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Review article

Mitochondrial defects in pancreatic beta-cell dysfunction and neurodegenerative diseases: Pathogenesis and therapeutic applications

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ABSTRACT

Mitochondria malfunction is linked to the development of β-cell failure and a variety of neurodegenerative disorders. Pancreatic β-cells are normally configured to detect glucose and other food secretagogues in order to adjust insulin exocytosis and maintain glucose homeostasis. As a result of the increased glucose level, mitochondria metabolites and nucleotides are produced, which operate in concert with cytosolic Ca^{2+} to stimulate insulin secretion. Furthermore, mitochondria are the primary generators of adenosine triphosphate (ATP), reactive oxygen species (ROS), and apoptosis regulation. Mitochondria are concentrated in synapses, and any substantial changes in synaptic mitochondria location, shape, quantity, or function might cause oxidative stress, resulting in faulty synaptic transmission, a symptom of various degenerative disorders at an early stage. However, a greater understanding of the role of mitochondria in the etiology of β-cell dysfunction and neurodegenerative disorder should pave the way for a more effective approach to addressing these health issues. This review looks at the widespread occurrence of mitochondria depletion in humans, and its significance to mitochondria biogenesis in signaling and mitophagy. Proper understanding of the processes might be extremely beneficial in ameliorating the rising worries about mitochondria biogenesis and triggering mitophagy to remove depleted mitochondria, therefore reducing disease pathogenesis.

1. Introduction

In many eukaryotic cells, the mitochondria, a double-membrane-bound organelle, is the largest producer of reactive oxygen species, accounting for roughly 5 % of total reactive oxygen species in normal conditions [1]. It has a diameter of 0.8 m to 2.7 m and varies in structure and length. Many mitochondria display cable-like structures as a result of the oxidative phosphorylation (OXPHOS) activity, which supplies energy to cells. Mitochondria proteins number in the millions, the majority of which are encoded by the nuclear genome, with just 1 % encoded by mitochondria genes. Nuclear-encoded mitochondria proteins are synthesized in the cytoplasm and then transferred to the

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organelle via two complexes located on the outer and inner membranes, respectively. Sustained mitochondria injury causes energy metabolism to malfunction, resulting in decreased ATP generation, increased reactive oxygen species (ROS) load, and impaired calcium buffering, all of which contribute to neuronal loss in both acute and chronic degenerative neurological malady thereby increase the electron reduction of oxygen (O_2^-) to form superoxide anion (O_2^-) [2,3]. As a result, increasing O_2 promotes mtDNA discharge, cellular damage, oxidative stress, and genomic instability [4].

Some components of the insulin signaling cascade showed an essential regulators of mitochondria functioning, according to data from animal and human research, mitochondria dysfunction is a pathogenic characteristic of diabetes-affected brains [5].

The role of mitochondria is related to bioenergetics, but they have a variety of functions which is vital for neuronal homeostasis, such as producing ROS, regulating calcium homeostasis, signal transduction, and neuronal death, according to new evidence [6,7].

Furthermore, a number of neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's, have been linked to aberrant insulin levels. Among the most recent discoveries is that a gene related to insulin processing is found in a region of the chromosome associated with Parkinson's disease [8]. Research on brain insulin and Alzheimer's disease, which is characterized by significant memory loss, was published in 2008. Postmortem insulin and insulin receptor levels in healthy and Alzheimer's patient brains were investigated. The healthy brains also exhibited up to ten times as many insulin receptors, and their average insulin levels were up to four times higher in the neuronal regions connected to learning and memory [9]. According to de la Monte, Alzheimer's is as "type III diabetes," thereby experience same issues as in conventional diabetes but only in the brain. Diabetics are more prone to develop Alzheimer's because blood-brain barrier connects brain insulin to insulin in the rest of the body [10].

Similarly, studies have linked Alzheimer's to low levels of IGF-1 and its receptor, proteins with a structure similar to insulin and its receptor, in the brain (insulin occasionally binds to the IGF-1 receptor, and vice versa). "Therefore, it was hypothesized that the aggravated loss of IGF-1 support to brain cells may be the foundation of Alzheimer's disease [11,12]. Importantly, it was discovered after the mapping of GIGYF2's function is in its location from human genome and noted that GIGYF2, a protein that interacts with insulin and IGF-1 receptors, but still unsure of the gene's potential function in Parkinson's, patients. The study discovered that it was right next to the PARK11 location, where chromosome 2 associated with the disease [13].

In recent years, challenges of β-cells dysfunctions due to various cardiovascular diseases and neurodegenerative disorders are the two modern and age-related groups of diseases, being interconnected. Although both pathologies have a genetic component, many other factors are involved in the appearance of both disorders. During recent years, different mechanisms have been proposed in the linkage between these two groups of affections [14]. Based on the clinical development as well as the stage of the disease condition, the resistance effect of insulin section and insufficient insulin actions pancreatic β-cells which in turns paralleled by amylin deposition involves the producer of producer of reactive oxygen species [14,15].

