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Review *paper*

GENETIC AND NON-GENETIC FACTORS RESPONSIBLE FOR MITOCHONDRIAL FAILURE AND ALZHEIMER'S DISEASE

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The objective of this review article is to explain the factors responsible for damaged mitochondria and its association with Alzheimer's disease. Alzheimer's disease (AD) is fairly produced by dysfunctional mitochondria that are alternatively caused by excessive reactive oxygen species and mitochondrial dynamic imbalance. In the pathogenesis of AD, there is important role of many factors including amyloid-beta peptide (Aβ), tau-proteins, and mutations in presenilin-1. Additionally, mitochondrial-targeted antioxidants have also been explained because of their significance to mitochondrial alterations in AD. Moreover, alteration in mitochondrial dynamics is responsible for the generation of segregated, damaged mitochondria that are, later on, destroyed through mitochondrial autophagy in AD. Finally, various novel models used for studying Alzheimer's disease, have been discussed.

Key words: amyloid-beta peptide, brain, mitochondrial dysfunction, neurofibrillary tangles, senile plaques, tau-protein

INTRODUCTION

Mitochondria, the important cytoplasmic organelles, have capability of modifying their shape and size swiftly in accordance with their needs. Mitochondria are highly dynamic organelles, which are continuously recycled (CHANG and REYNOLDS, 2006). In mammalians, the life_span of mitochondria is different in different tissues, e.g. half-life of neuronal mitochondria is approximately 30 days (REDDY, 2008). This organelle consists of two lipid membranes i.e. the outer and inner mitochondrial membranes, separated by a matrix that houses tricarboxylic acid (TCA) and beta-oxidation. In contrast to highly porous outer membrane, the inner mitochondrial

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membrane is an efficient barrier where electron transport chain (ETC) takes place (Figure 1) (REDDY, 2007).

The functions of mitochondria include the regulation of intracellular calcium, arresting the free-radical, and ATP synthesis through OXPHOS within the inner mitochondrial membrane (WALLACE, 1999). As a byproduct of OXPHOS, free radicals are produced that are scavenged by antioxidant enzymes naturally present in adequate amounts in the mitochondria resulting in the protection of cells against oxidant-induced toxicities. However, imbalance between oxidants and antioxidant enzymes in certain cells (as in pyramidal neurons in cortex and hippocampus in Alzheimer's disease (AD) brain) creates oxidative stress (REDDY, 2012a). The neuronal death due to senile plaques and neurofibrillary tangles (Table 1) in brain is termed as AD (REDDY *et al*., 2012a; ALZHEIMER *et al*., 1907).

AD is medically recognized as a silent neurodegenerative disease since it remains asymptomatic until its diagnosis (SAVVA *et al*., 2009). There are evidences that the oxidative stress in the central and peripheral nervous system (CECCHI *et al*., 2002; MOREIRA *et al*., 2007a) is responsible for mitochondrial dysfunction (MD) (BONDA *et al*., 2010a). It results in the development of various neurodegenerative disorders (AVILA, 2010), including AD (ZHU *et al*., 2013; MURTAZA *et al*., 2014) that can be categorized into two types: familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease (SAD) (Table 2). FAD is found to be originated from mutations in at least one of the three genes recognized as amyloid precursor protein (APP) and presenilin-1 and -2(ps-1 and ps-2) (PRICE *et al*., 1998). The FAD involves the over-expression of beta-secretase (BACE1) protein that results in the excessive release of amyloid-beta peptide (Aβ) (XIONG *et al*., 2007; TAMAGNO *et al*.,2005; GAO *et al*., 2013). The augmented production of Aβ elevates the levels of reactive oxygen species (ROS) (BELKACEMI and RAMASSAMY,2012; SANTOS *et al*.,2010), which induce the development of SAD involving tau accumulation (TAGA *et al*.,2011; BONDA *et al*.,2011; KOPEIKINA *et al*.,2011) and the enhanced Aβ formation under the effect of high levels of ROS (LEUNER *et al*.,2012). These cascade changes may initiate further MD, resulting in even higher levels of ROS (LAFERLA *et al*., 2007; SUN *et al.,* 2013). These cyclic changes promote the neurodegeneration.

