Published in final edited form as:

Ageing Res Rev. 2022 January ; 73: 101529. doi:10.1016/j.arr.2021.101529.

Deregulated mitochondrial microRNAs in Alzheimer's disease: Focus on synapse and mitochondria

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia and is currently one of the biggest public health concerns in the world. Mitochondrial dysfunction in neurons is one of the major hallmarks of AD. Emerging evidence suggests that mitochondrial miRNAs potentially play important roles in the mitochondrial dysfunctions, focusing on synapse in AD progression. In this meta-analysis paper, a comprehensive literature review was conducted to identify and discuss the (1) role of mitochondrial miRNAs that regulate mitochondrial and synaptic functions; (2) the role of various factors such as mitochondrial dynamics, biogenesis, calcium signaling, biological sex, and aging on synapse and mitochondrial function; (3) how synapse damage and mitochondrial dysfunctions contribute to AD; (4) the structure and function of synapse and mitochondria in the disease process; (5) latest research developments in synapse and mitochondria in healthy and disease states; and (6) therapeutic strategies that improve synaptic and mitochondrial functions in AD. Specifically, we discussed how differences in the expression of mitochondrial miRNAs affect ATP production, oxidative stress, mitophagy, bioenergetics, mitochondrial dynamics,

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Declaration of competing interest

We would like to inform you that we have a pending patent 'MicroRNA-455-3p as a Potential Peripheral Biomarker for Alzheimer's Disease (US 20200255900)' related to the contents of our manuscript.

synaptic activity, synaptic plasticity, neurotransmission, and synaptotoxicity in neurons observed during AD. However, more research is needed to confirm the locations and roles of individual mitochondrial miRNAs in the development of AD.

Keywords

Alzheimer's disease; MicroRNAs; Mitochondria; Synapse; Bioenergetics; Synaptic activity

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder and is the most common cause of dementia in older people, making up 60 to 80% of dementia cases. Dementia refers to a decline in brain functioning in multiple areas including memory, reasoning, and language (Bulgart et al., 2020). Cellular changes occur at least two decades before clinical symptoms develop in patients with AD. The main characteristics of AD are memory loss and cognitive impairment that adversely affect patients' ability to independently carry out their daily activities. Causes of AD are still unknown and no curative treatments exist (DeTure and Dickson, 2019; John and Reddy, 2021; Sheladia and Reddy, 2021).

AD is one of the major public health concerns in the world (DeTure and Dickson, 2019). An estimated 6.2 million Americans over the age of 65 currently live with AD, 72% of them being 75 or older (Alzheimer'sAssociation, 2021). AD is becoming an increasingly bigger problem in the United States as its population with age 65 and older is projected to grow from 58 million in 2021 to 88 million by 2050 with the number of new AD cases predicted to double by 2050 (Alzheimer's Association, 2021). As the prevalence of AD increases, so will the resulting financial and family burdens.

The predicted aggregate cost of care for people, ages 65 and older with AD or other dementias in 2021 is $355 million in the United States (Alzheimer'sAssociation, 2021). The cost of care for AD patients is predicted to increase to $1.1 trillion due to increases in government spending through Medicare and Medicaid programs and out-of-pocket expenses (Alzheimer'sAssociation, 2021; Wong, 2020). In addition to financial burdens, AD patients have increased emotional and physical stress on family members and friends. Increases in stress is partly due to financial burdens caused by medical costs and reduced earnings by having to work less, increased responsibility of care due to progressively worsening symptoms, presence of other diseases, and watching a family member's condition deteriorate (Brodaty and Donkin, 2009). A meta-analysis report showed that 30 to 40% of family members who care for someone with dementia have stated having depression (Alzheimer's Association, 2021).

Research has shown that changes in the brain such as the presence of soluble and insoluble beta-amyloid (Aβ) (Kametani and Hasegawa, 2018; Sadigh-Eteghad et al., 2015), neurofibrillary tangles (NFTs) and accumulation of abnormal form of phosphorylated tau (p-tau) protein inside the neurons (Ashrafian et al., 2021; Hondius et al., 2021), mitochondrial dysfunction (Swerdlow, 2020; Weidling and Swerdlow 2020; Kodavati et al., 2020), atrophy

(Planche et al., 2021), and inflammation (Cullen et al., 2021) are found to be associated with AD.

The synapse requires large amounts of energy to effectively transmit signals. Mitochondrial dysfunction in AD prevents the synapse from properly carrying out its function, thus leading to decreased neurotransmission and weaker synaptic connections. This leads to cognitive impairment and worse memory that is present in AD. Therefore, understanding how mitochondrial miRNAs affects mitochondrial function at synapse and the role they play in the progression of AD will allow researchers to use these miRNAs as biomarkers or potential treatments. This article discusses how the change in the expression of mitochondrial miRNAs affects the production of energy by neurons in the brain during AD and how this leads to the progression of AD.

1. Alzheimer's disease

Alzheimer's disease occurs in two forms: early-onset (familial) and late-onset (sporadic). Familial AD develops well before the age of 65, typically between the ages of 30 and 50, and is extremely rare (one to two percent of all AD cases). Familial AD is caused by mutations in amyloid-beta precursor protein (APP), presenilin1 (PSEN1), and presenilin 2 (PSEN2) genes, which leads to overproduction of Aβ plaques (Ayodele et al., 2021; Lane et al., 2018; Mao et al., 2011).

Multiple factors are involved in late-onset AD, including lifestyle (unhealthy diet and physical inactivity), traumatic brain injury, diabetes/obesity, cardiovascular, hypertension, kidney disease, epigenetic factors, and environmental and occupational exposures (Sheladia and Reddy, 2021). In addition, APOE4 genotype is a major risk factor. Researchers have found that APOE-e4, a gene that supplies the blueprint for a protein that transports cholesterol in the bloodstream, increases the risk of AD (Safieh et al., 2019). Above all, age is the single most important risk factor causing both familial and sporadic AD and also in combination with aging, single nucleotide polymorphisms largely contribute to late-onset (Chakrabarti et al., 2015; Guerreiro and Bras, 2015; Van Cauwenberghe et al., 2016; Cannon-Albright et al., 2019). The symptoms of AD usually begin after the age of 60 and the percentage of people with AD exponentially increases with age: 5.3% for 65–74 age group, 13.8% for 75–84 age group, and 34.6% of 85 and older age group (Alzheimer's Association, 2021).

Regarding APOE4 in AD, every person inherits one of the three alleles of the APOE gene (e2, e3, or e4) from each parent leading to six possible APOE pairs (Strittmatter and Roses, 1996). However, occurrences of specific APOE pairs seem to differ in different racial and ethnic groups. For example, the percentage of African Americans inheriting the AD-causing APOE-e4 is about 38.8% compared to 26.2% for European Americans (Alzheimer'sAssociation, 2021). A meta-analysis by Ward and others (Ward et al., 2012) found that 56% of the people diagnosed with AD in the United States had one copy of the APOE-e4 gene followed by 11% with two copies of that gene. However, research findings related to the risk of the presence of APOE-e4 on AD are inconclusive. For example, many AD studies (Green et al., 2002; Liu et al., 2013; Hendrie et al., 2014) that involved Black

Americans have had inconsistent results regarding the presence of e4 allele in the risk of developing AD.

1.1. Synapse basis of Alzheimer's disease—Accumulation of Aβ monomers, oligomers, and deposits/plaques interfere with neuron-to-neuron communications at synapses contributing to neurodegeneration (damage and death of neurons) (He et al., 2019; Kumar and Reddy, 2020). Similarly, tau tangles inside neurons block the transport of essential molecules for the normal functioning and health of neurons (Niewiadomska et al., 2021). Figure 1 depicts how the presence of p-tau and Aβ oligomers contribute to synaptic dysfunction.

The research related to the sequence of events that leads to the death of neurons is limited; however, researchers believe that increases in tau are associated with an increase in Aβ (Gerrits et al., 2021; He et al., 2019). Further, the presence of these toxic proteins is believed to activate microglia, the principal immune cell in the brain, to remove toxic proteins and dead cells (Azam et al., 2021). Figure 1 highlights the resulting activation of microglia in the brain. When microglia cannot keep with their cleaning function, chronic inflammation in the brain can occur. Therefore, inflammation is considered a biomarker of AD and can be used to measure the presence or absence of AD (Park et al., 2020). Researchers have become increasingly interested in microRNAs (miRNAs) and their association with mitochondrial and synaptic functions in neurons as the progression of AD involves mitochondrial and synaptic dysfunctions, both of which contribute to the impaired neurotransmission and memory loss that is seen in AD. Many miRNAs have been found to be deregulated in AD, many of which have been associated with mitochondrial and synaptic dysfunctions (Kumar and Reddy, 2020). Therefore, the deregulation of miRNAs is potentially involved in the progression of AD and can serve as treatments or biomarkers.

2. MicroRNAs

MicroRNAs (miRNA) are small, conserved non-coding RNAs (average 22 nucleotides long) that post-transcriptionally regulate gene expression through complementary binding to messenger RNA (mRNA) (O'Brien et al., 2018). Most miRNAs are transcribed in the nucleus by RNA polymerase II or III to primary miRNA (pri-miRNA) (Wahid et al., 2010). Pri-miRNA is cleaved into precursor-miRNA (pre-miRNA) by DROSHA and DGCR8 proteins (O'Brien et al., 2018; Starega-Roslan et al., 2011). The pre-miRNA is transported to the cytoplasm by the Exportin 5/RanGTP complex (Bohnsack et al., 2004). Pre-miRNA is digested by RNAse III Dicer and TBRP, forming a miRNA duplex. Helicase then unwinds the duplex, creating a single-stranded mature-miRNA while the other strand degrades (Ambrus and Frolov, 2009). The mature-miRNA interacts with Ago2 protein to form an RNA-induced silencing complex (RISC) (Treiber et al., 2019). Figure 2 presents the many potential pathways for miRNA biogenesis and localization to the mitochondria. The RISC binds to 3'UTR of the mRNA through complementary base pairing and downregulates gene expression by repressing translation or degrading mRNA (van den Berg et al., 2008; Liu et al., 2014). Some miRNAs have also been found to bind to the 5'UTR region and coding sequence of the mRNA and others have been found to upregulate translation (Orom et al., 2008; Truesdell et al., 2012).

2.1. MicroRNAs and Alzheimer's disease—Differing levels of miRNA between healthy and diseased states have been discovered in many diseases, such as cancer, atherosclerosis, and many neurodegenerative diseases, including AD (Kemar et al., 2014; Kumar et al., 2017; Kumar and Reddy, 2016; Vijayan et al., 2018; Zhao et al., 2019; Lukiw, 2020). In AD, under expression and overexpression of certain miRNAs have been associated with many of the physiological effects that accompany the disease (Silvestro et al., 2019). For example, the downregulation of miR-193b, which targets Amyloid Beta Precursor Protein (AβPP), is associated with the accumulation of Aβ plaques (Liu et al., 2014). The miRNAs also play important roles in aging (Kenyon, 2010; Smith-Vikos and Slack, 2012), mitochondrial dysfunction, tau accumulation, and in regulating enzymes associated with Aβ production (Reddy et al., 2017). Therefore, further research on the role and mechanism of miRNAs in the brain and how the disease develops from the deregulation of miRNAs will provide great insight into how AD progresses and how miRNAs can be used as potential biomarkers for AD. Kumar and others has currently been focusing on mitochondrial dysfunction in AD, how this dysfunction harm the synaptic function, and how miRNAs may be related to mitochondrial (Gong et al., 2017; Hong et al., 2017; Kumar et al., 2019) and synaptic functions (Di Rita et al., 2020; Wingo et al., 2020).

3. Mitochondria and Alzheimer's disease

Mitochondria are organelles located within eukaryotic cells that produce about 90% of cell energy as adenosine triphosphate (ATP) among many other functions (Garcia et al., 2019). Mitochondria are believed to have originated from the integration of an alphaproteobacterium into anaerobic host archaea (Roger et al., 2017). There still exists a lot of controversy regarding the specifics of the origin of the mitochondria. However, it is believed that both organisms had a symbiotic relationship where the bacterium aerobically produced energy for the archaea, thus removing oxygen, which would have been toxic to the anaerobe. Evidence for this includes that mitochondrial DNAs are similar to bacterial DNA and they reproduce through binary fission. Over time, the bacterium eventually evolved into the mitochondria seen in eukaryotic cells today.

Reddy's laboratory has done extensive research on mitochondrial dysfunction in AD and published many articles discussing both what mitochondrial dysfunction looks like in AD and how it develops (Reddy and Oliver, 2019; Oliver and Reddy, 2019; Pradeepkiran and Reddy, 2020; Bhatti et al., 2021). Mitochondrial dysfunction in AD such as impaired dynamics and mitophagy are areas that researchers are focusing on as these functions are heavily involved in synapse impairment (Cai and Tammineni, 2016). Figure 3 depicts the mitochondrial dysfunction that is present at the synapse during AD and highlights the deregulation of mitochondrial miRNAs associated with each dysfunction. An increased emphasis in this article is being placed on synaptic mitochondria and how mitochondrial miRNA affects its function.

3.1. Mitochondrial genome—Mitochondrial DNA (mtDNA) is circular and double-stranded with 16569 base pairs and has been found to encode 37 genes, 22 tRNAs, 13 polypeptides, and two rRNAs (Taanman, 1999). The human mitochondria have between two and 10 copies of mtDNA located in the matrix and is replicated using DNA polymerase γ

(Copeland, 2010; Turnbull et al., 2010; Oliver and Reddy, 2019; Morton et al., 2021). The mtDNA is predominantly inherited matrilineally (Radzvilavicius et al., 2017) and for this reason, offspring may inherit most maternal mtDNA diseases. Most proteins that localize to the mitochondria are encoded by the nuclear genome. However, complexes I, III, IV, and V are encoded by both the nuclear and mitochondrial genomes (Reddy and Beal, 2005). The mtDNA is more easily mutated than nuclear DNA as it can be damaged by interaction with reactive oxygen species (ROS) produced during oxidative phosphorylation (OXPHOS) in aerobic respiration (Kujoth et al., 2005; Ishikawa et al., 2008).

3.2. Mitochondrial structure—Mitochondria are surrounded by a double membrane consisting of the inner membrane and the outer membrane (Kuhlbrandt, 2015). The space between outer and inner membranes is known as the intermembrane space. One of the main processes associated with this space is the passive diffusion across the inner membrane through ATP synthase to produce ATP (Klingenberg, 2008). The folded protrusions in the inner mitochondrial membrane are known as cristae that penetrate the inner mitochondrial matrix. Cristae have several cylindrical connections, 12–40 nm in diameter, to the inner membrane called cristae junctions (Mannella, 2020). These formations play a key role in inter-mitochondrial communication and increase the surface area for mitochondrial reactions to occur, thus allowing for more ATP to be generated (Mannella, 2020). The matrix is the space within the inner membrane and contains ribosomes, mtDNA, and metabolic enzymes (Klingenberg, 2008; Greber and Ban, 2016). Many biological processes occur in the matrix, one of the main processes being the tricarboxylic acid cycle (TCA cycle), which plays a major role in energy production and biosynthesis in cells (Martinez-Reyes and Chandel, 2020).