The major energy source used by mitochondria to create ATP is glucose. Glucose transporter 3 transports it into neurons, where it is transformed to pyruvate via a glycolytic process. Pyruvate enters mitochondria to create NADH and $FADH_2$ for ATP production via the Krebs cycle. A balance between glucose transit, glycolysis, and ATP production is required to maintain optimum cellular energy [16,17]. With mitochondria's dominance in the domain of exocytosis in synapses having been described as a key source of intracellular ATP and ROS, the anticipation that mitochondria affect neurotransmission should not be unexpected [18]. The mitochondria of the cell are known to produce metabolic coupling factors, or messengers, that mediate plasma membrane depolarization and an increase in cytosolic Ca^{2+}, the event that triggers glucose-stimulated insulin release. As a result, signals created by circulating hormones, neurotransmitters, and food metabolism drive the exocytosis process. By using a specific gene expression profile, cells could quickly modify insulin production to changes in glucose concentration [19].

1.1. Trafficking mitochondria

It is well known that mitochondria movement from the soma to the axons region necessitates a major important function in mitochondria trafficking within the cell due to the constant demand for energy, especially in neurons (synapses) where high energy demand necessitates ATP along the entire neuron through the association with KIF1Ba and KIF5 (kinesin family motor proteins), while movement back to the cell soma is interceded by cyto, Miro, the heavy chain of kinesin-1 (KHC), Milton, and dynein were all part of this complex. Miro is a mitochondria Rho-like GTPase linked to the OMM that interacts directly with Milton, which attracts the KHC to mitochondria [20–22].

1.2. Molecular mechanisms of Mitophagy

Careful degradation of mitochondria by autophagy is termed mitophagy, which is very paramount in the quantitative and qualitative control of mitochondria [23,24]. This was first proposed in 2005 by Lemasters [25] and it comprises of several processes that includes mitophagy initiation, priming of mitochondria for recognition by autophagy machinery, engulfment of the marked mitochondria by formation of the autophagosome and lysosomal sequestration and hydrolytic degradation [26]. Several regulatory pathways of mitophagy are classified into PINK1/Parkin-mediated mitophagy and receptor-mediated mitophagy and are initiated in response to different stimuli [27].

1.3. Reactive oxygen species (ROS) and mitochondrial uncoupling

The detachment of electron-dependent oxygen consumption from ATP synthesis within the respiratory chain is referred to as uncoupling mitochondria. The properties of its homolog UCP2 found in β-cells, which are still unknown in comparison to UCP1 found in brown adipose tissue (BAT). Furthermore, overexpression of UCP2 in β-cells improves ATP and GSIS synthesis, whereas islets derived from UCP2-deficient animals on a mixed genetic background demonstrate enhanced ATP and GSIS synthesis [28,29]. The absence of UCP2 improves blood glucose levels and insulin secretory capability in a high-fat diet-induced type II diabetes mellitus (T2DM) mouse. Chronic exposure to FAs was found to suppress the secretory response to glucose in an INS-1 B-cell model. This happened in conjunction with the activation of the UCP2 gene and partial uncoupling [30,31]. Immunogenic signals activate immune cells in pancreatic islets that are sick, dying, deficient, or injured. Reduced UCP2 gene expression in obese and diabetic patients' mononuclear cells might contribute to metabolic problems caused by immunological abnormalities [32,33]. Inflammatory cytokines and chemokines are released by these activated immune cells, which activate macrophages and T-cells inside and surrounding pancreatic islets, exacerbating inflammation [34]. These metabolic perturbations increase the number of dysfunctional or apoptotic β-cells [34]. The findings suggested that UCP2 plays a crucial role in β-cell dysfunction and T2DM etiology, according to the researchers [35].

2. Relationship between β-cell failure and depleted mitochondria

Insulin secretions are influenced by a number of metabolic processes, including glucose glycolysis, pyruvate transformation, ATP synthesis, and the activation of voltage-dependent Ca^{2+} channels [36–38]. Glucose transporter 2 is involved in the absorption of glucose into the cytosol by the cell, and this cytosolic action from glycolysis results in the

production of pyruvate via glucokinase phosphorylation [36–39]. The pyruvate product was converted to acetyl-CoA by an enzyme called pyruvate dehydrogenase complex, which was then transported into mitochondria, where ATP was created by the TCA cycle and OXPHOS to up-regulate the cytosolic ATP concentration [39]. This result balances the ATP-sensitive K^+ channel's lockdown effect against the voltage-dependent Ca^{2+} on the plasma membrane in order to allow more Ca^{2+} to pass into the cytosolic area, resulting in insulin exocytosis [36,37].

2.1. Cellular source of ROS in β-cell function

ROS are a category of reactive chemicals formed from molecular oxygen that include superoxide anion (O^{2-}), hydroxyl radical (OH), and hydrogen peroxide as by-products of biological metabolism (H_2O_2) ROS are tightly controlled in cells by antioxidant defense mechanisms that include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), ascorbic acid (vitamin C), tocopherol (vitamin E), and glutathione (GSH). Oxidative stress is caused when the generation of ROS overwhelms the antioxidant defense system. The majority of neurodegenerative disease causative variables can result in excessive ROS production, emphasizing the critical role of ROS in disease pathogenesis [40,41].

