nerves, heart and kidneys.
- Wild-type amyloidosis. This variety is known as a senile systemic amyloidosis, affects heart of aged men over 70. It occurs when the TTR protein though being normal, produces amyloid for any unknown reasons.
- Localized amyloidosis. This type of amyloidosis typically affects bladder, skin, throat or lungs, but often has a better prognosis.

C. Tauopathies

Tauopathies are the deposition of agglutinated tau protein in the brain, and include AD, FTLD-Tau, PSP, PiD, frontotemporal dementia with Parkinsonism linked to chromosome 17, and corticobasal degeneration [22–24]. Mutations in 10+16 MAPT of the tau protein induce hyperpolarization of the mitochondria, ultimately results in mitochondrial dysfunction [25,26]. Interestingly, Aβ favor the interaction of truncated tau fragment with the mitochondria [27]. Further it was shown that only in the presence of Aβ fragment the Asp421 tau can induce mitochondrial failure [28]. These evidences suggest that some specific pathological tau fragment may not induce primary tauopathies but in mitochondrial dysfunction in AD.

Another factor, mitochondrial OS whether could be an inducer of tauopathies, is a matter of consideration. At the early stages of the disease, even before the non-agglutination of *tau*, OS might occur [29]. It was shown before that the reduction in SOD1 and SOD2 led to increase the tau pathology in mice [29,30], as well as in a drosophila [31]. It appears that mitochondrial OS tauopathies might appears due to the age-dependent decrease of antioxidant molecules [32].

D. α-synucleinopathies

α-synuclein protein precipitation causes PD, DLB, and MSA [33–35]. Symptoms

α-synucleinopathies include autonomic nervous system dysfunctions along with many other, like constipation, urinary, sexual dysfunction, and reduced heart rate variability, etc. This disease is caused by synuclein gene mutations, with autosomal dominant PD variants linked to PARK, LRRK2, VPS35, and PARK2 [36,37]. Families with PD due to SNCA triplication show orthostatic hypotension (OH), sympathetic cardiac denervation, and frequent falls.

A sympathetic cardiac denervation while linked to PARK2 mutations, the LRRK gene mutations showed some abnormal symptoms like neurogenic bladder, constipation and erectile dysfunction, in PD [36]. α-synucleinopathies vastly affect the central autonomic network, parasympathetic and preganglionic sympathetic neurons [38]. The pure autonomic failure (PAF) involves loss of sympatho-adrenomedullary cells, whereas in MSA and PD, organ-selective sympathetic denervation occurs [39].

E. Dementia with Lewy bodies (DLB)

DLB, a second most neurodegenerative dementia affects 24% global population, 0.7% above 60 years of age people [40]. In a case study with 90 DLB patients, more than 50% patients displayed dysautonomia symptoms before the expression of cognitive impairment [41].

F. Multiple system atrophy (MSA)

MSA is a rare dementia cause in older adults, with autonomic dysfunction causing motor symptoms in 50% of patients, with dysautonomic symptoms influenced by cerebellar or parkinsonian motor symptoms [42–45].

G. Pure autonomic failure (PAF)

PAF is a syndrome associated with chronic OH, but without any clinical signs of central neurodegeneration [34,46]. It also causes supine hypertension, constipation, urination difficulties and thermic dysregulation [47]. α-synuclein found in PAF patients' sympathetic neurons and skin biopsies, indicating common pathology [40,48].

H. TAR DNA-binding protein-43 (TDP-43) proteinopathy

TDP-43 proteinopathy results from the deposition of TDP-43 in the brain and in the spinal cord. Most ALS patients (~97%), with frontotemporal lobar degeneration, have TDP-43 deposition in the neuron. TDP-43 is essential for RNA metabolism and neuronal cell development during embryogenesis [49]. However, TDP-43-mediated neurodegeneration involves complex pathophysiological mechanisms. Hyper phosphorylated and ubiquitinated TDP-43 were identified in the cytoplasm of ALS and FTLD conditions [50]. TARDBP gene missense mutations cause pathogenic ALS and FTLD, with small percentages in familial cases [51]. Further, TDP-43 proteinopathy may cause ALS, FTLD, AD, and atypical Parkinsonism through C9orf72 expansion. However, the pathophysiological mechanisms of TDP-43-mediated neurodegeneration is complex.