The outer membrane controls mitochondrion’s shape and plays a vital role in communicating with other organelles. It consists of voltage-dependent anion channels (VDAC) and many other pores in the membrane, allowing for many molecules, including proteins, ions, and other low molecular weight solutes, to be able to diffuse unrestricted through the outer membrane (Camara et al., 2017). Also, the outer membrane consists of the protein complex, translocase of the outer membrane (TOM), which allows proteins to cross the outer membrane into the intermembrane space (Perry et al., 2008). The inner membrane is significantly less permeable and more selective in what can diffuse across the membrane. Certain molecules are only able to diffuse across the inner membrane through specific transporters. Translocase of the inner membrane (TIM) protein, TIM23, allows for the transport of proteins across the inner membrane into the matrix and TIM22 allows for the integration of proteins into the inner membrane (Jensen and Dunn, 2002). Protons are the main ions that diffuse across the inner membrane to generate the proton gradient for producing ATP during OXPHOS (Kuhlbrandt, 2015). Calcium, cofactors, biosynthetic precursors, and metabolites can also diffuse across the inner membrane (Zorova et al., 2018; Rossi et al., 2019). In addition, embedded in the inner membrane are enzymes involved in the electron transport chain (ETC) (Complexes I-IV) and the production of ATP (ATP Synthase) along with the mitochondrial calcium uniporter (MCU) (Finkel et al., 2015; Kuhlbrandt, 2015). Figure 4 illustrates the general structure of the mitochondria, including

various channels present in the outer and inner membranes along with the mtDNA and ribosomes present in the matrix.

3.3. Mitochondrial functions—Mitochondria produce ATPs through a variety of catabolic processes including aerobic respiration, ketolysis, and amino acid catabolism (Bhatti et al., 2017; Spinelli and Haigis, 2018). The number of mitochondria in a cell depends on the energy needs of that cell. For example, muscle cells have many mitochondria as they need to produce energy to move the body. The bioenergetics of the mitochondria is discussed in detail later in the article. In addition to producing ATP, mitochondria have many other functions including calcium homeostasis, participating in controlled cell death (apoptosis), cell signaling, redox balance/dealing with oxidative stress, thermogenesis, innate immunity, and being involved in many biosynthetic pathways (Tait and Green, 2012).

Currently, scientists do not completely understand the functions of mtDNA and their implications in diseases. However, recent research has shown that defects in mtDNA are associated with many human diseases such as diabetes, AD, Parkinson's disease (PD), Huntington's disease (HD), cancer, and aging (Bender et al., 2006; Wallace, 2010; Di Stefano et al., 2016; Yan et al., 2019) as it causes damage and dysfunctional mitochondria.

3.4. Mitochondria and calcium signaling—Calcium ion (Ca^{2+}) plays a vital role in neuronal function and plasticity (Burgoyne and Haynes, 2012). It serves as a messenger to transmit depolarization status and synaptic activity within a neuron thereby relaying neuronal activity status (Gleichmann and Mattson, 2011). Specifically, an action potential triggers the active transport of Ca^{2+} into the presynaptic terminal of the neuron by opening up Ca^{2+} channels which in turn triggers the release of neurotransmitters through exocytosis, thus allowing the action potential to continue to the postsynaptic neuron (Gleichmann and Mattson, 2011; Mochida, 2021). This process increases local Ca^{2+} concentrations at the presynaptic active zone (Gleichmann and Mattson, 2011). High-intensity Ca^{2+} signaling requires high ATP consumption for Ca^{2+} homeostasis in the neuron (Sudhof, 2012). One of the biggest functions of the mitochondria is to maintain Ca^{2+} homeostasis (Kannurpatti, 2017). Mitochondria works with the ER to maintain Ca^{2+} balance (Pedriali et al., 2017). It buffers Ca^{2+} concentrations by transporting calcium into the matrix and out of the mitochondria using VDAC1 in the outer membrane along with Na^{+}-dependent mitochondrial Ca^{2+} efflux transporter (NCLX) and MCU located in the inner membrane (Reddy, 2013a; Reddy, 2013b; Finkel et al., 2015; Shoshan-Barmatz and De, 2017). When the mitochondria gets overloaded with calcium, mitochondrial permeability transition pores (mPTPs) in the inner mitochondrial membrane open, thereby triggering apoptosis through the release of cytochrome c and activation of caspases in the cytosol, thus making calcium deregulation an important consideration during neurodegenerative diseases (Calvo-Rodriguez et al., 2020).

3.5. Mitochondrial dynamics—Mitochondrial dynamics, which involves both fusion and fission of mitochondria, and degradation of damaged mtDNA, also provide an important function in neurons (Youle and van der Bliek, 2012). The fusion (combining) allows mitochondria to significantly reduce the effects of changes in mtDNA (Vidoni et al., 2013). Changes in mtDNA must reach elevated levels to lead to dysfunction in the ETC, thus through fusion, the mutated mtDNA is split between both mitochondria, thus leading to

lower levels within each mitochondrion (Wang et al., 2020b). This allows mitochondria to tolerate high mutation levels. Also, fusion allows mitochondria with damaged components to regain functional versions of those components, thus protecting the cell from dysfunctional mitochondria (Vidoni et al., 2013). After fusion, the mitochondria undergo fission (splitting) back into separate mitochondria (Mishra and Chan, 2014). Due to fusion, the mitochondria that previously had impaired function regain its functionality. As a result, the fusion/fission mechanism leads to a variety of shapes and functions of mitochondria (Pagliuso et al., 2018; Ma et al., 2020). The dendrites consist of long and tubular mitochondria (Rangaraju et al., 2019) while axons consist of short and punctate mitochondria. This allows for the compartmentalization of specialized functions of mitochondria in the neuron and allows for local regulation. For example, the compartmentalization of specific mitochondria in the dendrite and axon are important for local translation, which requires large amounts of energy. Regulation and balancing of fission and fusion processes are managed by a set of fusion (dynamin GTPase regulators Optic Atrophy 1, OPA1; Mitofusin 1, MFN1; Mitofusin 2, MFN2) and fission (dynamin-like GTPase regulator Dynamin related protein 1, DRP1) proteins (Reddy et al., 2011; Kandimalla et al., 2016; Ali and McStay, 2018; Oliver and Reddy, 2019).

3.6. Mitochondrial differences between genders—Researchers have identified sex-based differences in mitochondrial functions in the brain. Human mitochondria and mtDNA are found to be mainly maternally inherited (Giles et al., 1980). However, recent research has found that mtDNA can also be paternally inherited (McWilliams and Suomalainen, 2019). Sex steroid hormones are known to play a role in the function of mitochondria and have been found to have neuroprotective effects. Steroids, known as neuroactive steroids, are produced in the brain, thus can impact neuronal functions (Melcangi et al., 2016). Understanding differences in mitochondrial functions due to sex allows development of better treatment strategies for mitochondrial dysfunction observed during neurodegenerative diseases.

Since more than two-thirds of those with AD are women, sex is an important factor to consider (Alzheimer'sAssociation, 2021). One major sex difference is that men have significantly higher levels of testosterone than women while women have higher levels of estrogen and progesterone. Mitochondrial content is approximately the same between sexes, thus indicating that differences in mitochondrial function are due to impacts by sex-based hormones and proteins associated with the mitochondria (Guevara et al., 2011). Women were found to have greater rates of mitochondrial ATP production from glucose metabolism than men due to increased Pyruvate Dehydrogenase Complex activity and decreased ROS production compared to men, thus resulting in lower oxidative stress (Gaignard et al., 2018). However, OXPHOS activity was found to be the same between males and females (Guevara et al., 2011). A study with rats showed that female rats had greater levels of mitochondrial function than male rats (Guevara et al., 2011). Not much literature was found analyzing the differences in the expression of mitochondrial miRNAs between genders. One study found that mitochondrial metabolism in an overloaded heart was subjected to sex-specific miRNA regulation (Sanchez-Ruderisch et al., 2019). Therefore, researchers should investigate sex-

specific miRNA regulation in neurons in the brain as this might give further insight into mitochondrial differences between genders.

3.6.1. Sexual hormones and mitochondria: Estrogen, progesterone, and testosterone are found to affect mitochondrial functions in both men and women as these three hormones are found in both sexes. Differing levels of these hormones between sexes might indicate which hormones have significant impact in each sex and how hormonal changes due to aging affect mitochondrial function. Studies showed that mitochondrial respiration was decreased substantially after the removal of ovaries but not from the removal of testicles, thereby showing that female sex hormones (estrogen and progesterone) have a greater impact on mitochondrial function than testosterone (Guevara et al., 2011). Estradiol, the prominent estrogen in humans, was found to increase OXPHOS activity, inhibit the production of ROS, and stabilize the potential of the mitochondrial membrane (Lejri et al., 2018). In addition, estrogen was found to suppress apoptosis and promote mitochondrial biogenesis (Klinge, 2008). Progesterone was also found to increase energy production by the mitochondria and reduce oxidative stress (Gaignard et al., 2016). Testosterone deficiency was found to damage mitochondria in the substantia nigra in the brain through increased oxidative stress and reduced the activity of Complex I, thus signifying the potential effect that testosterone has on mitochondrial dysfunction in the brain (Yan et al., 2017).

Researchers have found differences in brain mitochondrial dysfunction between sexes. As a person ages, the amount of sex hormones in the body decreases. Since these steroid hormones play a role in mitochondrial function, a decrease in these hormones contributes to mitochondrial dysfunction. Moreover, research has found that the mitochondria play a role in the synthesis of steroids, thus dysfunction in the mitochondria could in turn also be responsible for reduction in sex hormones' levels (Gaignard et al., 2017). Women have a higher life expectancy than men, thus indicating that age is one of the main contributors to why more women have AD as age is the most significant risk factor for AD (Ginter and Simko, 2013). However, differences in sex hormones and the decreased production of sex hormones as people get older may also play a major role in this discrepancy. Learning more about how differences in mitochondrial function between genders change with aging will allow researchers to get a better understanding of why more women have AD.

3.7. Mitochondrial function and aging—Mitochondrial changes occur with age in humans and all mammals, leading to progressively worse function. As a result, mitochondrial dysfunctions related to redox homeostasis, bioenergetics, dynamics, and mitophagy have been associated with many neurodegenerative diseases, including AD. Mitochondrial function changes with aging involve mtDNA changes and decreased ATP production, which then leads to damage/dysfunction of mitochondrial proteins.

ROS production contributes a significant amount to mitochondrial dysfunction during aging. Complexes I and III, which are part of the ETC, are known to produce ROS (Hirst et al., 2008). Complex I produce ROS in the FMN site and CoQ binding site due to electron leak that occurs when electrons transfer from NADH to CoQ, resulting in the reduction of O_2 to O_2^- (Zhao et al., 2019). In complex III, the electron from $CoQH^-$ leaks out and reduces O_2 to O_2^-. The ROS produced by CIII is released into the matrix and the intermembrane

space where O_2^- can be converted to H_2O_2 utilizing SOD1 and exit the mitochondria into the cytosol (Zhao et al., 2019). Complex II was also found to be involved in pathways associated with ROS production (Lenaz, 2001). Complex II generates ROS due to electron leak that occurs from electrons supplied from succinate and also in the reverse direction from electrons supplied by CoQH2 (Quinlan et al. 2012). In addition, alpha-ketoglutarate, an enzyme that is involved in the TCA cycle, was found to produce ROS (Starkov et al., 2004). At appropriate levels, ROS participate in many signaling pathways that contribute to important brain functions, such as synaptic plasticity (Cobley et al., 2018). However, as a person ages, oxidative stress increases due to the dysregulation of redox homeostasis. The build-up of ROS associated with aging contributes to increased oxidative stress and leads to changes in mtDNA (Stefanatos and Sanz, 2018). ROS that is generated in the mitochondria also damages mtDNA through base modifications caused by oxidation, resulting in the formation of 8-hydroxy-2'-deoxyguanosine (Mao and Reddy, 2011; Torres-Gonzalez et al., 2014). Furthermore, antioxidant enzymes in the mitochondria become damaged with age, further making the mitochondria of older people more susceptible to oxidative stress (Wei and Lee, 2002). Due to increased oxidative stress, the mitochondria of older people exhibit impaired functions.

In healthy adults, the mitochondria play a vital role in producing most of the energy used in neuronal function. Therefore, a vast number of functional mitochondria are needed for neurons to meet their high energy demands. As previously mentioned, mitochondria become increasingly damaged with age due to higher levels of oxidative stress. The energy provided by the mitochondria is used in a variety of mitochondrial and synaptic functions in neurons that are discussed throughout this paper. As a result, aging is associated with decreased ATP production by the mitochondria (Chistiakov et al., 2014). Decreased energy production in neurons contributes to further mitochondrial dysfunction, synaptic dysfunction and leads to neuronal death.

Mitochondrial trafficking, dynamics, and mitophagy also experience alterations as people get older. Researchers found that mitochondrial trafficking decreases early on in adulthood and continues to decline as people age (Morsci et al., 2016; Morton et al., 2021). Moreover, aging was found to impair mitophagy (Tyrrell et al., 2020). In healthy adults, mitophagy removes damaged mitochondria and trafficking allows for the transport of functional mitochondria to these areas. However, due to aging and age-dependent increased accumulation of mutant proteins, and abnormal interactions between Abeta/p-tau with Drp1 and VDAC1, mitophagy is decreased, thus contributing to the continued presence of dysfunctional mitochondria (Morton et al 2021, Manczak et al 2011, Manczak and Reddy 2012). As a result, these synaptic areas are unable to produce the energy needed for proper functioning. For example, neurotransmission has been found to be decreased in AD due in part to impaired mitophagy in neurons (Han et al. 2020; Kerr at al. 2017).

4.1. Mitochondrial dysfunction in AD and neurodegenerative diseases

—Alzheimer's disease is closely associated with various forms of mitochondrial dysfunctions including excessive ROS production, low ATP production, mitochondrial Ca^{2+} dyshomeostasis, and defects in mitochondrial dynamics and transport, and mitophagy. Figure 1 displays how the disruption of calcium homeostasis and increased presence of

damaged mitochondria contributes to synaptic dysfunction. These physiological changes contribute to the impaired function of mitochondria in neurons. Aβ plaques and NFTs work independently as well as together in causing mitochondrial dysfunction. Considering the critical role of mitochondria in energy production, calcium buffering and cell health, any impediment in the mitochondrial movement and function can lead to neurological (Deheshi et al., 2013; Misgeld and Schwarz, 2017; Norat et al., 2020) and neuropsychiatric (Millar et al., 2000; Belmaker and Agam, 2008; Pei and Wallace, 2018; Zilocchi et al., 2020) disorders.

4.2. Impaired mitochondrial ATP production in Alzheimer's disease—

Production of ATP by mitochondria through OXPHOS is essential for cellular functions (Verschueren et al., 2019). Mitochondria produce ATP using five enzyme complexes in their inner membrane. Numerous studies have shown declined levels of all five-enzyme complexes in multiple areas of the AD brain (Liang et al., 2008). A decrease in the production of ATP in neuronal cells is associated with ROS overproduction and may fail to meet the energy requirements of neurons and glia. Aβ buildup is also associated with decreased energy production. Research has shown that Aβ oligomers inhibit the activities of cytochrome c oxidase (Complex IV) and ATP synthase, thus impairing the ATP production during OXPHOS (Morton et al., 2021; Wang et al., 2020b). In addition, the α-ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex showed decreased activity. Decreased energy production prevents the neuron from carrying out its function properly, thus leading to neuronal death. Low ATP production impairs neurons' ability to release neurotransmitters, leading to decreased neurotransmission and cognitive impairment.