Therefore, the said ROS here refers ultimately to H_2O_2, which is much more lasting than O_2^- within the cells [42]. In diabetics, increased oxidative stress and free radical-induced damage have been noted as problems. Nonetheless, food metabolism raises ROS while having no negative impact on cell function [43]. Report validated that ROS probably part-take in cell signaling and reported that both ROS and H_2O_2 serves as one of the metabolic coupling factor in glucose-induced insulin secretion [44,45]. As a result, the fluctuation mode of ROS may play a role in the physiological regulation of β-cell activities. Inability to control the entry of oxidants, or a decrease in their detoxification, could lead to free radical-mediated chain reactions, thereby results to pathogenic events (Fig. 1) [46].

2.2. ROS triggers β-cell dysfunction

With its importance as a signaling molecule in multiple pathways, the presence of ROS in cells cannot be overstated. As a result, excessive levels of ROS caused the breakdown of most proteins, lipids, and nucleic acids, which in turn damaged cell functioning and caused cell death. Furthermore, mitochondria ROS are increasingly involved in cellular activity, such as cell differentiation, multiplication, and death, and this might affect the life and function of cells [47,48]. When cells misplace, a large amount of ROS contributes to apoptosis, even in the differentiation condition of pancreatic β-cells, resulting in a limited regeneration ability. Thus, in the presence of increased β-cell loss, either by apoptosis or dedifferentiation, a scenario will arise in which β-cells are lost with insufficient replacement, resulting in inadequate insulin secretion to maintain proper glucose homeostasis [49,50].

Furthermore, in any organism, the inability of pancreatic β-cells to sense glucose levels or respond to the requirement for insulin results in impairment, which has a significant impact on systemic metabolism. The cells are severely harmed in a major condition like diabetes mellitus.

Temporary fluctuations in blood glucose may be readily rectified by altering insulin production, which lies mostly in the mitochondria structure [51,52]. When all of this is considered, mitochondria in pancreatic β-cells play a significant role in insulin production. As a result, this raises a set of questions about whether mitochondria-targeted therapies might be a feasible therapy strategy for diabetes patients to boost pancreatic β-cells). When all of this is considered, mitochondria in pancreatic β-cells play a significant role in insulin production. As a result, a number of questions have been raised about whether mitochondria-targeted therapies may be a feasible therapy strategy for promoting pancreatic β-cells in diabetes patients.

2.3. Stress and mitochondrial dysfunction have a role in neurodegenerative illnesses

An enormous quantity of energy (ATP) is required to maintain normal brain activity. The brain, along with the heart and skeletal muscle, is the most energy-dependent of all the body's main

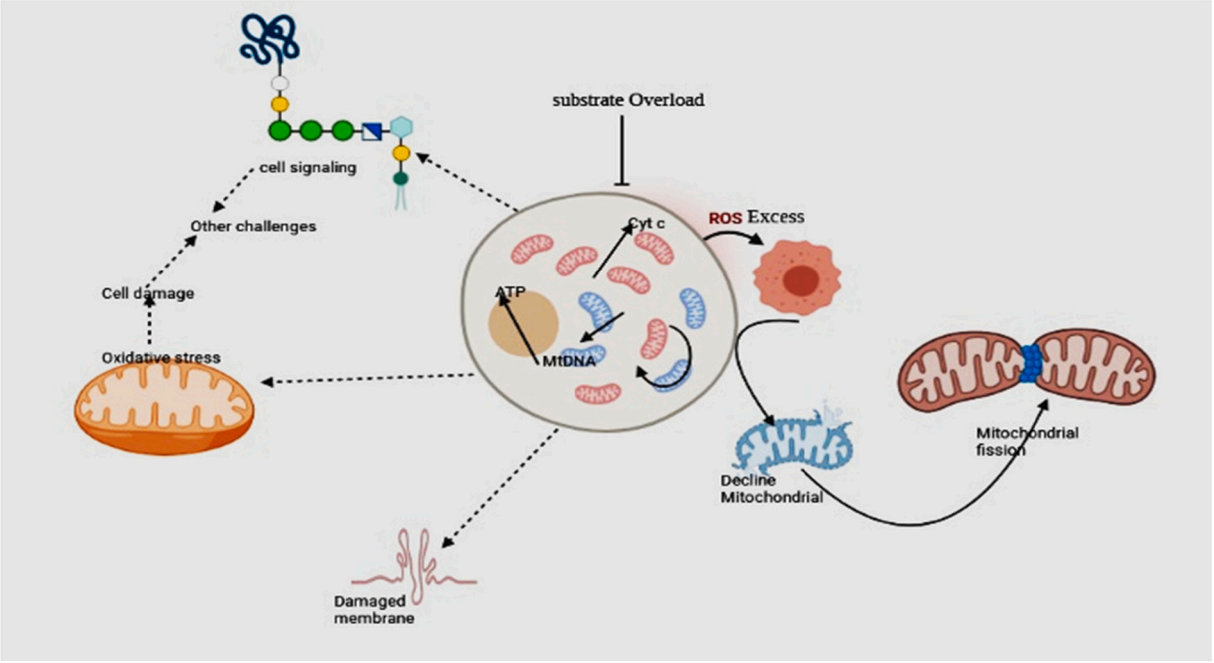

Fig. 1. ROS overproduction in malfunction mitochondria. This shows excessive generation of ROS could lead to overload on the substrate in most of the metabolic disorder thereby leading to depletion in mitochondria function and mitochondria fission. An enhanced mitochondria fission causes overproduction of ROS and is frequently associated with metabolic disorder.