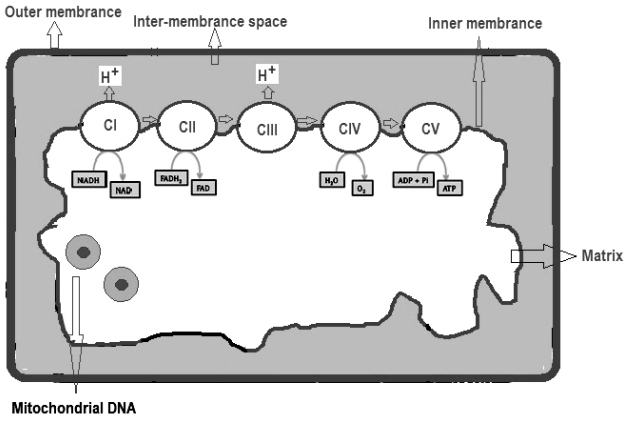

Figure 1. Structure of mitochondria and electron transport of chain [1]

Table 1. Features of two abnormal structures, senile plaques and neurofibrillary tangles, present in the brain of AD patients [6]

No.	Features	Senile plaques	Neurofibrillary tangles
1	Name of main constituent	Amyloid-beta peptide (Aβ)	Tau-protein
2	Shape of main constituent	Thread-like aggregates	Microtubule-like structure
3	Stage of appearance in brain	At last stage of AD disease	At last stage of AD disease
4	Diagnostic approach	Autopsy	Autopsy
		Positron emission tomography imaging using the Pittsburg compound B	Positron emission tomography imaging using 18F-THK23

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Table 2. Types of Alzheimer's disease and their features [6]

No.	Types of Alzheimer's disease	Features
1	Familial Alzheimer's disease (FAD)	Mutations in at least one of the three genes recognized as amyloid precursor protein (APP) and presenilin-1 and -2(ps-1 and ps-2) Over-expression of beta-secretase (BACE1) protein Excessive release of Aβ High levels of ROS Mitochondria dysfunction
2	Sporadic Alzheimer's disease (SAD)	Tau accumulation Enhanced Aβ formation Very high levels of ROS Mitochondria dysfunction

Dysfunctioning of mitochondria

Deregulation of oxidative phosphorylation proteins

Mitochondia, being energy generator of cell, is characterized with the redox potential gradient in mitochondria that drives the ETC through mitochondrial complexes (CI to CIV) (OTERA *et al*., 2010). After accepting electron at CIV stage, oxygen is changed into water with simultaneous release of energy. This energy activates ATP-synthase, which induces the generation of ATP by the mitochondria (Figure 1). It is observed that normal and dysfunctional mitochondria produce ROS in low and high concentrations, respectively (MOREIRA *et al*., 2010). These ROS deteriorate the mitochondria through oxidation of the mitochondrial macromolecules including proteins, lipids, and mitochondrial DNA (mtDNA) (SCHMITT *et al*., 2012; HAUPTMANN *et al*., 2009; XIE *et al*., 2013). The ROS also play a role in the production of toxic substances such as hydroxynonenal (HNE) which may assist the aggregation of Tau protein into neurofibrillary tangles (SANTA-MAR´IA *et al*., 2004). In dysfunctional mitochondria, there is

progressively diminished brain glucose metabolism, due to various deregulating molecules (Table 3) and reduced expression of either nuclear or mitochondrial genes responsible for the oxidative phosphorylation in the neocortex of AD patients (RHEIN *et al*.,2009; DAVID *et al*.,2005; ECKERT *et al*.,2010; CASPERSEN *et al*.,2005). This abnormality can be envisaged by positron emission tomography (CHANDRASEKARAN *et al*., 1996; CHANDRASEKARAN *et al*., 1997).