I. Prion diseases

Prion diseases include CJD, insomnia, and protease-sensitive prionopathy. These diseases result from aggregation of misfolded cellular prion protein, PrP^C. Porosity-related human prion diseases can be hereditary or acquired. *Kuru, iatrogenic CJD* transmitted to humans through meat consumption, accounts for 5% of human prion disease cases [52].

J. Alzheimer's Disease

In 1906, Dr. Alzheimer discovered many abnormal clumps and tangled bundles of fibers (now known as Aβ) plaques, and hyper-phosphorylated tau tangled protein, respectively) from a deceased brain of a woman who was suffering from memory loss, language problems, and many unpredictable behaviors [6]. Neurons are known to transmit messages from different parts of the brain, to muscles and other organs in the body. Damages of these connective and collective functions of the brain result in memory loss, and later affects the cerebral cortex, which is responsible for language, reasoning, and social behavior. Eventually, many other areas of the brain are damaged [6].

An imbalance among the levels of a production, its aggregation and clearance, might lead to synaptic damage by forming pore-like structures with channel activity. Molecular analysis reveals signaling proteins like *fyn* kinase, GSK3β, and CDK5 linked to AD neurodegenerative progression [20].

The free radical concept of aging though has inspired to use many antioxidants such as alpha-tocopherol, ascorbate and coenzyme-Q to treat the neurodegenerative diseases (NDDs), but in fact the results are with limited success. In AD, the abnormal aggregation of Aβ and tau proteins are similar to prion disease, suggesting the formation and spread of corruptive protein templating [53]. While the antioxidant cannot reverse the autophagy but can serve in removing the damaged or dysfunctional proteins and organelles to preserve the neuronal function as well as their survival [53].

Senescent cells and their mechanisms of action are still understudied but potentially important in the field of neuro-inflammation and subsequent neuro-degeneration. Characterization of cellular process and molecules involved in senescence in the brain (cells) could focus on some novel therapeutic targets for the prevention of chronic age-related NDDs [54]. Here below we summarize the key players of AD (Figure 1).
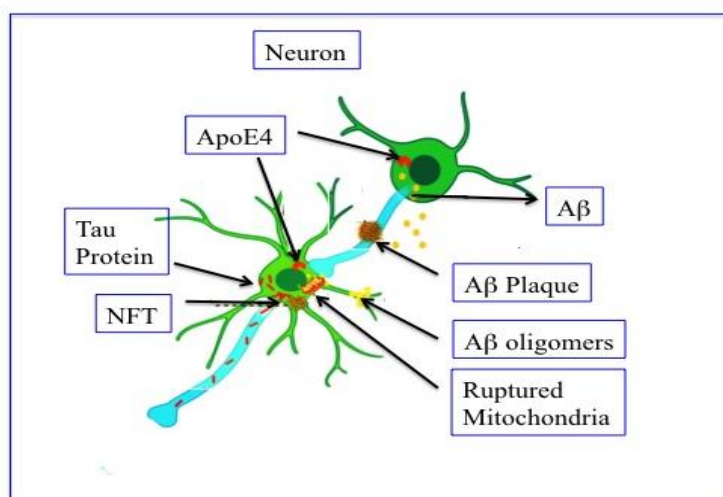

Figure 1. Keyplayers of AD.