components. The major source of energy necessary for the correct functioning of the brain is produced mostly by mitochondria cells' normal activity. ATP production in mitochondria is primarily associated with an ETS, through which the passage of electrons through various electron carriers is coupled with the transport of protons from the mitochondria matrix into the inner-membrane space, and then these protons re-enter the mitochondria matrix via ATP synthase for ATP production. [53–55]. Given the importance of mitochondria in cell stimulus-secretion coupling, there are little or no genetic evidence in humans that link mitochondria malfunction to diabetes mellitus etiology [56–58]. Nevertheless, research had revealed that mutation in the mitochondria tRNA synthase $tRNA^{Leu}$ result to inherited diabetes while the variant in the mitochondria transcription factor TFB1M have been implicated world-wide by GWAS (genome-wide association studies) [57]. The mitochondria and ER took a larger size, closed to each other with mitochondria looking swollen and round the diabetes condition, thereby reflecting the stress of ER and dysfunction of mitochondria [59]. Apart from changed energy and increased ROS generation, mitochondria malfunction also causes changes in Ca^{2+} buffering, apoptosis, and senescence, all of which can contribute to the gradual deterioration of post-mitotic cells thereby developed to varieties of neurodegenerative disorders [60].

Furthermore, despite the importance of cytotoxic reactive oxygen species (ROS) in maintaining intracellular signaling molecules for varieties of cellular responses, such as insulin sections from pancreatic β-cell, their major contribution as an intermediate to signaling may have propose how greatly they would be related with ROS- scavenging potential and status of antioxidant in the cells [61]. Therefore, cellular ROS-scavenging capacity would be induced via the nuclear factor erythroid-derived factor 2 (Nrf2) as well as transcriptional induction of a suite of antioxidant enzymes as a result of continual exposure of the cells to oxidative stressor(s) [61].

However, dysfunction to mitochondrial, as well as abnormal interactions with mis-folding of synaptic proteins and oxidative stress within the CNS are examined and explored as the major fundamental features in apostasy of several neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS) [62]. Therefore, most of their underlying mechanisms are deciphered below.

3. Neurodegenerative diseases and mitochondria

3.1. Parkinson's diseases (PD)

Parkinson's disease was ranked second among neurodegenerative diseases in terms of total dopaminergic neuron loss in the substantia nigra (SN) [52]. Shortcoming experienced in mitochondria function and kinetics in several gene occurs because of their pathogenic mutations in PD [63].

Meanwhile, mitophagy occurs when-synuclein aggregates, it results in phagosome-lysosome union. Synaptic neurotransmission and axonal transport are normally carried out at a high energy level as a result of mitochondria ATP generation. Normally, the process of oxidative phosphorylation in the electron transport chain within the inner mitochondria membrane results in a complete reduction of molecular O_2 to water (H_2O). This oxidative phosphorylation process may also result in an incomplete reduction of O_2 to O_2 rather than H_2O for a variety of reasons, and this superoxide anion generation is particularly noticeable in complexes III and I Superoxide. The cellular antioxidant system, which includes superoxide dismutase (SOD), reduced glutathione (GSH), and others, protects the cell from free radical damage. As a result of an imbalance between the generation of free radicals and the cellular antioxidant defense mechanism, “oxidative stress” occurs, which is defined as an accumulation of excessive reactive oxygen species (ROS) and the resulting damage to biological molecules such as lipids and nucleic acids [22].

In recent years, several genes such as *α-synuclein, parkin, ubiquitin carboxy-terminal hydrolase L1, DJ-1, phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), leucine-rich-repeat kinase 2 (LRRK2), nuclear receptor NURR1 and HTRA2* play a major role in the pathogenesis of PD patients [3,64,65]. *PINK1*, a mitochondria kinase whose deficiency has been linked to higher levels of ROS and increased vulnerability to oxidative stress, is ideal for protecting cells from oxidative stress-induced apoptosis by regulating cytochrome *c* release from mitochondria while mitochondria quality control is inhibited by mutated parkin. Because of its antioxidant activity, DJ-1 mutations are linked to oxidative stress and apoptotic cell death due to its interaction with import receptors via -synuclein. By interacting with inhibitory apoptotic proteins, the mitochondria serine protease HTRA2 is implicated in apoptotic cell death (Fig. 2).

3.2. Huntington's diseases (HD) and amyotrophic lateral sclerosis (ALS)

In this type of neurodegenerative disorder, uncoordinated muscle and genetic abnormality results in mental and behavioral symptoms, thereby leads to the depletion of polyglutamine shape (PolyQ), which encodes CAG, by repeating itself in the exon 1 of the HD protein, causing aggregation. The disease strikes around the age of 35, with the beginning of age correlating to the number of CAG repeats, aggravating the severity of the sickness [66,67]. Once the protein is misfolded, the mutant *Htt* is directly interacted with the outer mitochondria membrane and modify the membrane thereby causing an elevation in Ca^{2+} sensitivity and several apoptotic inducers [66,68].