Table 3. The molecules and mitochondrial targets involved in deregulation of oxidative phosphorylation proteins in tricarboxylic acid cycle [6]

No.	Target	Deregulating molecules
1	Mitochondrial complex I	Tau
2	Mitochondrial complex IV	Aβ
3	Mitochondrial complex V	Tau

In Alzheimer's disease, change in activity of some enzymes such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase has been observed. Physiologically, these enzymes are involved in the tricarboxylic acid cycle. Table 4 shows the effect of mitochondrial dysfunction on its enzyme activity (PERRY *et al*., 1980; GIBSON *et al*., 1988; SHEU *et al*., 1994)

Table 4. Effect of mitochondrial dysfunction on its enzyme activity [6]

No.	Pathological change	Effect on enzymes	Effects of reduced enzymatic activity
1	Changed level of enzymes involved in TCA cycle	1. Reduced activity of pyruvate dehydrogenase 2. Reduced activity of ATP-citrate lyase 3. Reduced activity of acetoacetyl-CoA thiolase	1. Reduced production of acetyl coenzyme A 2. Cholinergic defects
2	Loss of α-ketoglutarate-enriched cells	Reduced activity of α-ketoglutarate dehydrogenase	

Imbalanced Mitochondrial Dynamics

Healthy mitochondria normally undergo rapid and reversible fission and fusion processes in a programmed manner. This phenomenon, termed as mitochondrial dynamics, plays a vital role in the preservation of mitochondrial structure and functions such as metabolism, ROS production, and apoptosis regulation (ZHU *et al*., 2013; WAHLSTER *et al*., 2013). Fission is involved in the recycling of mitophagy-mediated destructed mitochondria. This feature is important for the correct assembly of mitochondrial complexes involved in ETC. Conversely,

fusion protects the mitochondria from autophagy-provoked demolition. This protective process also manages the correct distribution of mitochondrial elements including lipid bilayer membranes, oxidative phosphorylation complexes, and mtDNA. A very delicate balance between fission and fusion is needed for proper mitochondrial distribution in the cell, especially in neurons (DETMER and Chan, 2007; ZHAO *et al*., 2011; LUO *et al*., 2013) and is executed under the control of numerous mitochondrial proteins, e.g. outer mitochondrial membrane (OMM) proteins. Various types and activities of OMM proteins involved in mitochondrial dynamics are presented in Table 5.

Table 5. Outer mitochondrial membrane (OMM) proteins and their activities [6]

No.	Fission		Fusion	
	Name	Function	Name	Function
1	GTPase dynamin-like protein 1 (DLP1), or dynamin-related protein, (Drp1) imported from cytosol		GTPases-related Mitofusin 1 and 2 (Mfn1 and Mfn2)	Outer membrane fusion
2	Fis1	Regulatory functions	Optic atrophy (Opa1)	Inner membrane fusion, cristae formation, and mtDNA inheritance)
3	Mitochondrial Fission factor (Mff)	Influx of DLP1	Mitochondrial elongation factor 1 (MIEF1)	Inactivation of DLP1

As evident from studies conducted in neurodegenerative disorder models, mitochondrial dynamics imbalance may results in mitochondrial dysfunction (WANG *et al*., 2008a). This alteration, along with synaptic degeneration, is considered an initial stage in AD (REDDY *et al*., 2012b; ZHAO *et al*., 2013). In AD, fission is a dominant process over fusion in the presence of damaged mitochondria in neurons (BONDA *et al*., 2010b; OETTINGHAUS *et al*., 2012) or fibroblasts (ZHU *et al*., 2013, WANG *et al*., 2013). These cells also exhibit altered mitochondria distribution, particularly accumulated into perinuclear region (WANG *et al*., 2009). Twisted, long mitochondria are seen in fibroblasts from sporadic AD patients, this alteration is attributable to differences in the expression prototype of proteins engaged in dynamics, revealing diminished DLP1 (ZHU *et al*., 2013; WANG *et al*., 2008a). In AD brain, overall size of mitochondria is increased due to its fragmentation and thickening in damaged neurons, which suggests mitochondrial dynamics alterations (WANG *et al*., 2008b), as confirmed from ADDLs (Aβ-derived diffusible ligands)-treated primary hippocampal neurons (WANG *et al*., 2009). These cells also exhibit the diminished levels of OPA1, Mfn1, and Mfn2 as well as elevated levels of Fis1 in AD. About the alteration in DLP1 level in neurons and fibroblasts, researchers have narrated mixed opinions (WANG *et al*., 2008b; BOSSY *et al*., 2010: MANCZAK *et al*., 2011). Its import from cytosol to mitochondrial membrane to intervene fission events is dependent on posttranslational modifications (ZHU *et al*.,2013), this explanation may account for higher levels of DLP1 in

mitochondrial fraction (WANG *et al*.,2009) in addition to elevated levels of Ser616 phosphorylation and S-nitrosylation in AD brains (CHO *et al*.,2009). Moreover, an increase in abnormal interaction of DLP1 with Aβ monomers and oligomers with the advancement of AD might be a likely reason of abnormal mitochondrial dynamics and synaptic failure (MANCZAK *et al*., 2011).

