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Mitochondrial Dynamics in Alzheimer's Disease Opportunities for Future Treatment Strategies

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Abstract

The complexities that underlie the cognitive impairment and neurodegeneration characteristic of Alzheimer's disease have yet to be completely understood, although many factors in disease pathogenesis have been identified. Particularly important in disease development seem to be mitochondrial disturbances. As pivotal role players in cellular metabolism, mitochondria are pertinent to cell survival and thus any deviation from their operation is certainly fatal. In this review, we describe how the dynamic balance of mitochondrial fission and fusion in particular is a necessary aspect of cell proliferation and that, as the cell ages, such balance is inevitably compromised to yield a destructive environment in which the cell cannot exist. Evidence for such disturbance is abundant in Alzheimer disease. That is, the dynamic balance of fission and fusion in AD is greatly shifted toward fission, and, as a result, affected neurons contain abnormal mitochondria that are unable to meet the metabolic demands of the cell. Moreover, mitochondrial distribution in AD cells is perinuclear, with few metabolic organelles in the distal processes where they are normally distributed in healthy cells and where they are needed for exocytosis, ion channel pumps, and synaptic function, among other things. AD neurons are thus characterized by increases in reactive oxidative species and decreases in metabolic capability, and notably, these changes are evident very early in AD progression. We therefore believe that oxidative stress and altered mitochondrial dynamics contribute to the precipitation of AD pathology and thus cognitive decline. These implications provide a window for therapeutic intervention (i.e., mitochondrial protection) that has the potential to significantly deter AD progression if adequately developed. Current treatment strategies under investigation are herein described.

The uncertainty surrounding the causes of the vastly debilitating neurodegenerative disorder Alzheimer's disease (AD) has fostered much debate. That it is the leading cause of senile dementia in the US, affecting 15% of people aged >65 years and almost 50% of those aged >85 years,[1] generates further controversy and warrants increased investigation, as the aging population demands an effective therapeutic measure to facilitate disease prevention/control. Fortunately, studies have begun to connect the pathological 'dots' that characterize the disease, such that the immeasurably complex interactions that yield AD are now becoming clear.

The disorder is characterized by progressive neuronal loss and an accompanying cognitive deterioration that eventually proves fatal. Extracellular aggregates of amyloid- β (A β)-containing senile plaques have long been implicated in disease onset and progression, as

mutations in the amyloid- β protein precursor (A β PP) are known to initiate early onset, familial AD,[2,3] and concentrations of anti-A β antibody have been shown to be an effective marker for the disease and its progression.[4] Similarly, the microtubule associated protein tau has been confirmed as a role player in AD, as its hyperphosphorylated, aggregated fibrils occupy neuronal space in vulnerable regions of AD brains (i.e., hippocampus/cortices) in the form of neurofibrillary tangles (NFTs).[5,6] Notably, these hallmarks of AD, while once thought to be primary mediators of the sporadic form of the disease (responsible for 90–95% of all AD cases[7]), are now understood to be secondary role players in AD pathogenesis.[8] Although much is unclear about the origins of AD, evidence supports the role of mitochondrial dynamics as a potential suspect.

Indeed, malfunctions in mitochondria have been documented in AD brains.[9,10] Given that mitochondria are immensely pertinent to cellular proliferation as they are the metabolic and energy centres of the cell, and that abnormalities in mitochondrial dynamics widely precede many of the hallmark pathologies of AD,[9,10] it is not unreasonable to investigate them as progenitors of the disease. Moreover, the mitochondria provide a potential access point for therapeutic intervention that, if appropriately harnessed, could yield remarkable treatment strategies for patients and as yet unaffected individuals. As we shall see, although there are still some points that must be clarified, the prognosis for mitochondria as instigators of AD is strong, and thus an effective preventative measure in this regard will certainly be beneficial.

1. Mitochondrial Dynamics: Fission, Fusion and Function

Mitochondria are not static organelles, but are dynamic bodies that constantly divide and fuse within the cell as the environment demands.[11] They are composed of an inner membrane (almost entirely impermeable) and an outer membrane (permeable to ions and small molecules), such that establishment of a proton gradient during oxidative phosphorylation is possible. Maintenance of membrane integrity is vital to mitochondrial and cellular functioning: 95% of the cell's energy supply is generated in mitochondria via the citric acid (tricarboxylic acid [TCA]) cycle and oxidative phosphorylation.