However, mitochondria dysfunction mediated by increased ROS generation in HD patients lowers respiratory illness and motility while increasing mitochondria fragmentation. [52,69]. Because of the mutation of *Htt*, an interaction of HD with mitochondria outer membrane is obvious, resulting in the release of cytochrome *c* and apoptotic cell death, which in turn affects mitochondria transport and dynamics. As a result, the *Htt* mutant in striatal neuron expression resulted in a decrease in *HTRA2* in HD patients (Fig. 3) [3,64].

Additionally, amyotrophic lateral sclerosis develops as a result of the gradual loss of motor neurons in the anterior horn of the spinal cord and brain, resulting in widespread weakness, muscular atrophy, and respiratory failure. In 5 % of cases of ALS, mutations in genes like cytosolic SOD1, FUS, UBQLN2, and C9orf72 were found, as well as overrun of ROS/ RNS and dramatic gliosis characterized by abnormalities of astrocytes, astrocytosis specificity, and elevation in expression of inducible nitric oxide synthase (iNOS) and activated microglial cells [70]. Furthermore, structural flaws in mtDNA and mitochondria genome anomalies have been found in ALS patients.

3.3. Friedreich's Ataxia

This is a genetic condition that is defined by a continuous repetition in the frataxin gene extension, resulting in mitochondria dysfunction via the production of reactive oxygen species (ROS) [71]. As a result, oxidative stress leads to a shortage of iron-sulphur clusters, which leads to the inhibition of the electron transport chain complexes (Complexes I, II, and III), resulting in ROS leakage from oxidative phosphorylation processes.

Several investigations have demonstrated that a lack of frataxin inhibits mitochondria respiration, upregulating ROS leakages, and eventually leading to mitochondria malfunction, oxidative stress, and ion mitochondria coagulation [72,73]. The result in this case caused neuronal atrophy that show dorsal root ganglia and dentate nucleus of the cerebellum [74,75]. Pathophysiology investigations of mitochondria on post-mortem tissues or fibroblasts may be harmed due to inconsistencies in tissue harvest and conservation protocols, while fibroblasts are not impacted in the FRDA. Although nonsense mutations have been suggested as a possible source of frataxin disruption, the primary reason is due to the flexibility of the GAA polymorphic trinucleotide that

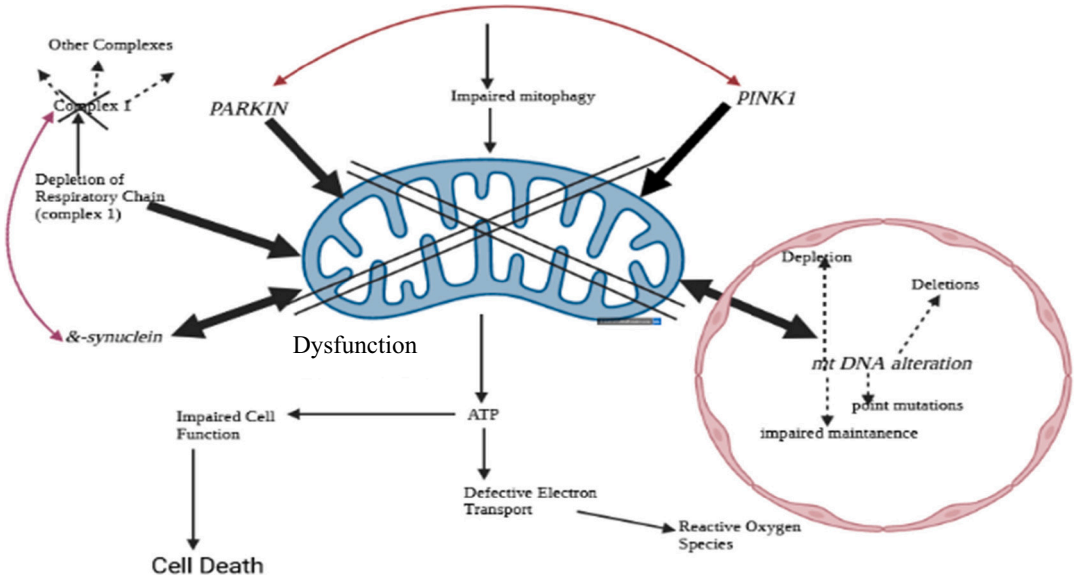

Fig. 2. Malfunction of Mitochondria in Parkinson's disease. The figure briefed the major event in mitochondria-related mechanisms that occurred in PD pathogenesis. Taken together all the cases, abruption in mitochondria membrane occurs, which causes changes in mitochondria permeability. ATP production attenuation causes an impaired cell function and cell death. Otherwise, it may shunt the functions of electron transport chain, thereby resulting into further generation of excessive mitochondria ROS and the ultimate outcome is the mtDNA destruction.