The mitochondrial fission and fusion processes can be coupled with its transport. This phenomenon is evident from a study that elaborates the interaction of Mfn2 with two adaptor proteins, Miro and Milton (MISKO *et al*., 2010; ZHANG *et al*., 2013). This outcome reveals that mitochondrial mobility is also altered in AD; it causes the mitochondrial reduction in neuritis (ZHU *et al*., 2013). Another study exhibits the impairment in mitochondrial mobility by Aβ (VEGA *et al*., 2013) and ADDL (VEGA *et al*., 2013) , respectively. In short, mtDNA damage, elevated oxidative stress, abnormal cristae, and synaptic failure are possible consequences of altered mitochondrial dynamics (ZHU *et al*., 2013; CHEN *et al*., 2013).

Role of Amyloid Beta, Presenilin, and Tau in Mitochondrial Damage and Alzheimer's disease

In FAD, the built up of APP and Aβ in the protein import channels (translocase of the outer mitochondrial membrane 40, TOM40, and translocase of the inner mitochondrial membrane 23, TIM23) of mitochondrial membranes of human AD brains causes the structural and functional damage by producing elevated levels of ROS and oxidative stress (SCHMITT *et al*., 2012; BELKACEMI and RAMASSAMY, 2012; BUTTERFIELD, 2002; PAGANI and ECKERT, 2011; DEVI *et al*.,2006). It is associated with diminished cytochrome c oxidase activity, possibly due to decreased entrance of cytochrome c oxidase subunits IV and Vb proteins into mitochondria (BELKACEMI and RAMASSAMY, 2012). In addition, the inactivation of presequence protease (PreP) by Aβ-induced oxidative stress also results in the aggregation of Aβ in mitochondrial matrix leading to elevated levels of ROS (ALIKHANI *et al*., 2009). Moreover, Aβ interact with phosphorylated Tau in VDAC1 (voltage-dependent anion channel 1) in AD brains of human and mice leading to blockage of mitochondrial pores, and eventually failure of mitochondria (MANCZAK and REDDY, 2012; XING *et al*., 2013). Another study states that cyclophilin D is an important constituent of the mitochondrial permeability transition pore (mPTP). On interaction with mitochondrial Aβ, the opening of the mPTP occurs. Simultaneously, cyclophilin D initiates the generation of free radicals, promote the synaptic failure and induces the apoptosis (DU *et al*., 2008; XING *et al*., 2012). Moreover, cytoskeletal abnormalities may also appear due to the accumulation of Aβ (KANG *et al*., 2011). On interaction with Aβ oligomers, integrins inhibit the cofilin-mediated actin dynamics that is linked with enhanced ROS generation and diminished mitochondrial potential. In response to oxidative stress, the translocation of cofilin to the mitochondria occurs leading to induction of swelling as well release of cytochrome c. Finally, the opening of mPTP occurs followed by the induction of apoptosis.

In AD brains of human and transgenic mice, the upregulation of mitochondrial protein ABAD (Aβ-binding alcohol dehydrogenase) is observed (LUSTBADER *et al*., 2004). The interaction between Aβ and ABAD results in the formation of a complex, which averts the binding of NAD^+ (nicotinamide adenine dinucleotide) to ABAD. Because of this situation, alteration of mitochondrial membrane permeability as well reduction in the respiratory enzymes activities occurs causing increased levels of ROS. In addition, DLP1 is nitrosylated by Aβ leading to nitrosative stresss that produces mitochondrial fission in neurons (CHO *et al*., 2009).