K. Parkinson's Disease

PD manifest a movement disorder, happens when nerve cells in the brain don't produce enough of a brain chemical called dopamine. Sometimes it is genetic, but most cases do not seem to run in families. Exposure to chemicals in the environment might play a role. Symptoms begin often on one side of the body. Later they affect both sides. They include: trembling of legs, hands, and also face,

difficult postures, slowness of the movement and poor balance and coordination. As symptoms get worse, they may also have issues like depression, ultimate prognosis is not in favorable condition [55]. PD likely caused by genetics and environmental factors, with exact cause unknown [56]. Apart from the motor symptoms, non-motor symptoms also appear in PD [57,58], such as:

- Neurobehavioral Changes:
  - Depression
  - Anxiety
  - Phobia
  - Cognitive impairment
  - Dementia, and
  - Social interaction
- Sleep Disorders:
  - Fragmented sleep
  - Insomnia
  - Restlessness of the legs
  - Excessive daytime sleeping
  - Nocturnal awakening
- Sensory impairments:
  - Visual impairments
  - Smell problems
  - Color blindmess
  - Dryness of the eyes
- Autonomic failure:
  - Blood pressure irregularities
  - Gastrointestinal malfunction
  - Urinary dysfunction
  - Sexual abnormalities, and
  - Abnormal Thermoregulation
- Miscellaneous:
  - Weight loss
  - Malnutrition
  - Osteoporosis
  - Sarcopenis, and
  - Fatigue

Non-motor symptoms may precede motor symptoms; and early diagnosis of Parkinson's is challenging [59].

K.1. Mechanism of action of Parkinson's disease

Nerve cells, or neurons produce dopamine in the substantia nigra (SN) region of the brain. Dopamine is a chemical messenger for the transmission of messages to the periphery of body. Degeneration of these cells found impaired and/or dead in the brain of the PD victims. Loss of dopamine results impaired movement [60–63]. Studies have shown that most Parkinson's victims have lost 60 to 80 percent of the dopaminergic (DA-ergic) cells in the SN region. PD patients also lose the nerve ending that releases the norepinephrine neurotransmitter—the main chemical

messenger to the part of the nervous system that controls many automatic functions of the body, such as pulse and blood pressure. The loss of norepinephrine might explain several of the non-motor features seen in PD, including fatigue and abnormalities of blood pressure regulation [64–68].

- **The protein alpha-synuclein (SNCA)**—Aggregated-synuclein, also called Lewy bodies, deposit in the brain cells of PD patients. Researchers are not sure yet why and how Lewy bodies form and cause PD. It is being thought that the cell's protein disposal system may not be working properly therefore causing the accumulation of the tangled proteins in their brain, which trigger the neural cell death [69].

- **Genetics**—Several genetic mutations, including SNCA, LARK, PRKN, PINK, etc. genes are found to be linked in inherited cases, although found to be linked also with sporadic cases [70].

- **Environment**—Exposure to certain toxins or chemicals like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), or some metals like manganese, can turn on the PD symptoms [71].

- **Mitochondria**—Abnormalities in mitochondrial structure and function can produce free radicals, and that damage membrane proteins, DNA, and other parts of the cell. These are called oxidative stress, which causes free radical damage to DNA, proteins, and fats, in the brain of individuals with PD. Some mutations that affect mitochondrial function have been identified as causes of PD [72].

K.2. Genes linked to PD

Several genes have been definitively linked to PD:

- **SNCA**—This gene product is -synuclein protein, which was the first gene identified in PD patients. In all the cases of PD, Lewy bodies were found in their brain, which are actually the clumps of -synuclein [69].

- **LRRK2**—LRRK2 gene mutations were first detected in late-onset of PD among several English and Basque families. Subsequent studies have identified mutations of this gene in other families with PD (such as European Ashkenazi Jewish families, in North Africa and the Middle East) as well as in a small percentage of people with apparently sporadic PD [73].

- **DJ-1**—This gene protects cells from oxidative stress, and its mutation can result an early form of PD [74].

- **PRKN (Parkin)**—The parkin gene product breaks down the abnormal protein followed by recycling of proteins. Mutations of this gene results the formation and accumulation of plaques and tangles [75].

- **PINK1**—PINK1 gene product is an active protein in mitochondria. Mutations in this gene increase the susceptibility to cellular stress, and found to be linked with early forms of PD [76].