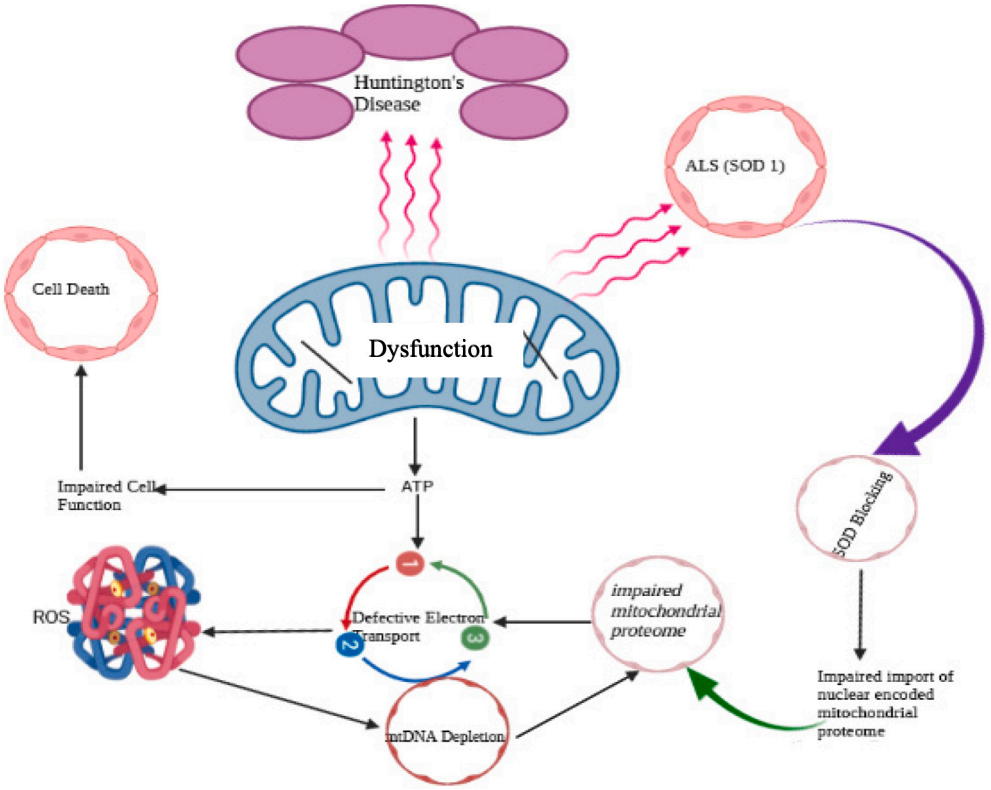

Fig. 3. Mitochondria dysfunction and reactive oxygen species in Huntington's diseases. Mitochondria membrane disruption occurs, which in this case, there is a change the mitochondria permeability which give rise to mitochondria membrane depletion and in turn reduces the level of ATP that eventually causes impaired cell function and cell death. Therefore, the functions of electron transport chain are totally shunt down resulting in further generation of excessive mitochondrial ROS.

appears in the first intron of the target gene, resulting in frataxin mRNA down-regulation. Research findings pointed out that a gene from yeast is corresponding to that of frataxin gene in human [76] where the gene encoded for mitochondria protein that contain iron homeostasis and respiration function. This human gene (*frataxin*) have been traced to green fluorescent protein, which is found in mitochondria [77,78]. As a result of the deletion of the relevant gene, respiration was unable to execute phosphorylatory activities (oxidative phosphorylation), resulting in mitochondria DNA loss [76–78]. As a consequence, the research's suggestive role revealed that decreased activities of this protein are a

result of mitochondria depletion, which finally leads to oxidative stress over-reactivity that is treated with iron catalyzed reactions. Endomyocardial biopsies of individuals with Friedreich's ataxia have been used to support Fenton chemistry [79].

3.4. Alzheimer's disease

It is estimated that more that 10 % population of 65 years above could be affected by this disorder called Alzheimer's disease (AD) in 2040 with around 3 % of population of 65 years above suffering from the disease [80,81]. This is characterizing with dementia, the main clinical feature among the complicated molecular events where presence of neurofibrillary tangles (NFTs), senile plaques, and neuronal loss are the most remarkable. Reduced 18-FDG uptake in the temporoparietal cortex is particularly striking in AD brains, according to research, although metabolic defects in the brain are a prevalent problem, according to other studies [81–83]. Furthermore, the pace at which people with Alzheimer's disease use deficient oxygen is substantially higher, indicating that mitochondria dysfunction and bioenergetics paralysis are common in Alzheimer's disease. The amyloid hypothesis, which has a lot of evidence, is commonly accepted as the pathophysiology of this illness, although mitochondria malfunction and ROS build-up enhance redox imbalance and tau-induced neurotoxicity.

Furthermore, stimulation of pro-inflammatory gene transcription and release of cytokines, such as interleukin (IL)-1, -6, and tumor necrosis factor-alpha (TNF-α), is caused by an increased level of ROS thereby causing a loss of neurons from chronic neuro-inflammation [84]. Furthermore, ROS is produced in huge quantities by activated microglia and astrocytes driven by inflammatory responses, which is a primary source of persistent oxidative stress. As a result of the cumulative effects of oxidative stress and neuroinflammation, pathological events such as the formation of NFTs, inflammatory reactions, stress in the endoplasmic reticulum, altered acetyl-cholinergic neurotransmission, increased oxidative stress, and mitochondria dysfunction result in cell death and dementia [3,85,86]. Mitophagy has also been linked to Alzheimer's disease patients. Several investigations in both human and animal models have found that the mitophagic machinery plays a role in Alzheimer's disease, with mitophagy activation improving the neuropathological and clinical aspects of those models [87–90]. Shown in Fig. 4.