As such, the number and morphology of the mitochondria in a cell are controlled by delicate balance of organelle fission and fusion mechanisms.[9,11] In particular, genetic inactivation of fission results in elongation of mitochondria, whereas inactivation of fusion yields fragmentation.[12,13] It is through this balance that the cell ultimately maintains mitochondrial integrity and homogeneity: fusion allows the exchange of lipid membranes and mitochondrial contents, such as mitochondrial DNA (mtDNA), and fission (coupled with fusion and autophagy) allows sequestration and elimination of irreversibly damaged mitochondria and mitochondrial content.[14–16] Both processes effectively lower the percentage of defective mitochondria in the cell and ensure stability in cellular proliferation; indeed, metabolism, energy production, calcium signaling, reactive oxidative species (ROS) production, apoptosis and senescence all depend on the balance of fission and fusion.[17–22] Conversely, dynamic distortion (i.e., excessive fragmentation/elongation) results in inefficiencies in cell functioning, if not cell death. Studies have specifically demonstrated a direct reduction in metabolism and loss of mtDNA after dynamic misbalance.[9,19,23–25]

In fission, at least two proteins are involved: a large guanosine triphosphatase (GTPase), dynamin-like protein 1 (DLP-1) and a small molecule Fis1.[26–28] DLP-1 is a member of the conserved dynamin large GTPase superfamily that controls membrane tubulation and fission; it is primarily a cytosolic protein that is recruited to punctuate spots on the mitochondrial surface.[28] DLP-1 is believed to oligomerize to form large ring-like complexes that, once bound to the mitochondrial surface, hydrolyze guanosine triphosphate

(GTP) to constrict and twist tubules to initiate fission.[29] Fis1 then acts as a receptor to DLP-1, recruiting the complex-forming protein to the appropriate mitochondria. As such, Fis1 is evenly distributed along the mitochondrial surface.[30] Fission produces two daughter organelles with cristae and other inner structural remodeling, the mechanisms of which are not entirely clear.[26,27]

Fusion, on the other hand, is regulated by three large GTPases: mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) and optic atrophy protein 1 (OPA-1).[26-28] Mfn1/2 are transmembrane proteins localized to the outer mitochondrial membrane that appear to play similar roles in fusion, although they function independently of one another and have different rates of GTP hydrolysis.[19,28,31] Mechanistically, the two proteins form homo- or hetero-oligomeric complexes (through interactions of their coiled-coil extracellular domains) and tether two mitochondria together for fusion of the outer membranes.[31,32] Inner membrane fusion, while not as completely understood, occurs primarily through the functioning of OPA-1, which faces the intermembrane space, in correspondence with Mfn1.[19,33]

Within the cellular environment, mitochondrial dynamics are manipulated by regulations involving the above listed proteins, among others. While much of this dynamic interplay is yet unknown, studies have revealed the interactions and regulations that utilize DLP-1 to instigate or prevent mitochondrial fission.[28] Specifically, post-translational modifications of the fission protein have been examined and include phosphorylation, SUMOylation (i.e. the covalent attachment of a small ubiquitin-like modifier [SUMO]), ubiquitylation and nitrosylation.[34-39] Phosphorylation of DLP-1 at two serine residues (Ser616 and Ser637) has been demonstrated, although only that of Ser616 has been confirmed as actually facilitating fission. That is, while phosphorylation of Ser616 by mitosis promoting factor has been shown to directly induce mitochondrial fission,[34,35,39] there is still debate over the effect of Ser637 phosphorylation: two groups indicate Ser637 phosphorylation by protein kinase A inhibits fission[34,35] (while its dephosphorylation by calcineurin promotes fission[40]) and another group indicates that Ser637 phosphorylation by calcium/calmodulin dependent protein kinase-1 α induces DLP-1 translocation to mitochondria, thereby enhancing fission.[41] Further investigation is thus required to elaborate on the specificities of DLP-1 dynamics.

Similarly, SUMOylation of DLP-1 by SUMO-1 protects the protein from degradation, effectively enlarging the DLP-1 pool, and facilitates its translocation to the mitochondria from the cytosol.[28,36] S-nitrosylation of DLP-1 activates its GTPase activity and thus instigates fission.[42]

In addition to fission/fusion processes, mitochondrial activity depends on the physical location of the organelles within the cell. The distribution of mitochondria is orchestrated by the cytoskeleton and associated proteins such that regions with high metabolic requirements receive the highest concentrations of mitochondria.[9,43] Notably, mitochondrial distribution is affected by mitochondrial dynamics: both fission mutants with elongated mitochondria (i.e. DLP-1 mutants) and fusion mutants with short, rounded mitochondria (i.e. OPA-1 mutants) cause distribution changes within the cell.[44-46] Because a cell's functioning strongly relies on its ability to generate energy in the appropriate location at the appropriate time, the position of mitochondria within the cell greatly affect its performance, and thus the balance of fission and fusion is pivotal. Even more crucially, because neurons are particularly dependent on mitochondrial integrity as they have much greater energy demands than any other cell type (including the extremely energy taxing functioning of ion channels and pumps, synaptic transmission, axonal/dendritic transport of signal molecules and vesicles, etc.[28,47]), this balance is pertinent to brain functioning. Any perturbations in

mitochondrial fission/fusion and function would therefore expose the neuron to disastrous consequences which, as we shall see, include the neurodegeneration typical of AD.