4.3. Oxidative stress in Alzheimer's disease—

The overproduction of ROS in turn causes mitochondrial dysfunction through oxidative stress. Oxidative stress occurs when the production of ROS significantly increases, thus exceeding the antioxidant enzyme capabilities of a cell (Reddy and Beal, 2005; Reddy, 2006; Reddy, 2007; Reddy, 2009a; Reddy 2009b). The ROS are produced as a by-product of metabolism in mitochondria (Sies and Jones, 2020). Aβ has been found to contribute to the increased production of ROS by mitochondria by forming coordination compounds with metal ions (Cu and Fe) in the brain (Cheignon et al., 2018). In AD brains, increased ROS production is due to deficiency of cytochrome *c* oxidase in the mitochondrial ETC (Rak et al., 2016). The ROS consists of both radical and non-radical oxygen species such as superoxide radical anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (HO), nitric oxide (NO), and peroxynitrite ($ONOO^-$). An imbalance between production and degradation of ROS can cause oxidative stress as they are capable of oxidizing nucleic acids (DNA & RNA), proteins, and lipids and consequently damage brain cells (Arimon et al., 2015; Dumanovic et al., 2020; Misrani et al., 2021; Tauffenberger and Magistretti, 2021). Many studies have shown that ROS accounts for cellular injury in aging and many neurodegenerative diseases (Misrani et al., 2021). As a person ages, increasing ROS levels have been found to be associated with the accumulation of damaged mitochondria.

Oxidative stress leads to changes in mtDNA. The mtDNA changes that occur with age and are not inherited are known as somatic mutations. These mtDNA mutations have been

associated with decreased functioning of OXPHOS as mtDNAs have shown to help code for enzymes used in the ETC, thus damaging mitochondria and consequently leading to reduced ATP production. ROS also damage proteins and lipids associated with bioenergetics, such as cardiolipin found in the inner membrane (Reddy and Beal, 2005; Reddy, 2006; Reddy, 2007; Reddy, 2009a; Reddy, 2009b). As a result, neurons die over time from apoptosis/necrosis due to not meeting their energy needs or increased damage by ROS, thus leading to the development and progression of neuroinflammation and neurodegenerative diseases. Moreover, increased ROS levels are associated with promoting senescence in other cells by leading to the damage and shortening of telomeres in nuclear DNA and through ROS-mediated cell signaling pathways. Oxidative stress and consequent substantial increase in their by-products have been widely reported in AD (Bhattacharyya et al., 2014). These oxidized biomolecule by-products are more stable and therefore used as ROS markers in monitoring the progression of AD (Marrocco et al., 2017). Table 1 presents some of the by-products that are studied in AD as oxidative stress markers. Neuronal mitochondria themselves are the victims of oxidative stress as it leads to their progressive destruction. Increased oxidative stress is important as it damages mitochondria, thus causing neurons to become dysfunctional. Oxidative stress also damages mtDNA, thus further damaging the respiratory complexes. The overproduction of ROS in turn causes mitochondrial dysfunction through oxidative stress. This vicious cycle of decreased ATP production due to compromised OXPHOS, elevated oxidative stress, mitochondrial dysfunction, and cell death is the hallmark of AD progression (Reddy and Beal, 2008).

4.4. Impaired mitochondrial Ca^{2+} production in Alzheimer's disease—Ca^{2+} is a crucial second messenger for the normal functioning of neurons as it modulates different neuronal processes such as secretion, motility, metabolic regulation, synaptic plasticity, proliferation, gene expression, and apoptosis (Horigane et al., 2019). It also plays a key role in learning and memory (Berridge, 2014). Studies have found that dysregulation involves elevated levels of cytosolic calcium due to increased influx of Ca^{2+} through voltage-gated calcium channels, reduced calcium buffering, reduced expression of Ca^{2+}-binding proteins, and impaired handling of calcium by the mitochondria (Catterall, 2011; Nanou and Catterall, 2018; Strickland et al., 2019; Ureshino et al., 2019). Sustained overloading of cytosolic Ca^{2+} promotes cell death while their deficiency might affect signal transmissions (Esteras and Abramov, 2020). Research has found that Aβ plaques build up significantly in the synaptic mitochondria contributes to Ca^{2+} dysregulation (Calvo-Rodriguez et al., 2020). In cortical neurons, Aβ is believed to increase the release of calcium from ER, leading to a significant increase in cytosolic calcium levels (Green, 2009). This results in increased uptake of Ca^{2+} by the mitochondria (Tillement et al., 2011). High cyclophilin D levels also have been found to disrupt Ca^{2+} balance by synaptic mitochondria (Naga et al., 2007; Modesti et al., 2021). The excessive amount of Ca^{2+} in the mitochondria contributes to the collapse of mitochondrial membrane potential due to the opening of mPTPs, activation of pro-apoptotic proteins, and increased production of ROS (Calvo-Rodriguez et al., 2020). Also, the Aβ-mediated impediments in Ca^{2+} regulation at multiple cellular levels include increased inositol 1,4,5-trisphosphate receptor activity at the ER (Supnet and Bezprozvanny, 2010) and the dysregulation of voltage-operated channels. This impairment in mitochondria's activity

has been widely observed in AD brains (Berridge, 2014; Britti et al., 2018). Figure 5 summarizes Ca^{2+} regulation in healthy synapse compared to its deregulation in AD brains.

4.5. Impaired mitochondrial dynamics and mitophagy in Alzheimer's disease

—The transport of mitochondria in neurons is essential for supplying ATP to synapses, Ca^{2+} buffering, and repairing of mitochondria (Calkins et al., 2011; Course and Wang, 2016). This is facilitated through microtubule tracks. The integrity of these tracks is known to be affected by tau proteins in AD cells negatively impacting mitochondrial transport (Perez et al., 2018). Further, fusion protein MFN2 has been shown to participate in mitochondrial transport by interacting with mitochondrial Rho small GTPase (MIRO), a protein associated with motor proteins to transport mitochondria in the anterograde direction (Majstrowicz et al., 2021). Mutations or deletions in MFN2 lead to the slowing of axonal transport in both directions (Misko et al., 2010). In AD, impaired mitochondrial axonal transport is known to precede the accumulation of toxic protein compounds and is linked to distressed synaptic function (Calkins et al., 2011; Calkins et al., 2012; Cai and Tammineni, 2017; Morton et al., 2021). However, precise underlying molecular mechanisms of how it affects mitochondrial transport are not known. The development of neurodegenerative diseases has also been associated with the reduction in mitophagy (Bakula and Scheibye-Knudsen, 2020; Swerdlow and Wilkins, 2020). Mitophagy is the selective degradation of mitochondria through autophagy. PD, HD and AD all have been found to have decreased mitophagy (Cai and Jeong, 2020; Norat et al., 2020; Choi and Han, 2021). Moreover, cristae disorders have been observed in humans with diseases such as ALS, AD, and PD (Stanga et al., 2020).

Disruption in mitochondrial dynamics through increased fission and the accumulation of changes in mtDNA also contribute to the increased presence of dysfunctional mitochondria. Aβ interacts with many proteins located in the mitochondria, thus altering mitochondrial dynamics. For example, Aβ interacts with VDAC1 and stops the transport of mitochondrial proteins, resulting in the formation of free radicals (Rajmohan and Reddy, 2017). Researchers have found that Aβ interacts with Drp1 which causes increased mitochondrial fragmentation and reduced fusion in the synapses (Manczak et al., 2011). In addition, mitochondrial fission is more pronounced with an increase in Aβ and Tau levels as they interact with fission regulator proteins (Kandimalla et al., 2016). Tau has been found to disrupt the transport of mitochondria along microtubules to the synapse, thus hindering the release of neurotransmitters and leading to synaptic dysfunction (Forner et al., 2017). Consequently, increased fission leads to reduced mitophagy, thus leading to the presence of more dysfunctional mitochondria fission. As a result, if dysfunctional mitochondria are not removed, it can lead to build-up of ROS and decreased energy production, ultimately resulting in neuronal death (Misrani et al., 2021).

5. Mitochondrial Bioenergetics

The mitochondria are responsible for up to 95% of the energy produced in the Central Nervous System (CNS) (Benaroya, 2020). Moreover, the brain has the highest energy demand in the body due to the constant synaptic activity, generation of action potentials in neurons, and complex processing. As previously mentioned, the brain consumes about 20% of the total energy of the body while accounting for only 2% of the body weight (Silver and

Erecinska, 1998). There are an estimated two million mitochondria in a neuron (Misgeld and Schwarz, 2017).

Most of the energy produced in the brain is used for synaptic activity (Harris et al., 2012). Mitochondria in neurons produce energy in a variety of different pathways. The main pathway utilized to make ATP is aerobic respiration as glucose is the most used fuel source by neurons. The first step of aerobic respiration, glycolysis, takes place in the cytosol. During glycolysis, glucose is oxidized into two molecules of pyruvate (Yetkin-Arik et al., 2019). Pyruvate is then able to enter the pyruvate dehydrogenase (PDH) complex in the mitochondrial matrix (Gray et al., 2014). Another contributor to the formation of pyruvate is the formation of lactate in astrocytes (Descalzi et al., 2019). The lactate produced by astrocytes can be transported to neurons and converted into pyruvate for use in energy production. PDH oxidizes pyruvate into acetyl-CoA, producing carbon dioxide and NADH. Acetyl-CoA then enters the TCA cycle where Acetyl-CoA is used to produce ATP through substrate-level phosphorylation and NADH/FADH2 which are electron carriers (Gray et al., 2014). Both NADH and FADH2 are then used in the respiratory chain (Complexes I-IV) to pump protons across the inner membrane from the matrix to the intermembrane space (Cooper, 2000). Then the protons flow across its gradient through ATP synthase, generating the production of ATP through oxidative phosphorylation.

Under conditions of prolonged starvation, the brain can derive up to $^{2}/_{3}$ of its energy from ketone bodies (Naithani and Karn, 2020). Ketone bodies can cross the blood-brain barrier and be used as a fuel source for cells in the CNS. Through ketolysis, ketone bodies are converted into acetyl-CoA, which can then enter the TCA cycle. Amino acids and fatty acids can also feed into the TCA cycle (Swerdlow, 2012). The localization of miRNAs to the mitochondria allows them to regulate energy production along with all other mitochondrial functions that have been discussed. Learning about the mechanism of miRNA localization to various cellular organelles will allow for a better understanding of the specific mechanisms of how miRNAs localize and impact mitochondrial functions.

6. Mitochondria and neuronal function

The human brain consists of about 86 billion neuronal cells wired in complex networks from which our emotions, movements, and experiences arise (Azevedo et al., 2009). Not surprisingly, the CNS is known for extraordinarily high metabolic rate as neurons are highly differentiated cells that require large amounts of ATP for maintaining ion gradients across cell membranes and for neurotransmission (Chamberlain and Sheng, 2019). For example, ATP is required to power the Na^{+}/K^{+} pump to create the ion gradients necessary to generate action potentials along the axon. Not surprisingly, the brain consumes about 20% of the total energy produced by the body while accounting for only 2% of the body weight (Silver and Erecinska, 1998). Any deficit in the generation of energy can have catastrophic effects on neuronal functioning (Lax et al., 2011). Mitochondria are central to various processes including ATP production in neurons, intracellular Ca^{2+} signaling, and activating apoptosis while also producing ROS (Ames, 2000; Kann and Kovács, 2007). Therefore, mitochondrial dysfunction has harmful effects on the integrity of cells including cell death, and may be

critically involved in aging, metabolic and degenerative diseases (Wallace, 2005; Reddy et al., 2012; Mandal and Drerup, 2019; Sharma et al., 2021).

7. Cellular organelles and miRNAs locations

Organelles are subcellular structures that have one or more specific functions to perform within a cell. miRNAs have been identified in many different organelles including endoplasmic reticulum (ER), trans-Golgi network, nucleus, and mitochondria (Maurel and Chevet, 2013). The mechanism of subcellular localization and trafficking of miRNA is not fully understood (Simion et al., 2020; Trabucchi and Mategot, 2020). However, it is known that miRNA expression is related to the regulation of proteins that help with the function of many organelles in the cell (Leung, 2015; O'Brien et al., 2018). For example, there is a functional connection between the expression of miRNAs and ER^{UPR} signaling that has shown that miRNA regulates ER as well as regulated by ER signaling (Maurel and Chevet, 2013; Almanza et al., 2019; Ortega et al., 2020). By targeting the expression of proteins that are found in different organelles, miRNA plays a significant role in the function of organelles. Moreover, research has found miRNAs that are localized to the mitochondria and alter mitochondrial gene expression by targeting mRNA located in the mitochondria (John et al., 2020). Therefore, studying miRNA specific to the mitochondria will provide great insight in determining the mechanism that miRNA has towards the progression of AD and as biomarkers for the early detection of this disease. The next sections focus specifically on the function of mitochondria and how alterations in levels of mitochondrial miRNAs are associated with mitochondrial dysfunction that is typical of AD.

8. Mitochondrial miRNAs

Mitochondrial miRNAs are target genes that code for proteins that are essential for proper mitochondrial function. A vast number of mitochondrial miRNAs have the potential to be directly involved in the pathogenesis of AD. Table 2 gives a list of mitochondrial miRNAs that researchers have found to be differentially expressed in AD and present in neurons in the brain. It highlights the target gene, mRNA binding region, mitochondrial functions, and the importance of these miRNAs to AD. In addition, Table 3 shows how the miRNAs are related to other neurodegenerative diseases such as PD, HD, and Amyotrophic Lateral Sclerosis (ALS) as these diseases are similar to AD. These miRNAs have the potential to be therapeutic targets for the treatment of AD or as biomarkers.

8.1. Mitochondria localized miRNAs—

Mitochondria-localized miRNAs (mitomiRs) are miRNAs that are found inside the mitochondria. These mitomiRs have been hypothesized to be encoded by the nuclear genome or by the mitochondrial genome. Figure 2 illustrates the many potential mechanisms of mitomiR biogenesis. The presence of miRNA in the mitochondria has only been discovered this past decade in various species. In 2009, Kren and others discovered the localization of mitochondria in rat liver and Bian et al. found miRNA located in the mitochondria of mouse liver (Kren et al., 2009; Bian et al., 2010). Research on mitomiRs in humans is limited. In 2011, Bandiera and others found 13 miRNAs at high levels in mitochondria that were purified from HeLa cells (Bandiera et al., 2011). The same study found that the outsourcing of miRNA by the nucleus to the mitochondria is highly conserved in mammals. Barrey and others have found both pre-miRNA (pre-mir-302a

and pre-let-7b) and miRNA (miR-365) that are localized to the mitochondria in human myocytes, thus showing how both pre-miRNA and miRNA are found in the mitochondria (Barrey et al., 2011).

8.2. MitomiRs biogenesis—Where the mitomiRs originate from, how they are transported, how they know where to localize, if RISC forms in the cytosol and/or the mitochondria, and whether they are synthesized in the mitochondria or only processed in the mitochondria are not known. In addition, if and how interactions occur between mitomiR and mtDNA transcripts are not fully understood. Most mitomiRs encoded in the nucleus were found to originate from loci that are either transcribed from mitochondrial gene clusters or located close to mitochondrial genes, thus the linking to mitochondrial-related genes could play a role in mitomiR being able to localize to the mitochondria (Vendramin et al., 2017). Also, mitomiRs atypical size (17–25 nucleotide length) and distinctive thermodynamic properties increase the possibility that their structures are involved in mitochondrial localization and being able to transport through the mitochondrial membranes (Bandiera et al., 2011; Vendramin et al., 2017). Since, Ago2 was found to localize to the mitochondria, this suggests that miRNA may be processed in the mitochondria; however, Ago2 has functions unrelated to miRNA processing, thus the localization might not be related to mitomiRs (Zhang et al., 2014). P-bodies have been stated to allow the transport of the miRNA-Ago2 complexes directly into the mitochondria (Macgregor-Das and Das, 2018). Another proposed mechanism is that miRNA-Ago2 complexes can travel through TOM20 and SAM50 into the outer membrane and then polynucleotide phosphorylase (PNPAse) in the intermembrane space can assist in the transportation of the complex across the inner membrane and into the matrix through TIM complexes (Macgregor-Das and Das, 2018).