High molecular weight, ps-γ-secretase complex is obtained because of association between presenilins 1/2 (ps-1/ps-2) and nicastrin/APH-1/PEN-2 (ANKARCRONA and HULTENBY, 2002; HANSSON *et al*., 2004) in mitochondria associated endoplasmic reticulum membranes (MAM) which are engaged in mitochondrial activity and dynamics (AREA-GOMEZ *et al*., 2012). This complex is capable of modifying mitochondrial membrane potential (BEHBAHANI *et al*., 2006). Because of mutations in presenilins, impaired mitochondrial function, elevated levels of mitochondrial ROS, oxidative damage, and mitochondrial apoptosis have been observed. In addition, intra-membrane cleavage of APP produces Aβ.

Tau-mediated axonal translocation of mitochondria is crucial for synaptic activity (TRINCZEK *et al*., 1999), which is adversely affected by hyperphosphorylation of Tau resulting in neurodegeneration due to energy deficiency and oxidative stress at the synapses (STAMER *et al*., 2002; IIJIMA-ANDO *et al*., 2012). The study of brain proteins obtained from P301L mutant human tau transgenic mice exhibited the deregulation of mitochondrial respiratory chain complexes such as reduced complex I activity, a damaged mitochondrial respiratory energistics accompanied by decreased ATP levels, ROS accumulation, and increased susceptibility to oxidative stress (DAVID *et al*.,2005; SCHULZ *et al*.,2012). Moreover, annonacin-mediated inhibition of complex I resulting in apoptosis is also reported (ESCOBAR-KHOHDIKER *et al*.,2007) When hyperpho-sphorylated Tau interact with mitocho-ndrial fission protein (DLP-1), an alteration in mitochondrial dynamics is observed accompanied by mitochondrial dysfunction and apoptosis (MANCZAK *et al*.,2011; DUBOFF *et al*.,2012). As far as morphology is concerned, tangled, filamentous mitochondria are observed from studies conducted on *Drosophila* (R406W) and mouse neurons (P301L).

Therapeutic strategies for AD

Usage of Mitochondria-Targeted Antioxidants

Considering mitochondrial dysfunction and oxidative stress as some etiologies of AD, many antioxidant therapies, including vitamin E, huperzine A, curcumin, Gingo biloba, and melatonin, have been tested (CONTE *et al*., 2004; YANG *et al*., 2005; STACKMAN *et al*., 2003; MATSUBARA *et al*.,2003)for their efficiency to improve mitochondrial function and cognitive behavior by decreasing Aβ levels in animal models of AD. In clinical trials, non-significant effect of these antioxidants in cognitive function is observed, which is attributable to very severe disease state or ineffective supply of blood through blood-brain barrier (MISKO *et al*., 2010). In this regard, mitochondria-targeted antioxidants including choline esters of glutathione, N-acetyl-l-cysteine (SHEU *et al*., 2006), triphenylphosphonium-based molecules (MitoQ, MitoVitE, Mito-α-lipoic acid, and MitoPBN) (MURPHY and SMITH, 2007), and peptide-based antioxidants (Szeto-Schiller or SS peptides including SS31, SS02, SS19, and SS20) (SZETO, 2006) have also been investigated (Table 6). Accordingly, triphenylphosphonium-based molecules are the resultant products when hydrophobic triphenylphosphonium cation reacts with ubiquinol, α-tocopherol, α-lipoic acid, and α-phenyl N-tert-butylnitrone, respectively. Due to cationic nature, tremendous built up of this group of antioxidants in mitochondria promisingly protects the mitochondria against oxidative stress (MURPHY and SMITH, 2007).

Table 6. Various classes of mitochondria-targeted antioxidants and their examples

No.	Classes	Examples
1	Triphenylphosphonium-based molecules	MitoQ, MitoVitE, Mito-α-lipoic acid, MitoPBN, and SKQ1
2	Peptide-based antioxidants	SS31, SS02, SS19, and SS20

MitoQ and SS31 have been tested for in vitro antioxidant study and found effective for prevention of hazardous effects (as explained above) of Aβ in mouse cell models of AD (neuroblastoma cells, N2a cells, and Aβ precursor protein transgenic mouse cells, Tg2576 cell line) (CALKINS *et al*.,2011; MANCZAK *et al*.,2010). The mode of antioxidant activity of MitoQ and SS31 is related to its potential to decrease in cyclophilin D expression, while alone SS31 mitigate the oligomeric Aβ effects by restoring mitochondrial mobility and alone MitoQ averts the cognitive failure in 3xTg-AD mice by scavenging the free radicals (MCMANUS *et al*., 2011). One more example of mitochondria-targeted antioxidants is SKQ1 (plastoquinonyldecyltriphenylphosphonium) that is a membrane-penetrating cationic specie having capability of accumulation in the inner mitochondrial membrane (SKULACHEV, 2012). Because of ROS scavenging activity, SKQ1 has a potential feature of anti-aging in rats (STEFANOVA *et al*., 2010).