4. Therapeutic approach to the challenged mitochondria

Through the introduction of a better chemical, improving mitochondria activity must be the first major therapeutic strategy in the etiology of cell failure, depleted mitochondria, and any neurodegenerative illnesses. Ubiquinone is one of these molecules, which has the potential to absorb and give electrons along the electron transport chain while also having high antioxidant characteristics, especially in mitochondria. Researchers discovered that ubiquinone protects cultured cerebellar cells against glutamate toxicity, resulting in dose-dependent protection against striatal lesions caused by the succinate dehydrogenase inhibitor malonate [91,92].

Furthermore, creatine stimulates mitochondria respiration and phosphocreatine synthesis, a direct energy source for glutamate uptake into synaptic vesicles thereby sustain ATP levels under stress conditions [93,94]. Rosiglitazone and Bezafibrate have been added to those therapeutic compounds, with Rosiglitazone demonstrating a superior

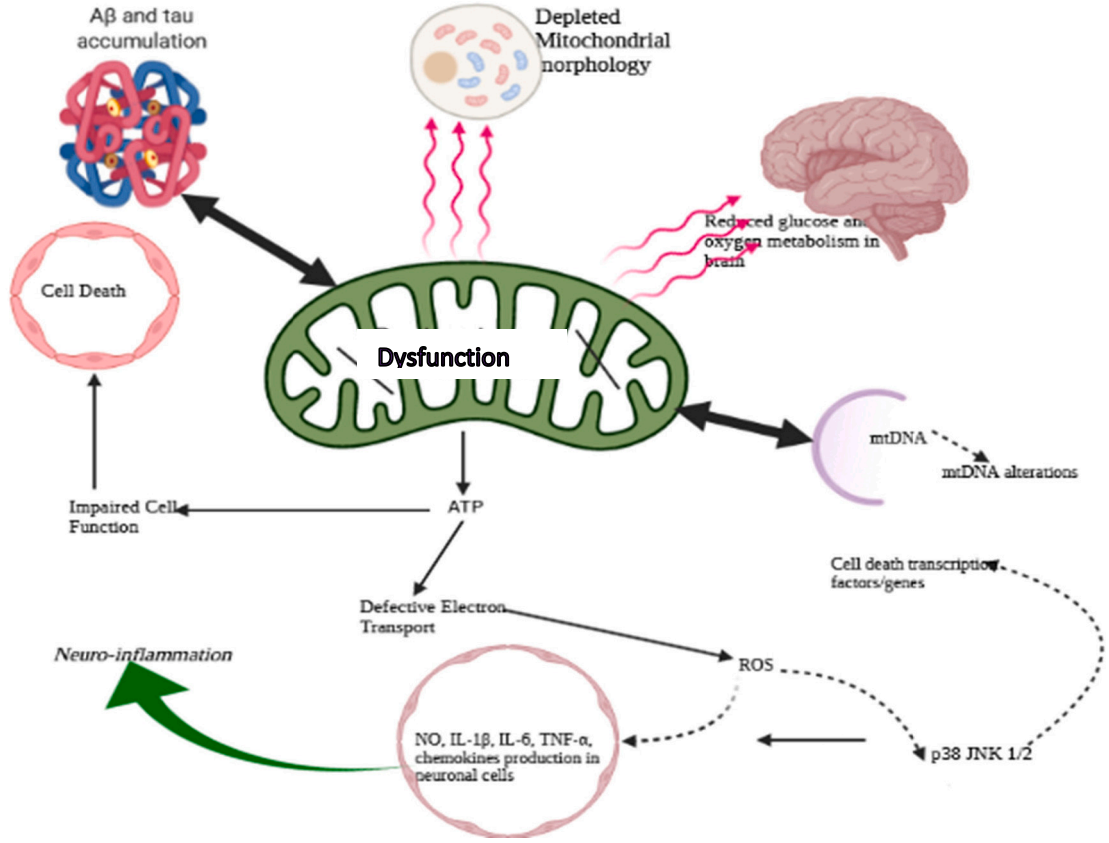

Fig. 4. Major mitochondria-related mechanisms in the pathogenesis of AD. This revealed a malfunction mitochondria morphology and reduced glucose and oxygen consumption in patients' brains. Furthermore, reactive oxygen species mediated neuro-inflammation and neuronal cell death was summarized where several route of ROS could result in generation of NO thereby forming other different inflammatory mediators like interleukin-1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and chemokines in neuronal cells that later results in cell death. Differently, ROS via p38 and JNK1/2 pathways may affect cell death transcription factor/genes (c-JUN, AP-1, JUN-β/−δ) and cause neuronal cell.

neuroprotective role in a mouse model of mitochondria encephalopathy through increased mitochondria ATP capacity and mitochondria proteins, and Rosiglitazone demonstrating a reduction in mitochondria depletion in mutant *Htt*-expressing cells [95].

The development of antioxidants finally reduced the damage to mitochondria caused by oxidative stress, which is a big step forward in the treatment of depleted mitochondria. MitoQ, an antioxidant containing a quinone moiety that binds to a triphenyl-phosphonium moiety, has been shown to reduce mitochondria depletion in in-vivo tests as well as two phase II human trials. As a result, the molecule may be obtained orally for a year at dosages that have been shown to be helpful in reducing liver damage [96].