MitomiRs are hypothesized to play a regulatory role in various mitochondrial functions. No specific research has been done regarding mitomiRs in neurons. Because mitochondrial dysfunction is one of the main indicators of AD, discovering the specific functions and mechanism of actions of mitomiRs in human neurons and the differential expression of mitomiRs in neurons during AD will provide greater insight in the impact of mitomiRs in the progression of AD and potential targets for treatments.

8.3. How to study mitochondrial miRNA in neurons—A few studies have been performed in analyzing the localization and specific function of mitochondrial miRNA in neurons, especially in the synapse where mitochondrial miRNA have important regulatory functions (John et al., 2020). Separation of the cytosol and synaptosome components of the neuron through centrifugation and extraction reagents allows for the isolation of miRNA that is specifically located in the synapse. Moreover, mitochondria can be extracted from the synapse using commercial kits or differential centrifugation and then characterized using transmission electron microscopy and through the immunoblotting of mitochondrial marker genes (Liao et al., 2020). Afterwards, mitochondrial miRNA can be extracted and used to produce cDNA, and then qRT-PCR can be used to quantify how much of a specific miRNA is present in the mitochondria from the synaptosome. This procedure can be used with transgenic APP or Tau mice tissue samples, postmortem human tissue samples, or

transfected cells to analyze the altered regulation of miRNA in AD vs WT samples. Next, miRNAs can be quantified in both healthy and diseased states to identify mitochondrial miRNAs of interest. The removal or addition of specific mitochondrial miRNA into neurons can be used to better understand what functions they regulate by measuring mitochondrial activity.

8.4. Techniques for mitochondrial miRNAs analysis—Mitochondrial miRNAs can be analyzed utilizing many different methods. Once mitomiRs of interest are isolated, qRT-PCR, Northern blot, NC2 hybridization, miRNA microarray, and cellular fractionation combined with deep sequencing can be used to learn more about them (Larriba et al., 2016). Moreover, mitochondrial miRNAs can be knocked-in or knocked-out of mice/isolated cells and then changes in mitochondrial function can be analyzed through various techniques. Mitochondria biogenesis/mitophagy can be measured using electron microscopy, fluorescence microscopy, and western blotting along with recently developed techniques using MitoTimer, Mt-Keima, and Mito-QC (Williams et al., 2017; Pradeepkiran and Reddy, 2020). Mitochondrial dynamics can be measured using fluorescence wide-field microscopy and 3D image processing (Song et al., 2008). More specifically, mitochondrial fusion is measured using polyethylene glycol (PEG) fusion assay alongside imaging flow cyclometry (Nascimento et al., 2017). Gokerkucuk and others have identified a variety of methods to measure mitophagy, dynamics, and calcium signaling using fluorescent dyes and proteins (mitophagy = GFP-LC3; dynamics = tetramethylrhodamine ethyl ester (TMRE), Rhodamine 123 (R123), tetramethylrhodamine methyl ester (TMRM), and 5,5,6,6’-tetrachloro-1,1’,3,3’ tetraethylbenzimidazoylcarbocyanine iodide (JC-1), naphthalimide (NPA-TPP), boron-dipyrromethene (BODIPY)) and genetically-encoded sensors (mitophagy = RFP-GFP; dynamics = mitochondria-targeted photoactivable GFP (PAGFPmt), mitochondrially-targeted DsRed fluorescent protein (mtDsRed); calcium signaling = genetically-encoded Ca^{2+} indicators (GECIs) (Gokerkucuk et al., 2020).

Mitochondrial calcium regulation can also be measured using fluorescence microscopy with Fluo-4, AM, TMRM, Fura-2, Indo-1, Rhod-2 as indicators (McKenzie et al., 2017; Gokerkucuk et al., 2020). ATP production can be measured using bioluminescence assays and high resolution respirometry (Drew and Leeuwenburgh, 2003; Lanza and Nair, 2010). Amplex Red Assays, which detects the presence of H_2O_2, can be used to quantify ROS production (Karakuzu et al., 2019). Mitochondrial trafficking can be analyzed by using a photo-switchable fluorescent protein (dendra2) that can track movement and be used to determine a velocity distribution or utilizing fluorescent microscopy on neurons that are transfected with fluorescent proteins, such as enhanced yellow fluorescent protein (eYFP), that target the mitochondria and can be used to measure mitochondria localization frequency, mitochondrial residence time, number of passing mitochondria per minute, and fraction of passing mitochondria that stop (Chang et al., 2006; Niescier et al., 2016). Apoptosis can be analyzed using flow cytometry (Chen et al., 2019b; Wang et al., 2020b).

Furthermore, researchers can work to develop methods to isolate mitochondria from tissue samples and isolate miRNA. Mitochondrial miRNAs can be analyzed to see if they bind to mtDNA and to which sequences in the mitochondrial genome and then observe mitochondrial activities for any changes. Moreover, finding ways to label a specific

miRNA sequence that is known to localize to the mitochondria and observing its path to the mitochondria while also determining the presence of certain proteins associated with miRNA biogenesis in the mitochondria can give better understanding of how mitomiRs localize to the mitochondria. The next steps in mitochondrial miRNA analysis are to determine: 1) how mitomiRs are localized to the mitochondria, 2) the specific mechanism of actions of these mitomiRs, 3) to identity the function of all neuronal mitomiRs and which mitomiRs are specific to synaptic function, 4) the deregulation of specific mitomiRs in AD, and 5) how these mitomiRs can be used as a treatments or biomarkers of AD. Figure 6 presents the current techniques in sequential order, which researchers can follow when studying mitochondrial miRNAs.

8.5. Mitochondrial miRNAs and ATP production—miRNAs downregulate genes that code for proteins involved in energy production. For example, miR-743a was found to suppress malate dehydrogenase activity (Shi and Gibson, 2011). Malate dehydrogenase is involved in the oxidation of malate to oxaloacetate during the TCA cycle, producing NADH. Malate dehydrogenase activity is upregulated in AD, thus miR-743a might be downregulated in AD (Shi and Gibson, 2011). miR-23a/b are also known to disrupt the TCA cycle by downregulating glutaminase (Gao et al., 2009). Furthermore, miR-210 (Chen et al., 2010), miR-338 (Aschrafi et al., 2008), and miR-34a (Sarkar et al., 2016) inhibit the activity of enzymes involved in OXPHOS. Most of the ATP produced in neurons comes from OXPHOS, thus the suppression of this process prevents neurons from meeting their high energy demand, leading to neuronal death.

Membrane potential is important for maintaining the ETC. miRNAs such as miR-16-5p (Kim et al., 2020), miR-195 (Zhang et al., 2016), and miR-29b (Lungu et al., 2013) are known to disrupt mitochondrial membrane potential and integrity while miR-7 (Chaudhuri et al., 2016) is known to stabilize the membrane potential. Decreased production of energy also inhibits neurons' abilities to transmit signals. Ultimately, disrupted transmission and the loss of neurons contribute to the cognitive impairments seen in AD. Therefore, understanding how mitochondrial miRNA disrupts bioenergetics in neurons during AD will provide greater insight into the progression of AD and lead to the development of potential diagnostics and treatments for this disease.

8.6. Mitochondrial miRNAs and oxidative stress—Oxidative stress is a major contributor to mitochondrial dysfunction during AD. The dysregulation of many miRNAs in neurons have been found to be related to increased ROS production by mitochondria. Mitochondrial miRNAs were also found to affect the function of antioxidant enzymes that play a role in redox homeostasis. miR-98, miR-204, miR-34a, miR-15b, miR-375, miR-140, and miR-335 are all involved in the mitochondria's handling of oxidative stress. MiR-98 (Chen et al., 2019a), and miR-15b (Lang et al., 2016) were found to promote redox homeostasis and reduce oxidative stress. In AD, these miRNAs are downregulated, leading to increased ROS production and oxidative damage to neurons, which in turn, leads to cell death (Gong et al., 2017; Chen et al., 2019a). miR-204 (Zhang et al., 2021), miR-34a (Sarkar et al., 2016), miR-375 (Wang et al., 2020a), miR-140 (Liang et al., 2021), and miR-335 (Bai et al., 2011) were found to promote ROS production and inhibit the function

of antioxidant enzymes in the mitochondria. Therefore, the upregulation of these miRNAs leads to apoptosis in neurons during AD due to increased oxidative stress.

8.7. Mitochondrial miRNAs and mitophagy—Mitophagy is the removal of dead mitochondria through autophagy. Dysfunctional mitophagy leads to the increased presence of damaged mitochondria in neurons. Damaged mitochondria are unable to produce enough energy for neuron survival. Therefore, mitochondrial miRNAs play a vital role in regulating mitophagy and clearing damaged mitochondria. miR-137 (Li et al., 2014c), miR-34a (Xiong et al., 2019), and miR-218 (Di Rita et al., 2020) were found to inhibit mitophagy, thus the downregulation of these miRNAs in AD can increase the number of functional mitochondria in neurons. miR-204 (Zhang et al., 2021) and miR-351-5p (Woo et al., 2021) promote mitophagy and are found to be downregulated in AD.

8.8. Mitochondrial miRNAs and mitochondrial biogenesis—Mitochondrial biogenesis is the formation of new mitochondria and leads to an increase in the number of mitochondria in neurons. This process is important as it allows neurons to meet their high energy needs. Researchers have found that miR-455-3p (Kumar and Reddy, 2019) and miR-34a (Xiong et al., 2019) are involved in mitochondrial biogenesis while miR-23a/b regulates SIRT1, which is associated with mitochondrial biogenesis, thereby indicating a potentially link between miR-23a/b and biogenesis (Weinberg et al., 2015; Tang, 2016). Altered levels of these miRNAs in AD play a role in disrupting biogenesis, thus decreasing the number of functional mitochondria in neurons, leading to neuronal death.

8.9. Mitochondrial miRNAs and mitochondrial dynamics—Mitochondrial dynamics involve the fission and fusion balance of mitochondria and are important in maintaining functional mitochondria in neurons. Mitochondrial miRNAs were found to affect mitochondrial dynamics by either inhibiting or promoting fission or fusion. miRNAs including miR-484, miR-455-3p, miR-30, miR-351-5p, and miR-140 are associated with mitochondrial dynamics. In AD, miR-484 (Wang et al., 2012) and miR-30 (Li et al., 2010) were downregulated while miR-351-5p (Woo et al., 2021) and miR-140 (Li et al., 2014a) were upregulated, thereby leading to increased mitochondrial fission and neuronal cell death through apoptosis. miR-455-3p is produced in response to Aβ production and acts as a negative feedback inhibitor of APP, enhancing fusion (Kumar et al., 2017., Kumar et al 2019).

8.10. Mitochondrial miRNAs and apoptosis—Increased apoptosis in the brain leads to neuronal death during AD. Mitochondria are involved in the mechanisms of this pathway. Widespread neuronal death disrupts pathways involved in learning and memory; thus, miRNA works to limit apoptosis to only when needed. Therefore, the dysregulation of mitochondrial miRNA(s) related to apoptosis plays a key role in neuron survival and death. miR-7 (Chaudhuri et al., 2016), miR-98 (Chen et al., 2019a), miR-30 (Li et al., 2010), miR-132/212 (Wong et al., 2013), and miR-484 (Liu et al., 2021) were found to inhibit apoptosis. The downregulation of these miRNAs in AD leads to neuronal death via apoptosis. Conversely, miR-16-5p (Kim et al., 2020), miR-34a (Lin et al., 2015), miR-375 (Wang et al., 2020a), miR-125b (Hong et al., 2017), miR-29a (Bargaje et al., 2012),

miR-29b (Shi et al., 2012), and miR-140 (Liang et al., 2021) induce apoptosis and are consequently found upregulated in AD.

9. Synapse function in the brain

The synapse is a major component of the neuron and is responsible for neurotransmission (John and Reddy, 2021). Researchers have found that the human neocortex has approximately 150 trillion synapses (Finnema et al., 2016). The entire human brain was found to have around a total of quadrillion synapses (Ho et al., 2011). Due to the vast number of synapses in the human brain, the synapses are significantly involved in major brain functions. In neurons, action potentials travel from the axon hillock to the synapse. For the action potential to travel to the next neuron, the synapse must release neurotransmitters into the synaptic cleft via exocytosis at chemical synapses or by ions traveling through gap junctions directly into the next neuron at electrical synapses (John and Reddy, 2021). Both types of synapses allow for the transmission of signals from one neuron to the next. To release neurotransmitters, an influx of Ca^{2+} travels through voltage-gated calcium channels into the synapse. This influx of calcium ions leads to the fusion of vesicles filled with neurotransmitters to the synaptic terminals, resulting in the release of neurotransmitters. The neurotransmitters can travel through the synaptic cleft and bind to the dendrite of the postsynaptic neuron (John and Reddy, 2021).

9.1. Chemical and electrical synapse—Synapses are the locations where signals are transmitted from one neuron (presynaptic neuron) to the subsequent neuron (postsynaptic neuron). Synapses can be classified in many ways. For instance, synapses can be either chemical or electrical. Chemical synapses involve a gap between the presynaptic and postsynaptic neuron known as the synaptic cleft (John and Reddy, 2021). The presynaptic neuron releases neurotransmitters into the synaptic cleft where the neurotransmitters can bind to ionotropic or metabotropic receptors on the postsynaptic neuron. Ionotropic receptors initiate a rapid response but last for a short period while metabotropic receptors lead to slower, but longer-lasting responses. Chemical synapses also allow the postsynaptic neuron to receive and integrate signals from multiple presynaptic neurons. On the other hand, electrical synapses are formed by the connection of the presynaptic neuron to the postsynaptic neuron via gap junctions. This allows direct transfer of ions and signals from the presynaptic neuron to the postsynaptic neuron. Because the cytoplasm of the neurons is directly connected by gap junctions, electrical synapses transmit signals significantly faster than chemical synapses.

9.2. Excitatory and inhibitory synapse—Synapses can be classified as excitatory or inhibitory. Excitatory synapses contribute to the depolarization of the postsynaptic neuron by allowing the influx of Na+ ions. On the other hand, inhibitory synapses contribute to the hyperpolarization of the postsynaptic neuron by allowing the influx of Cl− ions. In chemical synapses, the postsynaptic neuron sums the signals it receives from both excitatory synapses (excitatory postsynaptic potentials) and inhibitory synapses (inhibitory postsynaptic potential), thus leading to either the transmission of the signal to the postsynaptic neuron or the termination of the signal. Glutamate is the main excitatory

neurotransmitter in the CNS while γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS.

9.3. Astrocytes, microglia and synapse—Many different cells in the brain are involved in synaptic processes. Astrocytes are glial cells that have been found to form the blood-brain barrier. Researchers have found that astrocytes are involved in the clearance of neurotransmitters along with the formation, maturation, alteration, and elimination of synapses (Chung et al., 2015). Moreover, cholesterol secreted by astrocytes has been found to enhance synaptic transmission by increasing the chance of the presynaptic neuron releasing glutamate (Mauch et al., 2001). Microglia are brain-specific macrophages and are known to play a role in the elimination of synapses, such as during synaptic pruning (Paolicelli et al., 2011). As a result, microglia have been found to play an important role in the removal of synapses during AD (Rajendran and Paolicelli, 2018). Finally, the synapses of neurons in the brain are involved in the transmission of signals, thus playing a vital role in neural processing and memory formation through long-term potentiation (LTP). The LTP is the long-lasting strengthening of synapses of neurons due to increased stimulation. Therefore, these different types of cells in the brain are all important to proper brain function, thus making them targets for analysis during AD.