Due to the tyrosine or dimethyltyrosine (Dmt) moiety, SS peptides are potential scavengers of H_2O_2 and $ONOO^-$ as well inhibitor of lipid peroxidation (SZETO, 2006). The ROS scavenging activity of Dmt is demonstrated to be higher than that of tyrosine.

An in vivo study compared the APP mice with APP transgenic mice loaded with human mitochondria-targeted catalase (MCAT) gene and found that life of later mice was 5 months more than the former mice (MAO *et al*.,2012). The increase in life-span of transgenic mouse could be due to the reduction in the levels of BACE1 and Aβ levels (40 and 42).

All these results elaborate that mitochondria-targeted antioxidants may be a successful remedy for the treatment of patients suffering from AD.

Autophagy of Damaged Mitochondria

Physiologically, the recycling process in which lysosomes degrade the macromolecules and cellular organelles is called autophagy, whereas the autophagy of mitochondria, termed as mitophagy, involves the engulfment of dysfunctional mitochondria into autophagosomes followed by their lysosomal degradation. In AD, alteration in mitochondrial dynamics is responsible for the generation of segregated, damaged mitochondria that are, later on, destroyed through mitochondrial autophagy (MOREIRA *et al*., 2007b). However, it is still under-discussion whether mitophagy is protective process or pathologic.

The proposed mode of mitochondrial autophagy starts with mitochondrial damage followed by a series of activities, i.e. E3 ubiquitin ligase Parkin-induced kinase 1 stimulates Parkin-mediated ubiquitination to recruit autophagy adapter proteins (p62). The interaction of p62 with LC3 provokes the autophagosomal engulfment. Accordingly, there are evidences that many mitochondrial proteins (e.g. VDAC1 and mitofusins) may inhibit mitochondrial fusion events resulting in the segregation of damaged mitochondria (GEGG *et al*., 2010; Burns *et al*., 2009). Moreover, all factors affecting mitochondrial dynamics in AD (as discussed above) may initiate mitochondrial damage and ROS buildup.

There is a strong association between autophagy and the aggregation of AD-related protein such as Aβ and Tau (NIXON *et al*., 2005) in neuronal cells. In neurons of AD patients, an increased number of mitochondria-containing autophagic vesicles has been reported that suggests a mitophagy alteration (MOREIRA *et al*., 2007c). Another study elaborates that the cortex of AD brains contains a reduced level of Parkin, which is a protein target of mitophagy (MOREIRA *et al*., 2007c). Beclin 1 is another protein target of mitophagy. In the diseased part of AD brain of an APP transgenic mouse model, reduced level of Beclin 1 is found at early stage of disease (PICKFORD *et al*., 2008; KHANDELWAL *et al*., 2011). Due to which an increase in the intra- and extra-cellular level of Aβ occurs resulting in neurodegeneration, it highlights the relationship bebtween autophagy and AD-associated pathology. In addition, the relationship between FAD and autophagy has also been reported in a study, which shows that autophagy is damaged by Alzheimer-related ps-1 mutations since autophagy requires functional Ps-1 for lysosomal activity (LEE *et al*., 2010). Therefore, mitophagy can be impaired through ps-1 mutations, and thus ultimately influences mitochondrial activity. Alternatively, the pathogenic role of autophagy in AD development has been proposed. The authors reported that autophagic vesicles are involved in the production and abnormal storage of Aβ in damaged neuronal cells of the AD brain (YU *et al*., 2004).

Moreover, numerous other molecules, such as rapamycin (CACCAMO *et al*., 2010; SPILMAN *et al*., 2010), cystatin B (YANG *et al*., 2011), trehalose (SCHAEFFER *et al*., 2012), scyllo-Inositol (LAI and MCLAURIN, 2012), and latrepirdine (STEELE and GANDY, 2013), have also been investigated to explore their potential to induce autophagy as a therapeutic approach in the AD animal models.