Antioxidants such as CoQ10, vitamin E, and vitamin C also play a significant role in the treatment of mitochondria disease patients. When paired with their equivalents, they are quite beneficial. In a patient with Leigh syndrome, Trolox ornithylamide hydrochloride, a vitamin E analogue, reduced ROS levels and increased mitochondria activity in complexes such as complex I, IV, and citrate synthase [97,98].

In addition to scavenging ROS and promoting mitochondria biogenesis, mitophagy induction may be employed to maintain mitochondria homeostasis. Urolithin A (an ellagitannin metabolite) produced by the human gut microbiota slows mitochondria dysfunction with age, increases lifespan in Caenorhabditis worms, and improves muscular performance in rats, and is one of the main inducers of mitophagy. As a result, the indicated mitophagy inducer can pass the blood-brain barrier, protecting neurons against neurodegenerative diseases [99]. Spermidine from putrescine is another mitophagy inducer. Its role is to operate as an acetylase inhibitor, inducing autophagy in a SIRT1-independent manner, improving basal autophagic flux and arousing mitophagy-repairing mitochondria activity in aged cardiomyocytes [100,101].

Feeding on spermidine preserves age-induced memory impairment in autophagy dependent manner thereby cause a reduction in the accumulation of depleted mitochondria via *PINK1/Parkin* pathway [102].

In certain individuals with mitochondria challenge, the location of an exercise has been proven to be an ameliorative point, especially in aerobic conditions, where endurance training can promote mitochondria biogenesis and activate muscle mitochondria enzyme activities and muscular strength. [103–106]. Aside the activation of resistance against rotenone (an inhibitor of complex I activity), exercise has been demonstrated to stimulates mRNA expression of TFAM and Ndufa6 subunits of mitochondria complex I [107]. Furthermore, exercise-induced increases in mtDNA repair in the mouse hippocampus activate the UCP1 protein, which regulates mitochondria multiplication [108]. Another significant element of exercise is the up-regulation of UCP2 in the hippocampus, which decreases oxidative cellular stress and increases autophagy, which helps to keep muscle mass functioning [109,110]. Therefore, increase in mitophagy abates the damaged level of mitochondria to maintain a better functioning and quality of mitochondria in cells.

Furthermore, calorie restriction, which decreases calorie consumption while maintaining all required nutrients without starvation, is a superior strategy to improve mitochondria activity. Reduced calorie intake reduces ROS generation, reducing oxidative damage and slowing the transcriptional changes associated with aging [111]. Caloric restriction causes an increase in the number of mitochondria cristae and mitochondria per cell, and this event typically prevents excitotoxic circumstances by causing indirect illness in mitochondria permeability and calcium retention. The process is mediated by calorie-restricted SIRT3 deacetylation and cyclophilin D inhibition [112,113]. Sirtuins play a critical role in mediating the beneficial benefits of calorie restriction on lifespan. As a result, overexpression of SIRT1 improves life expectancy and lowers neurodegenerative illness disease syndromes [114,115].

Due to their chronic ill health, lack of sun exposure (immobility), or nutritional inadequacy, many individuals with impaired mitochondria are at risk of vitamin D deficiency. As a result, blood vitamin D levels should be checked often, and vitamin D replacement should be considered if necessary.

5. Final remarks

Because insulin is a critical hormone that promotes a low blood glucose level, its production by pancreatic cells is closely controlled, this review highlights the role of mitochondria in pancreatic cell dysfunction. Any damage to or malfunction of cells can result in inadequate insulin secretion and, as a result, diabetes. The characteristic of neurodegenerative illnesses is mitochondria dysfunction, which is shown by an increase in reactive oxygen species generation, antidromic intracellular Ca^{2+} levels, and a decrease in mitochondria ATP synthesis. The reality remains that multiple pathways in neurodegenerative illnesses may be impacted, which may lead to alternative treatment approaches. These results will be converted into effective and new therapies for both cell dysfunction and mitochondria dysfunction-related neurodegenerative diseases. Moreover, in order to target malfunctioning mitochondria or reverse the chronic consequences of altered mitochondria dynamics, a variety of biomolecules-based treatment techniques have been proposed to alleviate the clinical symptoms of both cell dysfunction and neurodegenerative diseases. Furthermore, it is safe to state that current understanding of the role of altered mitochondria dynamics in the etiology of both cell dysfunction and neurodegenerative illnesses is still in its infancy. However, given its tremendous progress in both clinical research and therapeutic application, we expect major research efforts to be directed into this sector and new ways to be developed shortly. We also expect these results to be converted into successful and new therapies for both cell dysfunction and neurodegenerative illnesses caused by mitochondria malfunction in the future. As a result, in various processes that may induce mitochondria damage, a multifaceted treatment strategy would be a more essential and superior alternative.

CRediT authorship contribution statement

S.A.O designed and conducted the study and wrote the manuscript. B.L., B.E.O., B.O.A, S.U, C.W., T.B.E. and J.S-G. helped with analysis and literature review and revised the manuscript All authors read and approved the final version of the manuscript.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data presented in this study are available in article.

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