9.4. Synapse and synaptic plasticity—Synaptic plasticity is the strengthening or weakening of synapses and connections between neurons, which occurs due to either increased or decreased activity, respectively. The activation of neurons leads to the phosphorylation of synapsin, thus increasing the number of synaptic vesicles that are ready for release, thereby allowing for neurotransmitters to be released more quickly and efficiently in response to signals. (Ho et al., 2011). Also, RIM proteins regulate the interactions between the influx of calcium and the corresponding release of neurotransmitters and the localization of vesicles in the active zone and preparation for release (Ho et al., 2011). Synaptic plasticity can be both short-term, involving transient changes in the synapse over a few minutes, and long-term, leading to long-lasting changes in the strength of synaptic connections and the formation of new synaptic connections that can last from a few hours to a person’s lifetime and contributes to the depression or strengthening of synaptic connections (Deperrois and Graupner, 2020). In the brain, synaptic plasticity has its greatest importance in forming and maintaining long-term memory. The hippocampus is known to play a significant role in memory and learning, thus LTP is of vital importance in the hippocampus (Nicoll, 2017).

9.5 Mitochondria and synaptic energy—Mitochondria play an important role in the synapse as energy is needed for local translation in the synapse and synaptic maturation (Devine and Kittler, 2018). Mitochondria located in the dendrite have been found to provide the energy needed for local translation during synaptic plasticity (Rossi and Pekkurnaz, 2019). Studies show that blocking mitochondrial function was related to decreased synaptic potentiation and neurotransmission (Guo et al., 2017; Todorova and Blokland, 2017). More specifically, blocking oxidative phosphorylation in mitochondria in neurons inhibits long-term potentiation (Flippo and Strack, 2017; Todorova and Blokland, 2017). Long-term potentiation is important for the formation and retrieval of long-term memory and learning,

thus mitochondrial dysfunction can lead to weaker synaptic connections and less excitable neurons, leading to worse memory (Lynch, 2004). Synaptic activity requires large amounts of energy, which is provided by a large number of mitochondria present in the synapse, which also helps with calcium buffering (Devine and Kittler, 2018). ATP is used in the synapse for many functions involved in neurotransmission. For example, ATP is needed for synaptic recycling (Pathak et al., 2015). Also, ATP is needed for the removal of calcium from inside the neuron using calcium-ATPase, resetting potassium and sodium concentration gradients during the refractory period, synthesis of molecules, and mitochondrial trafficking to the synapse (Harris et al., 2012). Trafficking is also essential for the clearance of damaged mitochondria (Sheng, 2014). Therefore, mitochondrial dysfunction present in AD has a considerable impact on impairing neurotransmission and other synaptic functions.

9.6 Mitochondrial trafficking in the synapse—Proper positioning and a healthy pool of mitochondria in neurons are essential to develop and maintain functional neuronal connections (Mandal and Drerup, 2019). The neuron has mechanisms that transport mitochondria to the synapse in order for the synapse to have enough mitochondria to execute its function (Sheng, 2017). Mitochondria are synthesized in the cell soma and are transported along the axons to the synapse using kinesins associated with microtubules and KIF5 factors (Course and Wang, 2016). Mitochondria can travel bi-directionally between the soma and presynapse using motor protein complexes, kinesins for anterograde, and dyneins for retrograde directions (Pilling et al., 2006, Calkins et al., 2012). Mitochondria travel toward the synapse and arrest there due to the higher intracellular calcium levels in the synapse (Saotome et al., 2008). Calcium disrupts interactions between mitochondria and transport complexes consisting of kinesins and Miro1, thus allowing mitochondria to localize and remain in the synapse (Wang and Schwarz, 2009). However, the transport of mitochondria becomes less frequent as neuron ages (Morsci et al., 2016). The movement of mitochondria must be coupled with their proper positioning throughout the neurons to meet the varying energy demands. However, the positioning of these mitochondria is controlled by both docking proteins and local environmental conditions (Cai and Sheng, 2009). For example, docking of mitochondria in neurons is affected by intracellular glucose (Course and Wang, 2016) and calcium (Saotome et al., 2008) concentrations with mitochondria positioning itself in areas where these concentrations are higher. This allows more mitochondria to be available in the part of the neuron that is needing the most energy, such as the synapse and nodes of Ranvier (Misgeld and Schwarz, 2017).

In AD and other neurodegenerative diseases, mitochondrial trafficking is impaired, resulting in fewer mitochondria located in the synapse. As a result, the synapse has less energy available to perform its functions, thus leading to a variety of pathophysiologies during AD. For instance, impaired trafficking results in decreased clearance of dysfunctional mitochondria (Correia et al., 2015). Dysfunctional trafficking occurs for many reasons. Damaged bioenergetics and mitochondrial dynamics have been found to limit mitochondrial transport (Correia et al., 2012; Correia et al., 2016). Energy is required to transport mitochondria, so if the neuron is not producing enough energy, mitochondria are not able to localize to the synapse. Aβ and Tau were also found to disrupt mitochondrial trafficking (Zhao et al., 2010; Calkins and Reddy, 2011; Calkins et al., 2012; Shahpasand et al., 2012;

Morton et al., 2021). Both Aβ and Tau destabilize microtubules involved in transport and lead to potential loss, thus decreasing the polarity of the microtubules (Correia et al., 2016). In addition, they contribute to mitochondrial dysfunction thus limiting the energy available for mitochondrial trafficking. As a result, defective mitochondrial trafficking results in the breakdown of synapses, leading to neuronal death (Correia et al., 2016). With less functional synapses, neurotransmission, neural processing, learning, and formation/accessing memories are all impaired.

9.7 Synapse differences between genders—The organization and function of synapses are different between the biological sexes. In 2008, a study found that the synaptic density was significantly higher in men than in women in all layers of the temporal cortex (Alonso-Nanclares et al., 2008). Although men were found to have more synaptic connections in the cortex, this does not indicate greater and more complex processing capabilities. However, it is not known why these areas have greater synaptic densities in men than in women and if yes, how that leads to different functions in those areas of the brain between men and women is not known. Moreover, in men, nitrous oxide is involved in LTP while women are much less dependent on nitrous oxide (Hyer et al., 2018). Researchers also found differences in the mechanism of synaptic plasticity between sexes (Hyer et al., 2018).

Sex steroid hormones are involved in a variety of pathways that influence synapses. Estrogen is a part of signaling pathways that are involved in the formation of synapses in the prefrontal cortex and hippocampus, thus playing a key role in neurological development (Hara et al., 2015). As a result, estrogen is important for synaptic plasticity. Estradiol is of significant interest as it is involved in synaptic plasticity in both men and women as men can convert testosterone into estradiol using aromatase enzymes (Gillies and McArthur, 2010). Therefore, estrogen plays a protective role in the brain and the significant decrease in estrogen after menopause might contribute to why more women have neurodegenerative diseases than men as women are more reliant on estrogen. Currently, estrogen is being explored as a potential treatment for neurodegenerative diseases, but no treatments have been developed yet. Progesterone also has been found to assist in synaptic function and LTP alongside estrogen, although its role is less known (Baudry et al., 2013). Testosterone, the predominant sex hormone in men, also plays a role in synaptic function. One study found that the administration of testosterone to mice increased synaptic density in hippocampal neurons (Fattoretti et al., 2019). Moreover, testosterone was found to maintain the function and levels of presynaptic proteins and the lengths of neurites, thus indicating the neuroprotective effects of testosterone against Aβ. As previously mentioned, testosterone is also able to be converted to estradiol, thus further impacting synapse formation and function.

Therefore, hormonal differences between genders play a role in the formation and maintenance of the synapse, resulting in different mechanisms of neuroprotection. As a result, the development and progression of neurodegenerative diseases are different between the biological sexes. Learning more about how the differences in biological sex contribute to synaptic function and how decreases in hormone levels and other body responses contribute to the progression of the disease will allow researchers to potentially develop more effective treatments.

9.8 Synapse function and aging—The decreased synaptic function is associated with aging, thus leading to decreased neurotransmission over time. This section analyzes the effects of specific changes that happen in the synapse. One major mechanism of synaptic dysfunction attributed to aging as mitochondrial dysfunction starts occurring when person gets older. Mitochondria's functional changes concerning aging are discussed in Section 3.7. Reduced mitochondrial trafficking, decreased mitophagy, and impaired energy production prevents the synapse from making the appropriate amount of energy needed for its function. Therefore, synaptic impairment increases due to synapses not being able to recycle synaptic vesicles, regulate intracellular synaptic concentrations and reset concentration gradients across the axon and synapse. This leads to synaptic dysfunction and the loss of synaptic connections due to neuronal death which in turn decreases neurotransmission. Furthermore, synaptic strength decreases, as a person gets older. Researchers have found that aging is associated with the loss of synaptic connections (Bishop et al., 2010). Also, alterations in neurotransmitter levels are involved in aging (Anyanwu, 2007). In conjunction, aging results in decreased postsynaptic responsiveness. In addition, aging inhibits LTP and promotes LTD, thus making the formation and access of long-term memories more difficult (Foster, 1999). Together, these alterations weaken neurotransmission and decrease synaptic plasticity. These changes in synapses due to aging make older people more susceptible to AD and other neurodegenerative diseases. The deterioration of neurons leads to fewer synaptic connections, thereby leading to cognitive decline. For example, the loss and weakening of synaptic connections in the hippocampus contribute to the reduction in hippocampal volume and worsening memory (Kashyap et al., 2019). Furthermore, the weakening of existing connections due to aging leads to decreased processing capabilities of older people. Synaptic function changes associated with aging are also seen in synapse AD, thus aging-related changes could play a role in the early development of AD. Analyzing how synapses change due to age will allow researchers to better understand how synaptic changes due to age relate to synaptic changes due to AD. This allows researchers to find how synapses change due to AD and what treatments can be developed to preserve and enhance synapse function with age in elderly and patients with AD. Figure 7 illustrates how the variation and amounts of sex hormones in both genders are related to changing synapse density and mitochondrial respiratory activity as people age. Based on this figure, researchers can potentially explore the effects of sex hormones on mitochondrial and synaptic activity and density in different genders at various periods of life.

9.9. Synapse dysfunction in Alzheimer's disease—In AD, synaptic dysfunction leads to impaired neurotransmission, thereby contributing to a variety of pathophysiologies that are observed in AD (John and Reddy, 2021). The deterioration of synapses occurs early on in AD (Shankar and Walsh, 2009). Synaptic damage can occur due to disruption of mitochondrial trafficking (covered in a different section), the presence of toxic substances in the synapse, and due to mitochondrial dysfunction.

9.9.1. Aβ and synapse dysfunction: The accumulation of Aβ has been shown to contribute to neurotoxicity and corresponding dysfunction and damage in the synapse. Aβ disrupts the release of neurotransmitters, regeneration of synaptic vesicles, and anterograde transport of mitochondria to the synapse (Calkins and Reddy, 2011; Rajmohan and Reddy,

2017; Chen et al., 2019b; John and Reddy, 2021; Morton et al., 2021; Pradeepkiran and Reddy, 2020). Furthermore, Aβ were found to promote *N*-methyl-D-aspartate (NMDA)-dependent Long-Term Depression (LTD) and inhibit NMDA-dependent LTP, thus leading to weaker synaptic connections (Marsh and Alifragis, 2018; Tu et al., 2014). LTD is also enhanced by decreased reuptake of glutamate by the synapse (Li et al., 2009).

9.9.2. P-tau and synapse dysfunction: P-tau has also been implicated in synaptic dysfunction during AD. Synaptogyrin-3, a protein that interacts with Tau and is involved in vesicle movement, was found to restrict the movement of synaptic vesicles and decrease the release of neurotransmitters from vesicles in the presence of Tau (Zhou et al., 2017; McInnes et al., 2018; John an Reddy, 2021). Tau was also found to interact with microtubules, thus interfering with the binding of dyneins and kinesins with microtubules, thereby decreasing the movement of mitochondria via axonal transport (Dixit et al., 2008; Cheng and Bai, 2018), thus diminishing neurotransmission. Synaptic activity has been found to increase the spread of Tau to synapses, further leading to synaptic dysfunction (Calafate et al., 2015). Researchers found that the interactions between hyperphosphorylated tau and Drp1 lead to enhanced mitochondrial fission, thus leading to decreased functional mitochondria present in the synapse (Manczak and Reddy, 2012). Due to these pathologies, the number of synapses decreases in the brain due to degradation (Kashyap et al., 2019). Synaptic dysfunction contributes to slower and disrupted neurotransmission, leading to the memory loss and cognitive impairment that is characteristic of AD. As synapse continues to deteriorate and neurons die as a result, so does the neural processing capabilities of those with AD, thereby leading to dementia and the progression of AD. Recently our lab identified the critical synaptic miRNAs and their function in AD (Kumar and Reddy, 2020). Mitochondrial miRNAs are involved in various synaptic functions. Table 4 shows mitochondrial miRNAs that are specifically associated with various synaptic functions. This table highlights target genes, the dysregulation of these miRNAs in AD, and how they are related to synaptic function. The downregulation of these genes by binding to the 3’UTR of target mRNAs are found to contribute to various synaptic functions that are listed in this table. Figure 8 depicts which mitochondria miRNAs are associated with each synaptic function, whether these miRNAs are upregulated or downregulated in AD, and whether these miRNAs promote or inhibit a certain synaptic function. Understanding how synaptic dysfunction occurs in AD will allow researchers a better understanding of how AD progresses and determine potential targets for treatment.

9.10. Mitochondrial miRNAs and synaptic activity—Synaptic activity is essential for neurotransmission and brain function. The impairment of this activity can lead to neuronal death, weakened transmission, and decreased synaptic plasticity. Decreased synaptic activity leads to slower neural processing and decreases a person’s ability to form or access long-term memories. Two mitochondrial miRNAs have been found to enhance synaptic activity: miR-455-3p and miR-34a. miR-455-3p was found to enhance synaptic activity, thus the upregulation of miR-455-3p in AD indicates that this miRNA serves a protective role in neurons and can be used as a biomarker for AD (Kumar and Reddy, 2019). In addition, miR-34a leads to dysfunction in resting presynaptic and postsynaptic activities,

thus the upregulation of this miRNA in AD shows that this miRNA could be involved in the pathogenesis of AD (Sarkar et al., 2016).

9.11. Mitochondrial miRNAs and synaptotoxicity—Protection against toxic molecules is a major function of synapses. Synaptotoxicity results in dysfunctional synapses, thus impairing neurotransmission and leading to neuronal death. miR-218 is a mitochondrial miRNA that was found to downregulate PRKN (Di Rita et al., 2020). The PRKN plays a role in safeguarding neurons from toxins and metallic ions, thus allowing for synapses to remain functional (Di Rita et al., 2020). The downregulation of miR-218 in AD, suggests that this miRNA may potentially have a protective effect against synaptotoxicity, thus showing how maintaining miR-218 levels in neurons could be of importance in neuronal survival.

9.12. Mitochondrial miRNAs and neurotransmission—The primary role of synapse in neurons is neurotransmission, which is accomplished through the release of neurotransmitters. A few mitochondrial miRNAs (miR-484, miR-132, and miR-212) are related to this vital function. miR-132 and miR-212 were found to enhance neurotransmission, thus the impairment of these miRNAs in AD leads to decreased neurotransmission, thus limiting neural processing capabilities by those with AD (Remenyi et al., 2013). miR-484 was also found to be involved in neurotransmission, thus the deregulation of this miRNA has the potential to also alter signal transmission in AD patients (Wingo et al., 2020). Therefore, mitochondrial miRNAs are important to neurotransmission as altered levels of these miRNAs in neurons can contribute to disease.