Alzheimer's disease modeling

In comparison to image analysis, living cells should preferably be employed for the correct study of mitochondrial functions since mitochondria are extremely dynamic organelles that perform numerous cellular functions. Thus, novel models for studying AD include animal models, patient-derived non-neuronal cells, and postmortem investigation of the patient's brain. In this context, fibroblasts, the differentiated cells derived from adult patients, can be used to produce stem cells through retro-differentiation (TAKAHASHI and YAMANAKA, 2006; TAKAHASHI *et al*., 2007; YU *et al*., 2007); however, such results are needed to be adjusted/extrapolated to generate neuron-associated data, since fibroblasts and neurons are different from each other in many respects such as energy requirements, morphology, and gene/protein expression pattern (CHIN *et al*., 2009; POLOULIAKH, 2013). Currently, FAD animal models are generally available to study mitochondrial functions; however, SAD models should also be explored accordingly.

Moreover, there are evidences that cell encoding can be reversed, since the induced pluripotent stem cells (iPS) have been generated by four transcriptions factors, Oct3/4, Sox2, c-Myc, and Klf4 (TAKAHASHI and YAMANAKA,2006), which can be substituted by small molecules (HUANGFU *et al*.,2008; ICHIDA *et al*.,2009; LI *et al*.,2011) or microRNAs (JUDSON *et al*.,2009; LIN *et al*.,2011; ANOKYE-DANSO *et al*.,2011) for transcription factors. For studying AD, these iPS have been employed to generate neurons such as the usage of presenilin-associated FAD patient's fibroblasts and APP duplication associated AD fibroblasts for increased production of Aβ42 and Aβ40, respectively (YAGI *et al*.,2011; ISRAEL *et al*.,2012). In more advance studies, functional neurons (induced neurons, iN) have been directly obtained from fibroblast e.g. neural progenitor cells (KIM *et al*., 2011) or tripotent neural precursor cells (iNSC) (LUJAN *et al*., 2012)

have been derived from fibroblast. These conversions have been mediated by three transcription factors, Ascl1, Brn2 (also called Pou3f2), and Myt1l (THEIR *et al*., 2012; VIERBUCHEN *et al*., 2010) or one microRNA and two transcription factors (PANG *et al*., 2011; YOO *et al*., 2011). A recent study has reported the obtention of reprogrammed/functional neurons from human fibroblasts suffering from AD (AMBASUDHAN *et al*., 2011).

From above discussion, it is clear that the survival and differentiation of neurons is dependent on mitochondrial function. There, it is very crucial that the integrity of mtDNA should be maintained during differentiation of neuronal stem cells, since oxidative stress and protein levels (such as DLP1 and prohibitin) in mitochondria (QIANG *et al*.,2011) may damage mtDNA integrity and thus reprogramming from fibroblasts to neurons (ZHOU *et al*.,2012; WANG *et al*.,2010).

CONCLUSION

For studying neurodegenerative disorders such as Alzheimer's disease, various models including iPS, iN, or iNSC have increasingly been used, however these models, especially human cellular models, should also be employed to study mitochondrial functions. In order to execute such type of approach, future research can be focused on high through-put protocols such as fastening the neuron generation rate.

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GENETICKI I NEGENETICKI FAKTORI ODGOVORNI ZA NEFUNKCIONALNOST MITOHONDRIJA I ALCHAJMEROVU BOLEST

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Izvod

Alchajmerova bolet (AD) je u velikom stepenu prouzrovana disfunkcijama mitohondrijama alternativno izazvanim ekcesivno reaktivnim vrstama kiseonika i inbalansa dinamike mitohondrija. U patogenezi AD važna je uloga mnogih faktora koji uključuju amiloid-beta peptide (Aβ). Tau – protein i mutacije u presenilinu-1. Dodatno, mitohondrije – ciljani antioksidanti su objašnjeni zbog njihovog značaja za izmenu mitohondrija u AD. Uz to, promena u dinamici mitohondrija je odgovorna za izazivanje segregacije oštećenih mitohondrija koje se kasnije uništavaju mitohondrijalnim autofagama kod AD. Diskutovani su različiti novi modeli korišćeni u ispitivanjima Alchajmerove bolesti.

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