- **GBA** (glucocerebrosidase-beta)—GBA mutations cause Gaucher disease (in which fatty acids, oils, waxes, and steroids accumulate in the brain). Different changes in this gene are also associated with PD [77].

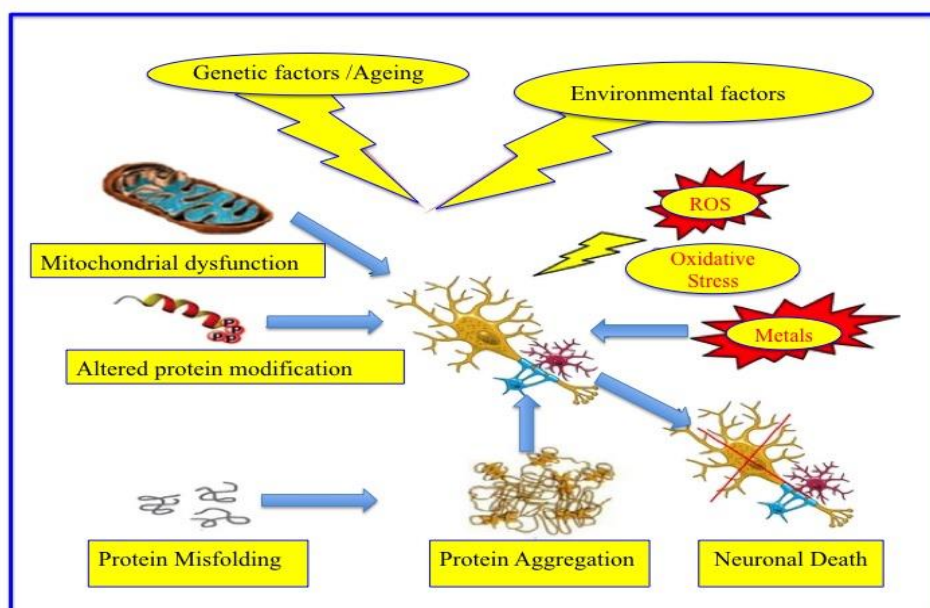## K.3. Onset Parkinson's Disease at a glance (See Figure 2)

Figure 2. Onset of PD at a glance is displayed.

3. Discussion

Cells naturally grow old and dies, therefore proper regulation of cellular proteins is crucial to maintain a healthy brain as we age. In neurodegenerative diseases, aggregation of clumped fragments of misfolded proteins, followed by spreading to neighboring cells, are still poorly understood. The Rutgers researchers studied roundworms, and found stressed nerve cells can extrude neurotoxic proteins in large packets called *exophers*. This exophers production was found during fasting and also neurodegenerative diseases like AD and PD [78].

Neuronal survival and their proper function depend on cell-cell communication mediated by ligand-receptor binding [79]. In neurodegenerative disease such as ALS, there is considerable disruption in synapse/neuromuscular junction (NMJ) that leads to neuronal cell death [80]. It is non-autonomous processes involve interactions between the neurons to its diverse extracellular microenvironments. The molecular basis for this neuronal dysfunction and death is still poorly understood.

Since a healthy brain is critical to overall health and longevity, it is important for to understand the brain health and the effect of neurological disorders on the brain. Many neurological disorders that disrupt the brain functions are:

- Traumatic brain injury, brain tumors, meningitis, and communication and sensory disorders [81].
- The overproduction of reactive oxygen species (ROS) may have their vulnerable effects on neuron cells [82].

In neurodegenerative diseases, toxic proteins spread to neighboring cells and promote cell death. Considering the importance of managing protein aggregates during aging and in neurodegenerative diseases, a detailed understanding of how those aggregates is formed and transferred. New research in the area of brain mechanisms may open a new avenue for the disease prevention and treatment.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

Conflict of interest

Both of the authors declare that the research was conducted without any potential conflict of interest from any commercial or financial institution.

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