9.13. Mitochondrial miRNAs and synaptic plasticity—Synaptic plasticity is essential for memory and learning. Mitochondria provide the energy necessary for plasticity and aid in calcium buffering that occurs at the synapse. Mitochondrial miRNAs have been found to be involved in synaptic plasticity. miR-132 (Lambert et al., 2010) has a role in regulating short-term plasticity while miR-484 (Wingo et al., 2020) impacts long-term plasticity. Both miRNAs are deregulated in AD. miR-34a is associated with the dysfunction of synaptic plasticity and is upregulated in AD, thus this miRNA could be implicated in the pathogenesis of AD (Sarkar et al., 2016). These miRNAs are most likely regulated to where synaptic plasticity is defective and existing connections are damaged.

Conclusions and future directions

The science of mitochondrial microRNAs is emerging and relatively new in mitochondrial and synapse areas of research in Alzheimer's disease. It is known that miRNAs play important roles in performing mitochondrial functions. Naturally, mitochondrial miRNAs are of higher interest to researchers pursuing to develop biomarkers, treatments, and/or targets for the treatment of AD. However, knowledge on mitochondrial miRNAs affecting specific synaptic functions is limited. For example, no miRNA has been associated with mitochondrial trafficking, Ca^{2+} signaling, and synaptic vesicle formation, all of which are important in neurotransmission. Moreover, only a few mitochondrial miRNAs were associated with synaptic activity, neurotransmission, synaptic plasticity, and neurotoxicity. Identifying more mitochondrial miRNAs in the synapse associated with these functions

and whether they are deregulated in AD or not will give a greater understanding of which miRNA should be of focus when analyzing the synaptic dysfunction present in AD.

In this meta-analysis study, we have identified 24 mitochondrial miRNAs that are associated with AD (Table 2) and mostly binding to the 3' UTR of the mRNA. For a better understanding, these miRNAs are classified into major mitochondrial functions, including bioenergetics, redox homeostasis, mitophagy, biogenesis, mitochondrial dynamics, and apoptosis. In addition, five mitochondrial miRNAs were found to be related to synaptic functions, including synaptic activity, neurotransmission, neurotoxicity, and synaptic plasticity. Many of the miRNAs are found to be involved in more than one function and are associated with other neurodegenerative diseases such as PD, HD, and ALS. Many of the studies that we reviewed also indicated that many miRNAs contribute to mitochondrial dysfunction in AD brains. However, which miRNAs initiate and contribute the most to the development and progression of AD is still unknown. Therefore, more research is needed to determine interrelationships among the different mitochondrial functions and their miRNAs.

Further exploration of mechanisms and proteins involved in mitochondrial and synaptic dysfunction is needed. Recently, defective mitophagy has been hypothesized as an early cellular event in neurodegenerative diseases. More research is needed to understand how mitochondrial miRNAs regulate mitophagy and how the deregulation of these miRNAs occurs. Further, how miRNAs localize to the mitochondria to exert their effects needs to be discovered. Enhancing synaptic activity can serve as one possible method of treatment for AD. In addition, researchers need to develop ways to decrease the harmful effects that Aβ and p-tau have on mitochondrial dysfunction.

Research on treatment strategies is of utmost importance. Mitochondrial miRNAs have a major potential to be used as biomarkers for the early detection and treating AD. Researchers can explore what happens when certain mitochondrial miRNAs are added at greater levels or completely knocked out and how this affects mitochondrial function in both WT and AD mice to determine the potential use of certain mitochondrial miRNA as treatments. Also, sex hormones are being analyzed as potential treatments for AD. Although many researchers are analyzed the protective effects of sex hormones, no successful treatment has been developed. Therefore, there are research opportunities to further explore sex hormones to identify potential biomarkers of AD, allowing for earlier diagnosis and to the development of treatments, and/or targets for treatment to prevent the progression of this disease.

Acknowledgements

The authors would like to thank NIH for funding various projects - R01AG042178, R01AG47812, R01NS105473, AG060767, AG069333, and AG066347 to (P.H.R) and K99AG065645 to (S.K.).

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Highlights

- Mitochondrial dysfunction is one of the major hallmarks of AD.
- Mitochondrial miRNAs are crucial for mitochondrial functions in neurotransmission at synapse.
- Mitochondria works differently with age and gender in AD.
- Synapse numbers varies with age and gender in AD.
- Mitochondrial miRNAs are potential targets for mitochondria and synapses in AD.

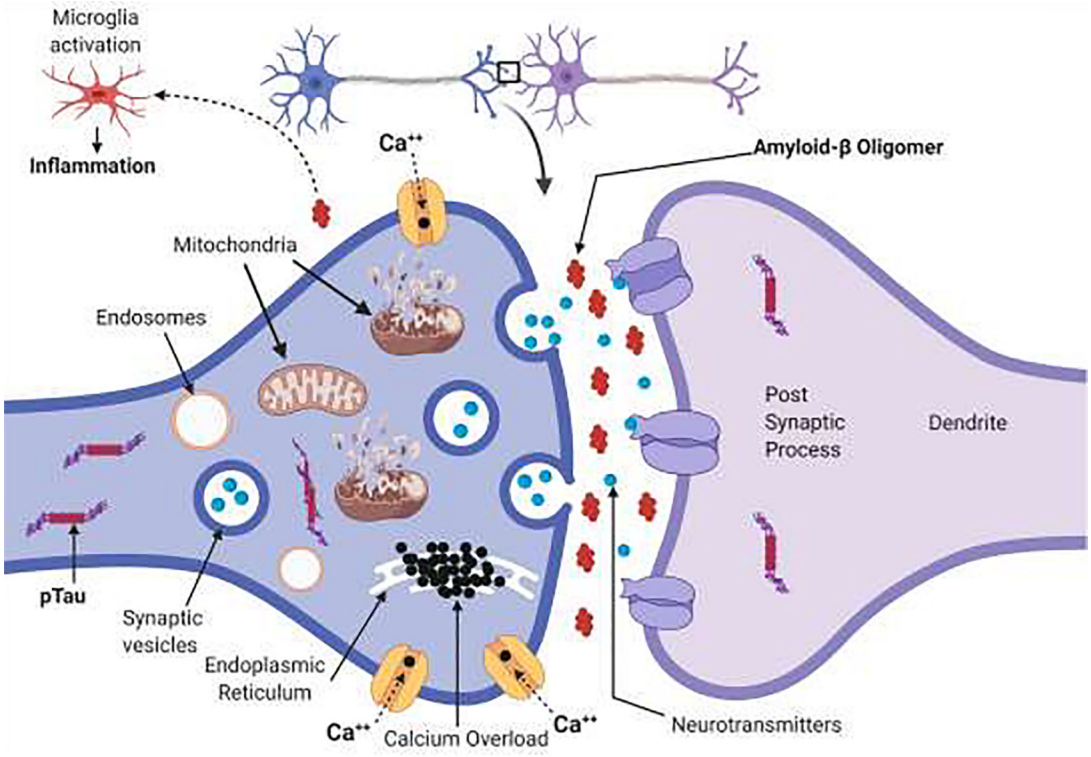

Fig. 1. Synapse dysfunction in Alzheimer's disease.

One of the major hallmarks of AD is synapse dysfunction, which as shown in the figure, leads to the activation of microglia. This figure depicts the presence of p-tau inside the synapse and Aβ oligomers in the extracellular space, both of which contribute to AD and the decrease in synaptic activity. Moreover, this figure illustrates how the presence of dysfunctional mitochondria and the resulting calcium overload in the synapse also contributes to the damage of synapse. The closed channels on the postsynaptic neuron show how neurotransmission is impaired due to synaptic dysfunction (*Adapted from "Synaptic Cleft Horizontal", by BioRender.com (2021). Retrieved from* https://app.biorender.com/biorender-templates.).

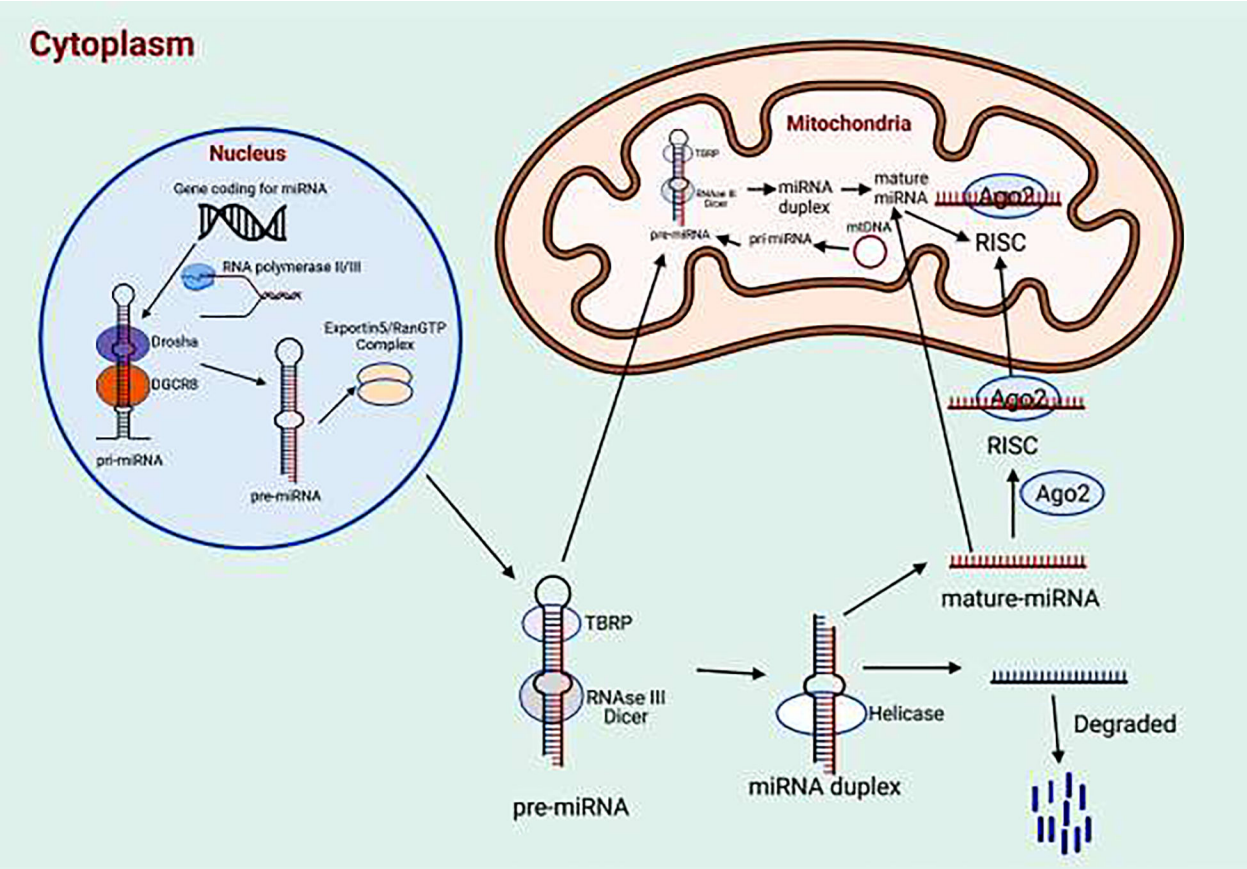

Fig. 2. Mitochondrial miRNA biogenesis.

There are many potential mechanisms of mitochondrial miRNA biogenesis. The first proposed mechanism is that RISC is formed in the cytoplasm and then transported into the mitochondria. Another proposed mechanism is that mature miRNA translocates to the mitochondria and then RISC is formed inside the mitochondria. Moreover, pre-miRNA might translocate into the mitochondria where it is able to be converted into mature miRNA and then RISC. The last proposed mechanism is that mitochondrial miRNA biogenesis occurs entirely in the mitochondria using mtDNA (*Created with BioRender.com*).

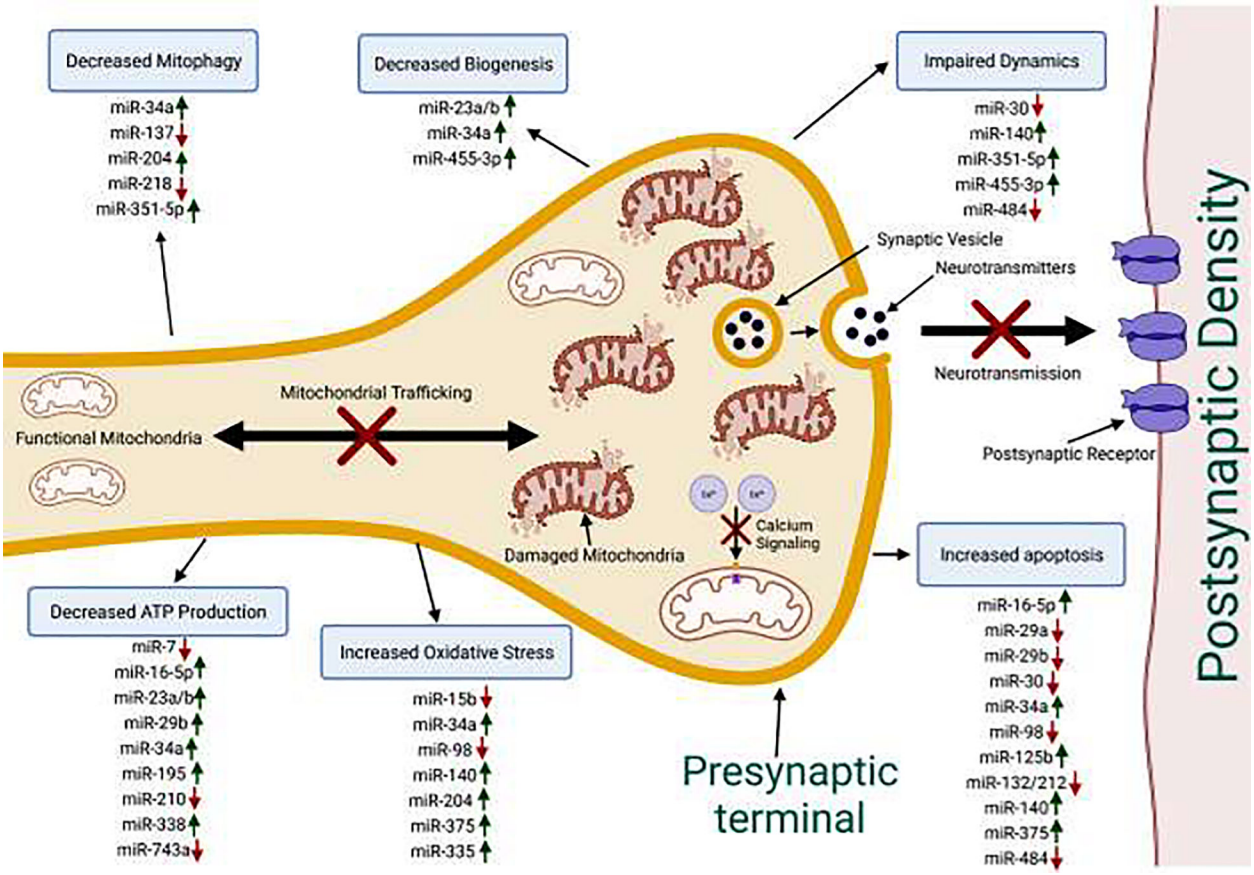

Fig. 3. Mitochondrial microRNAs and mitochondrial dysfunction in Alzheimer's disease.

This figure depicts the various mitochondrial dysfunctions present in the synapse during AD and highlights the deregulation of miRNAs that is related to each impairment. The green and red arrows indicate the upregulation or downregulation, respectively, of a miRNA in AD. Moreover, mitochondrial trafficking, neurotransmission, and calcium regulation are shown to be impeded. As a result, the synapse during AD has many damaged mitochondria and fewer functional mitochondria (*Created with BioRender.com*).

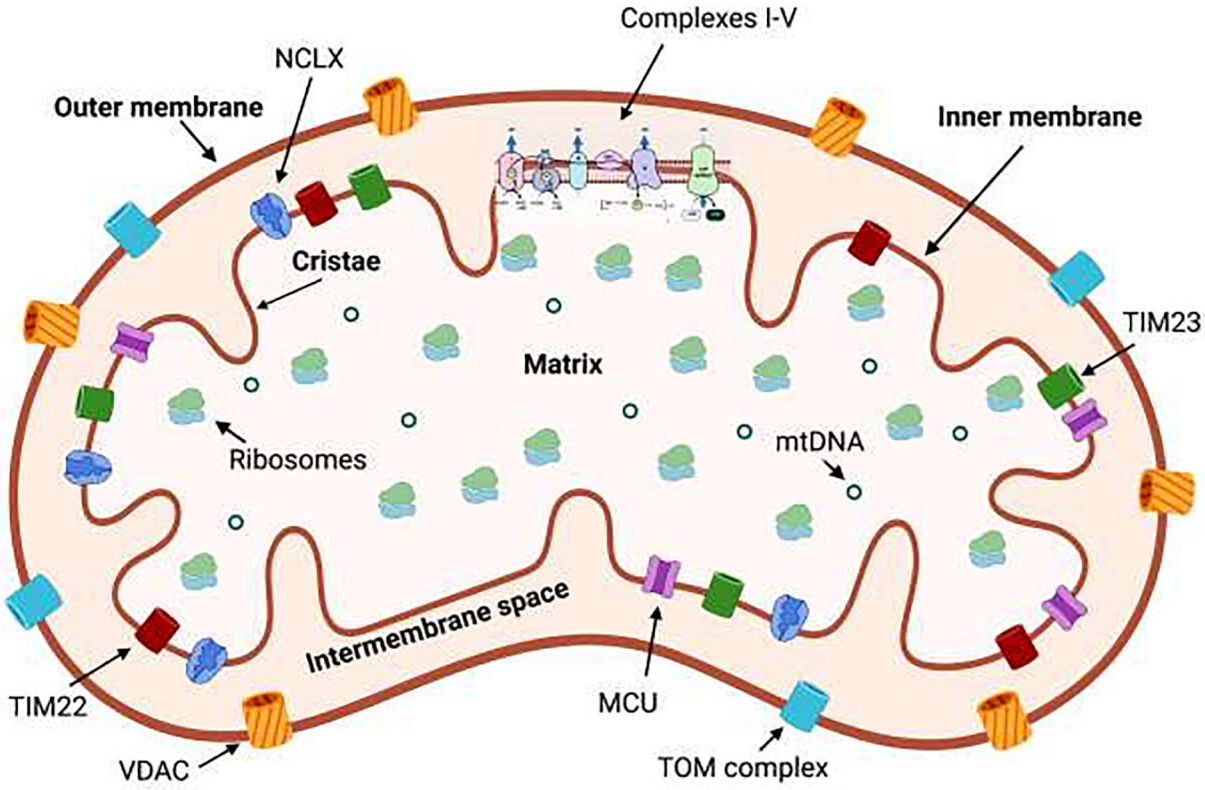

Fig. 4. Mitochondrial structure.

Mitochondria consists of a double membrane (outer and inner membrane), intermembrane space, cristae, and the matrix. The outer membrane has TOM complexes and VDAC embedded to allow the transport of proteins and ions respectively from the cytoplasm to the intermembrane space. The inner mitochondrial membrane has TIM complexes that allow for the transport of proteins from the intermembrane space to the matrix (TIM23) and the integration of proteins within the inner membrane (TIM22). MCU and NCLX, which are involved in calcium transport into and out of the matrix, and the respiratory complexes (I-V) that are involved in oxidative phosphorylation are also located in the inner membrane. The matrix consists of ribosomes and mtDNA (*Adapted from "Electron Transport Chain", by BioRender.com (2021). Retrieved from* https://app.biorender.com/biorender-templates.).

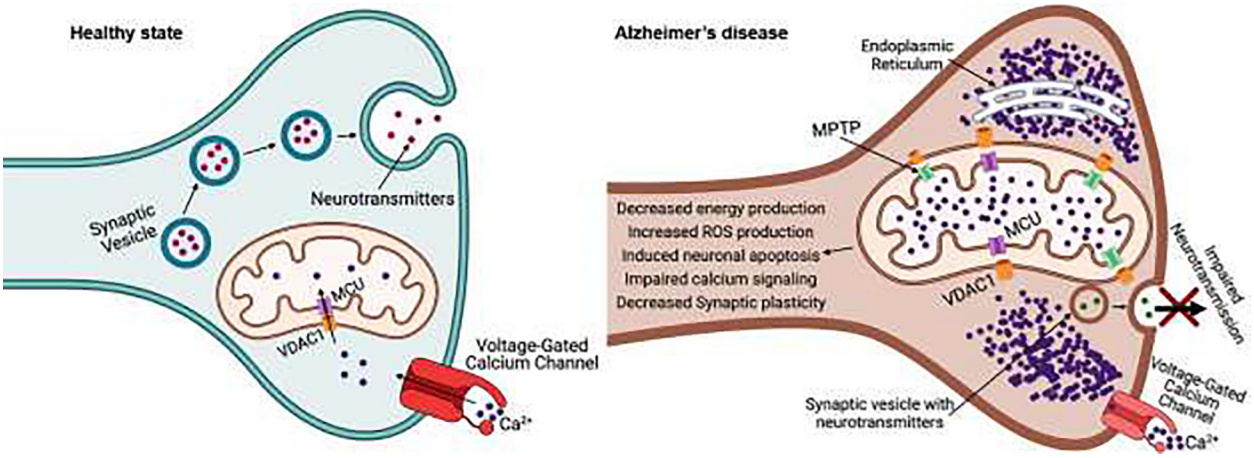

Fig. 5. Mitochondria and calcium regulation in healthy synapse (left) and in Alzheimer's disease (right).

During neurotransmitter release, the synapse experiences an influx of calcium through voltage-gated calcium channels. Mitochondria play a significant role in regulating calcium levels in the synapse. Calcium crosses the outer mitochondrial membrane through VDAC1 and then passes through the inner mitochondrial membrane and into the matrix through MCU. While the mitochondria control calcium levels, synaptic vesicles form in the membrane and fuse with the synaptic membrane to release neurotransmitters by exocytosis. However, in AD, cytosolic calcium levels are significantly elevated due to a greater influx of calcium ions through the voltage-gated calcium channels and increased release of calcium into the synapse by the endoplasmic reticulum. Calcium deregulation was found to occur due in part to Aβ. MPTPs open in the inner mitochondrial membrane and mitochondria experience a substantially greater influx of calcium. As a result, the mitochondria in the synapse become dysfunctional, thus leading to neuronal apoptosis and consequently impaired neurotransmission and decreased synaptic plasticity (*Created with BioRender.com*).

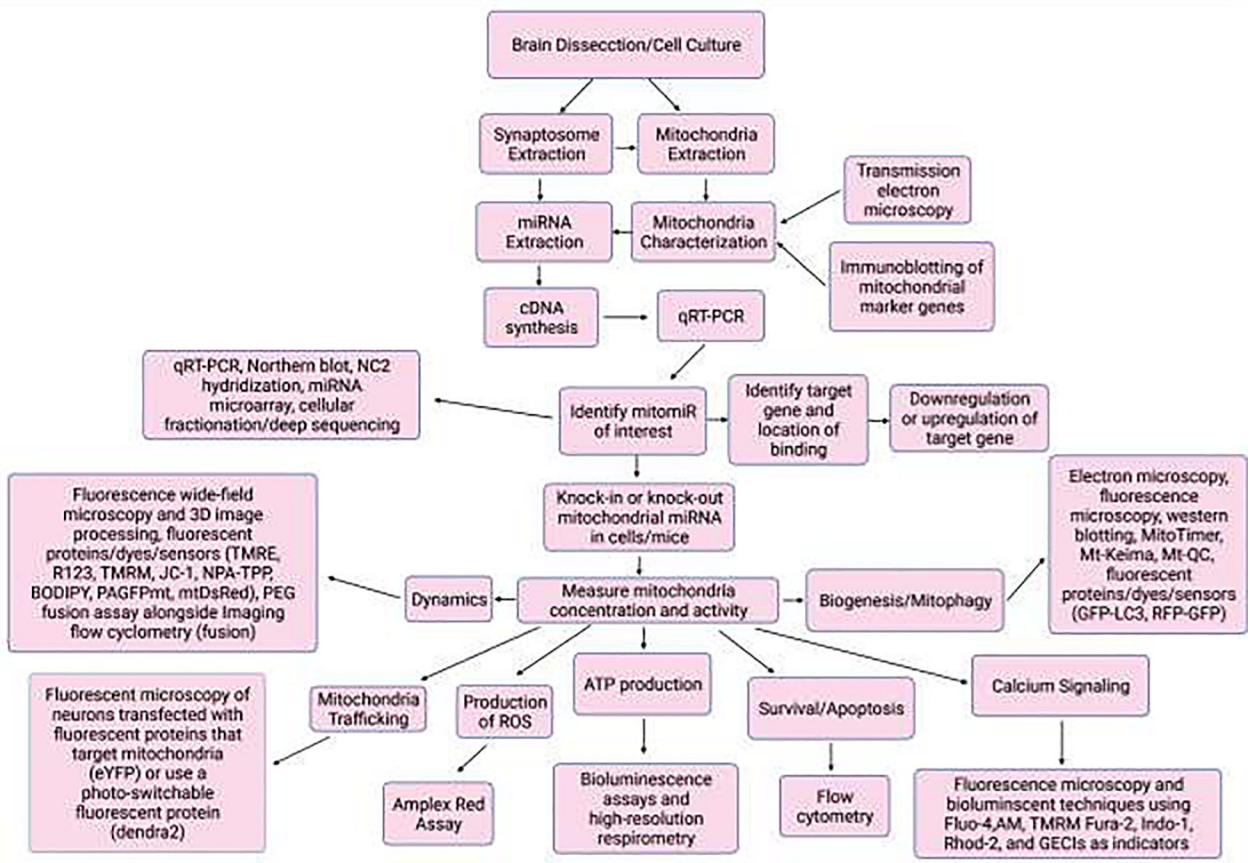

Fig. 6. Mitochondrial miRNA analysis flow chart.

This figure depicts a flow chart of how to study mitochondrial miRNAs. The first half of the flow chart involves how to identify and quantify mitochondrial miRNAs and mitomiRs in the synapse and mitochondria. Next, the chart portrays how these identified miRNAs should be analyzed for their target gene and whether or not they upregulate or downregulate that gene. The chart goes on to show how researchers should explore if these identified miRNAs are upregulated or downregulated in AD. At the bottom, the chart shows how the mitochondrial functions of these miRNAs can be determined by knocking-in or knocking-out a specific miRNA and measuring mitochondrial activity (*Created with BioRender.com*).

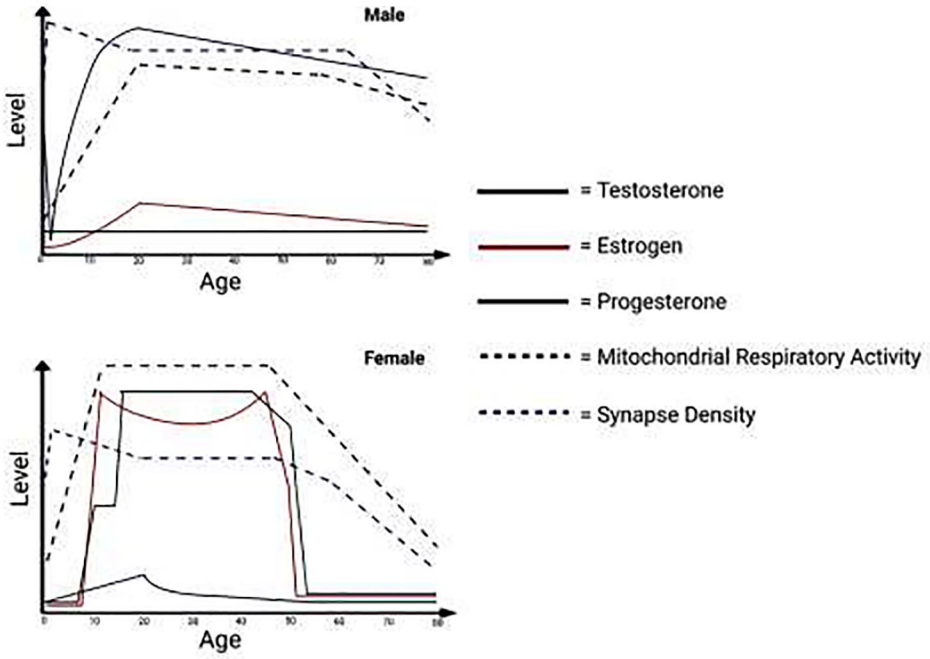

Fig. 7. Mitochondrial respiratory activity and synapse density related to age and gender.

In men, testosterone levels are significantly higher than estrogen and progesterone levels. Testosterone is initially high at birth before dropping down after the first week of life (Tomlinson et al., 2004). As boys gets older and goes through puberty, testosterone levels increase, peaking around 21 years of age (Chodick et al., 2020). Afterward, testosterone levels in men gradually decrease throughout adulthood (Chodick et al., 2020). About 80% of estradiol in men is derived from testosterone, thus estrogen in the figure is shown to follow roughly the same trend since less testosterone means less estradiol that can be produced (Finkelstein et al., 2013). Progesterone is involved in the synthesis of testosterone in men and is shown to remain constant as men get older (Hall and Klein, 2017; Oettel and Mukhopadhyay, 2004). For women, estrogen and progesterone levels are significantly higher than testosterone levels. Estrogen in girls stays low until puberty when estrogen levels significantly increase and then levels off around one year after menarche (Hoyt and Falconi, 2015). Perimenopause (transition to menopause) occurs in women in their 40s with menopause beginning, on average, between ages 45 and 51 (McCarthy and Raval, 2020). At early perimenopause, estrogen levels become elevated but drop off substantially in later stages, thus estrogen levels are low by menopause (Hoyt and Falconi, 2015). Progesterone levels are low until puberty where it significantly increases (Hall and Klein, 2017). Progesterone remains constant in adulthood prior to menopause (Hall and Klein, 2017). As women approach menopause, progesterone begins to drastically decrease until progesterone levels are low during menopause. Testosterone in women is found to increase from birth till adulthood and then gradually decrease as women continue to age (Ankarberg and Norjavaara, 1999; Davison et al., 2005). Mitochondrial respiratory activity is proposed to follow hormone changes during aging with decreasing hormone levels corresponding to decreasing activity. Mitochondrial respiratory activity is known to be significantly higher in women than men as reflected in the figure (Gaignard et al., 2018). Moreover, men

were found to have higher synaptic density than women in certain areas of the brain (Alonso-Nanclares et al., 2008). In both men and women, synapse density increases and peaks when people are 1–2 years old and then decrease through synaptic pruning as people become adults (Sakai, 2020). Because men have greater synapse density than women, the peak for men is predicted to be higher than that for women. Also, researchers found that the synapse density in layer 3 of the middle frontal gyrus increased till about age one, decreased thereafter until age 16 due to synaptic pruning, which removes unused synapses, and then remains constant till age 72 before decreasing significantly (Huttenlocher, 1979). Men are shown to follow the previously stated trend while this figure predicts women to experience a notable decrease in density closer to menopause. This figure is not to scale and only general trends and relative levels are shown (*Created with BioRender.com*).

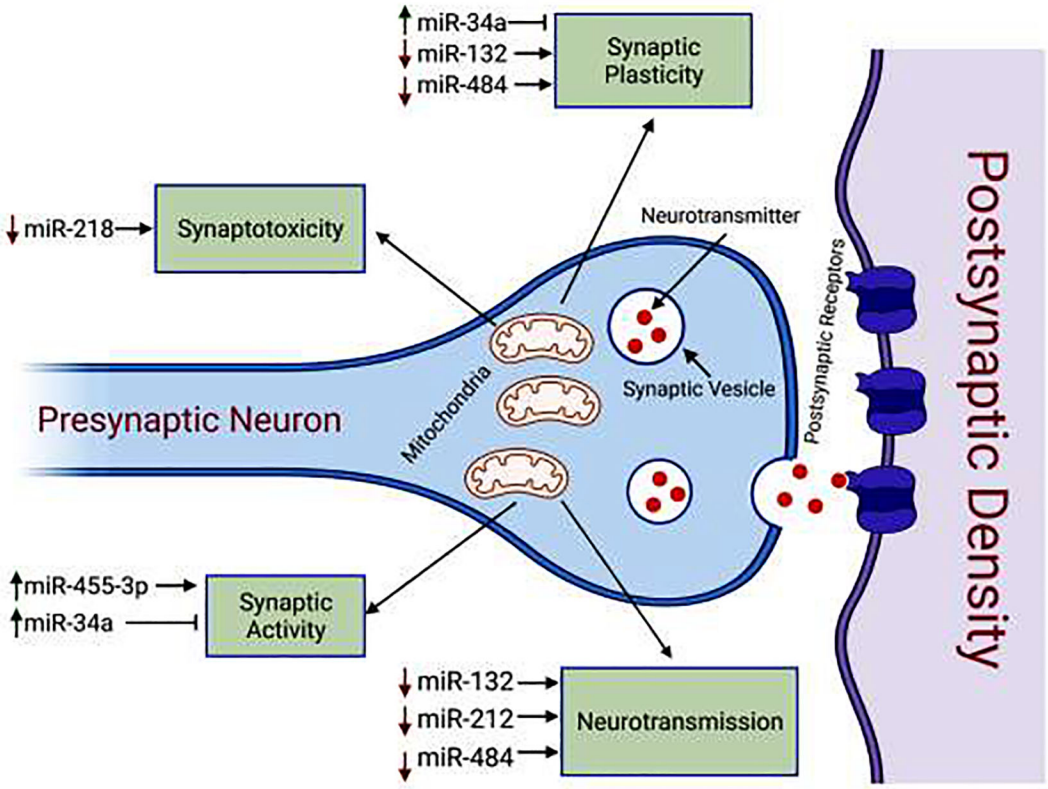

Fig 8. Mitochondrial miRNAs and synapse function in Alzheimer's disease.

Mitochondrial miRNAs that are shown in the figure are associated with synaptic functions and deregulated in AD. The green and red arrows indicate the upregulation or downregulation, respectively, of the miRNA in AD. miR-455-3p and miR-218 seem to have a neuroprotective impact on neurons while miR-34a, miR-132, and miR-212 are associated with synaptic dysfunction (*Created with BioRender.com*).

Table 1.

Oxidized biomolecule by-products produced in the brain cell due to overproduction of ROS in AD.

Sl. No.	Oxidation of	By-products or Oxidative stress markers	References
1	Nucleic acids (DNAs and RNAs)	8-OH-2'-deoxyguanosine 8-OH-guanosine	(Pena-Bautista et al., 2019; Zhang et al., 2013)
2	Proteins	Protein carbonyls 3-nitrotyrosine (3-NT)	(Butterfield and Boyd-Kimball, 2020; Butterfield et al., 2007)
3	Lipids	4-hydroxy-2-*trans*-nonenal (HNE) Malondialdehyde (MDA) 2-propenal (acrolein) F2-isoprostanes F4-neuroprostanes Thiobarbituric acid-reactive substances (TBARS) Free fatty acid release	(Dei et al., 2002; Di Domenico et al., 2017; Gamba et al., 2019; Lovell et al., 1997; Moldogazieva et al., 2019)
4	Carbohydrates	Advanced glycation end products	(Dei et al., 2002; Srikanth et al., 2011)

Table 2.

Mitochondrial miRNAs associated with Alzheimer's disease.

Sl. No.	microRNA	Target Gene(s)	Regulation	Region	Function	Importance	References
1	miR-7	VDAC1	Downregulation of target gene	3' UTR	Stabilizes mitochondrial membrane potential	VDAC1 significantly increased in AD so miR-7 might also have impact on AD	(Chaudhuri et al., 2016)
2	miR-15b	SIRT4, BACE1	Downregulation of target gene	3' UTR	Plays role in redox homeostasis and counteracts senescence-related mitochondrial dysfunction	Found downregulated in AD and plays a role in repressing BACE1. Downregulation of mir-15b could also upregulate SIRT4 in AD, leading to mitochondrial dysfunction.	(Lang et al., 2016; Gong et al., 2017)
3	miR-16-5p	BCL-2	Downregulation of target gene	3' UTR	Disrupts mitochondrial membrane integrity and promote apoptosis	Upregulated in AD due to Aβ, leading to neuronal cell death through apoptosis	(Leggio et al., 2017; Liguori et al., 2018; Kim et al., 2020)
4	miR-23a/b	SIRT1, GLS	Downregulation of target gene	3' UTR	Mediates protective neuronal stress response and regulates mitochondrial metabolism by targeting glutaminase	Found upregulated in frontal cortex in AD, thus indicating that mir-23a/b might play potential role in disease progression by decreasing energy production and stress response in neurons, leading to neuronal death	(Gao et al., 2009; Weinberg et al., 2015; Tang, 2016)
5	miR-29a	VDAC1, VDAC2, VDAC3	Downregulation of target gene	3' UTR	Triggers apoptosis by targeting mitochondrial voltage dependent anion channels in outer membrane of mitochondria	Downregulated in AD, thus potentially disrupting the control of neuron apoptosis and proliferation in brain	(Shioya et al., 2010; Bargaje et al., 2012)
6	miR-29b	Bcl2L2, Mcl-1	Downregulation of target gene	3' UTR	Promotes apoptosis and loss of mitochondrial membrane potential	Downregulated in AD, thus potentially serving a neuroprotective role	(Mott et al., 2007; Hebert et al., 2008; Shi et al., 2012; Lungu et al., 2013)
7	miR-30	DRP1, p53	Downregulation of target gene	3' UTR	Inhibits mitochondrial fission and apoptosis	Downregulated in AD, which then can lead to increased neuronal death through apoptosis	(Li et al., 2010)
8	mir-34a	NDUFC2, SDHC, UQCRB, UQCRQ, COX10, Bcl-2, SIRT1, Txnrd2	Downregulation of target gene	3' UTR	Downregulates antioxidant mitochondrial enzymes, impair energy production, and induce apoptosis	Upregulated in AD, leading to widespread mitochondrial dysfunction	(Yamakuchi et al., 2008; Bai et al., 2011; Lin et al., 2015)
9	miR-98	HEY2	Downregulation of target gene	3' UTR	Inhibits neuronal apoptosis and ameliorates oxidative stress and mitochondrial dysfunction	Downregulated in mice with AD and found to reduce the production of Aβ and improve mitochondrial dysfunction	(Chen et al., 2019a)

Sl. No.	microRNA	Target Gene(s)	Regulation	Region	Function	Importance	References
10	miR-125b	FOXQ1	Downregulation of target gene	3' UTR	Induces apoptosis by upregulating Bax and downregulating Bcl-2	Found upregulated in AD, thus suggesting that the increase in miR-125b during AD enhances apoptosis in neurons	(Hong et al., 2017; Ma et al., 2017)
11	miR-132/212	PTEN, FOXO3a, P300, NOS1	Downregulation of target gene	3' UTR	Inhibits neuronal apoptosis	Downregulated in AD neurons, thus contributing to the promotion of apoptosis of neurons in the brain	(Wong et al., 2013; Wang et al., 2017)
12	miR-137	FUNDC1, NIX	Downregulation of target gene	3' UTR	Inhibit mitophagy	Downregulated in AD patients, thus potentially having role in promoting mitophagy	(Geekiyanage and Chan, 2011; Li et al., 2014c; Li et al., 2017)
13	miR-140	PINK1, mfn1	Downregulation of target gene	3' UTR	Increases mitochondrial dysfunction and ROS production while also promoting autophagy, mitochondrial fission, and apoptosis	Reduced PINK1 and upregulated miR-140 is associated with AD. Induced PINK1 overexpression leads to decreased mitochondrial ROS and injury of the mitochondrial membrane, thereby preventing neuronal cell apoptosis. Therefore, silencing of miR-140 poses a novel therapeutic target for AD.	(Li et al., 2014c; Liang et al., 2021)
14	miR-195	mfn2	Downregulation of target gene	3' UTR	Decreases mitochondrial membrane potential and activity	Mfn2 is found to be downregulated in hippocampal neurons during AD, therefore upregulation of mfn2 by inhibiting miR-195 is a potential therapeutic strategy for AD.	(Zhang et al., 2016)
15	miR-204	TRPML1	Downregulation of target gene	3' UTR	Increases mitochondrial damage, ROS production, and mitophagy	Downregulation of miR-204 inhibits mitochondrial damage, ROS production, and mitophagy caused by Aβ	(Zhang et al., 2021)
16	miR-210	ISCU1/2, COX10	Downregulation of target gene	3' UTR	Downregulates mitochondrial respiration and activates glycolysis and ROS generation	Downregulated in the hippocampus of AD. Soluble Aβ leads to upregulation of miR-210, thus leading to greater inhibition of ETC and increased production of ROS. Downregulation of miR-210 during AD serves as protection against toxic effects of Aβ and reduces oxidative stress.	(Cogswell et al., 2008; Chen et al., 2010; Huang et al., 2010; Li et al., 2014b)
17	miR-218	PRKN	Downregulation of target gene	3' UTR	Inhibits mitophagy and mitochondrial clearance and protects against neurotoxicity that	PRKN found at higher levels in mice AD brain, thus showing that miR-218 is potentially	(Di Rita et al., 2020; Hou et al., 2020)

Sl. No.	microRNA	Target Gene(s)	Regulation	Region	Function	Importance	References
					is caused by metallic ions and other neurotoxins	downregulated in AD, thus leading to the dysreuglation of mitophagy and neuron homeostasis. miR-218 was found to be a potential therapeutic target for AD.	
18	miR-335	SOD2, Txnrd2	Downregulation of target gene	3' UTR	Downregulates antioxidant enzymes in mitochondria, leading to increase in ROS	Upregulated in AD and associated with senescence, thus potentially contributing to mitochondrial dysfunction associated with AD	(Bai et al., 2011; Satoh et al., 2015)
19	miR-338	COXIV	Downregulation of target gene	3' UTR	Decreases metabolic activity in axonal mitochondria	Overexpression of this brain-specific miRNA contributes to decreased energy production in neurons and could be involved in pathogenesis of AD	(Aschrafi et al., 2008)
20	miR-351-5p	Miro2	Downregulation of target gene	3' UTR	Regulates mitochondrial GTPase and induces mitochondrial fission, leading to mitochondrial dysfunction and promoting mitophagy	Found upregulated in AD and contributes to hippocampal neural progenitor cell death, which is associated with AD,	(Woo et al., 2021)
21	miR-375	SIX4	Downregulation of target gene	3' UTR	Promotes oxidative stress injury and apoptosis	Found upregulated in AD, which was found to promote oxidative stress injury and apoptosis in neurons	(Wang et al., 2020a)
22	miR-455-3p	APP	Downregulation of target gene	3' UTR	Regulates mitochondrial dynamics (decrease mitochondrial fission/increase mitochondrial fusion) and supports mitochondrial biogenesis and synaptic plasticity	Found upregulated in AD neurons compared to control neurons in response to increase in Aβ	(Kumar et al., 2017; Kumar et al., 2019; Kumar and Reddy, 2019)
23	miR-484	Fis1, BCL2L13	Downregulation of target gene	Coding region (Fis1) and 3' UTR (BCL2L13)	Inhibits mitochondrial fission and apoptosis	Lower level of miR-484 associated with mild cognitive impairment, cognitive decline and higher risk of having AD	(Wang et al., 2012; Wingo et al., 2020; Liu et al., 2021)
24	miR-743a	mdh2	Downregulation of target gene	3' UTR	Suppresses malate dehydrogenase activity	Malate dehydrogenase activity is elevated in humans with AD, thus indicating the potential inhibition of miR-743 a due to increased oxidative stress	(Shi and Gibson, 2011)

Table 3.

Mitochondrial miRNAs associated with Huntington Disease (HD), Parkinson's Disease (HD) and Amyotrophic lateral sclerosis (ALS).

Sl. No.	microRNA	Diseases	References
1	miR-7	PD & ALS	(Titze-de-Almeida et al., 2020)
2	miR-15b	PD & ALS	(Liguori et al., 2018; Zhao and Wang, 2019)
3	miR-16-5p	PD & ALS	(Leggio et al., 2017)
4	miR-23a/b	PD & ALS	(Campos-Melo et al., 2013; Leggio et al., 2017)
5	miR-29a	HD, PD, & ALS	(Marti et al., 2010; Shioya et al., 2010; Goh et al., 2019)
6	miR-29b	HD, PD, & ALS	(Marti et al., 2010; Kovanda et al., 2018; Goh et al., 2019)
7	miR-30	PD & ALS	(da Silva et al., 2016; Liguori et al., 2018)
8	mir-34a	HD, PD, ALS	(Ba et al., 2015; Rizzuti et al., 2018)
9	miR-98	PD	(Goh et al., 2019)
10	miR-125b	PD & ALS	(Parisi et al., 2016)
11	miR-137	HD & PD	(Kozlowska et al., 2013; Li et al., 2017)
12	miR-195	PD	(Ding et al., 2016)
13	miR-204	PD	(Talepoor Ardakani et al., 2019)
14	miR-210	HD & PD	(Watts et al., 2018)
15	miR-218	HD, PD, & ALS	(Lee et al., 2011; Hoye et al., 2018; Xing et al., 2020)
16	miR-335	PD & ALS	(De Luna et al., 2020; Oliveira et al., 2021)
17	miR-338	HD, PD, & ALS	(Diez-Planelles et al., 2016; De Felice et al., 2018; Xie et al., 2020)
18	miR-375	PD & ALS	(Bhinge et al., 2016)
19	miR-455-3p	ALS	(Kumar et al., 2017)
20	miR-484	PD	(Taguchi and Wang, 2018)

Table 4.

Mitochondrial miRNAs associated with Synaptic Function.

Sl. No.	microRNA	Function	Target Genes	Regulation in AD	References
1	mir-34a	Impacts presynaptic and postsynaptic activity and promotes the dysfunction of synaptic plasticity	VAMP2, SYT1, HCN, NR2A, GLUR1	Upregulated in AD	(Sarkar et al., 2016)
2	miR-132/212	Enhance neurotransmission and involved in synaptic plasticity	PTEN, FOXO3a, P300, NOS1, MMP-9 (miR-132), p250GAP (miR-132)	Downregulated in AD	(Wayman et al., 2008; Lambert et al., 2010; Remenyi et al., 2013; Wong et al., 2013; Jasinska et al., 2016; Wang et al., 2017)
3	miR-218	Downregulates protein involved in protection against neurotoxins, thus potentially resulting in synaptotoxicity	PRKN	Downregulated in AD	(Di Rita et al., 2020)
4	miR-455-3p	Enhances synaptic activity and is associated with the upregulation of the synaptic genes, synaptophysin and PSD95	APP	Upregulated in AD	(Kumar and Reddy, 2019)
5	miR-484	Potentially plays role in neurotransmission and long-term plasticity	Fis1, BCL2L13, 46 genes in common between predicted targets of miR-484 and module M1 turquoise	Downregulated in AD	(Wingo et al., 2020)