2. Mitochondrial Mechanistic Malfunction in Alzheimer's Disease (AD): Altered Metabolism Due to Dysfunctional Dynamics

Metabolic defects in AD are one of the best documented abnormalities in the disease.[10] In fact, neuropsychological testing and neuroimaging studies have demonstrated that such abnormalities precede evidence for functional impairment or brain atrophy attributed to traditional pathologies of neurodegeneration (i.e. senile plaques and tangles).[9,10] Damage to the components and structure of mitochondria are also well documented in AD,[48,49] and oxidative stress has recently been strongly implicated in disease pathogenesis.[8] As the process of oxidative phosphorylation inevitably yields ROS, damage to mitochondria are suspected to be the progenitors of oxidative stress, and therefore mitochondria themselves are thought to be integral to AD pathobiology.

Specific deficiencies in mitochondrial enzymes have been reported in AD. These include enzymes involved in the TCA cycle, such as ketoglutarate dehydrogenase complex and pyruvate dehydrogenase complex, as well as those involved in the electron transport chain of oxidative phosphorylation, such as cytochrome oxidase.[50-56] As these complexes orchestrate the oxidation/reduction reactions necessary for oxidative phosphorylation (and the generation of adenosine triphosphate (ATP)), any such deficiency will produce a malfunctioning metabolism. Sporadic mutations in mtDNA have also been reported in certain regions of AD at a much higher rate than in age-matched controls, and in some cases, mtDNA mutations are completely unique to AD cases.[9,57] Moreover, calcium homeostasis is altered in AD, and mitochondrial impairment is the proposed reason for its dysregulation.[58] Altogether, mounting evidence supports the role of mitochondrial disturbance in the pathogenesis of AD, and recent studies show that mitochondrial dynamics lie at the heart of these disturbances.

AD neurons are known to contain significantly lower percentages of normal mitochondria as well as relatively high percentages of mitochondria with broken cristae, when compared with age-matched controls.[9] Significant changes in mitochondrion size and number were also found in vulnerable AD neurons.[59] These specific trends provide a potential cause for the aforementioned mitochondrial disturbances and, notably, are associated with defects in fission/fusion dynamics and the corresponding proteins.[9]

In fibroblast cells, for example, altered dynamics was confirmed in AD in a series of studies by Wang et al.[9] While fibroblast cells are very different to the hippocampal neurons that are devastated in AD, these data nonetheless provide important insights into the specifics of dynamic alterations in the mitochondria of AD cells. Fibroblast mitochondria were significantly longer when compared with the short and rounded mitochondria of age-matched normal human fibroblasts, and were often joined together irregularly in a mitochondrial network.[60] Further investigation indicated that DLP-1 mutations were the likely cause of the shift in mitochondrial dynamics toward fusion: (i) DLP-1 levels were significantly decreased, while OPA-1 levels were unchanged; (ii) DLP-1 knockdown, as well as the expression of dominant negative DLP-1 in normal human fibroblasts, caused mitochondrial changes similar to those seen in sporadic AD (sAD) fibroblasts; and (iii) DLP-1 overexpression rescued abnormal morphology in sAD fibroblasts.[60] The distribution of mitochondria themselves was also altered in sAD fibroblasts when compared with controls: the organelles were mainly concentrated in the perinuclear area and were sparse in remote and peripheral regions of the cells. Notably, this phenomenon had little effect on the functioning of the fibroblast cell; however, in the vastly polarized

environments characteristic of neurons, such alterations in mitochondria distribution would be detrimental.

Indeed, mitochondrial fission/fusion proteins have been demonstrated to exist at altered levels and in altered distributions in AD hippocampal pyramidal neurons compared with age-matched controls.[61] Specifically, AD neurons had reduced DLP-1, OPA-1 and Mfn1/2 protein levels and increased Fis1 levels. These proteins, furthermore, were aggregated in neuronal soma and not in the neuronal processes, indicating abnormal mitochondrial distribution. Interestingly, synaptic dysfunction, an early and robust correlate of AD-associated cognitive defects,[62] may be the direct result of this altered mitochondrial distribution. Whereas under normal conditions mitochondria are abundantly located at synaptic terminals[63] due to the intense energy demands of an active neuron (which is engaged in synaptic transmission but also requires calcium buffering), in *Drosophila* containing a mutant Milton protein (which is involved in mitochondria transport via binding to kinesin heavy chain), loss of mitochondria at axon terminals led to synaptic dysfunction in photoreceptor cells.[64] Similarly, loss of Miro protein (which is involved in mitochondria morphology regulation) resulted in mitochondria accumulation in neuronal cell bodies at neuromuscular junctions with subsequent synaptic dysfunction.[65,66] DLP-1 mutations in *Drosophila* also produced impaired calcium buffering and dysfunction in the mobilization of reserve pool vesicles, and this effect was primarily due to the elongation of mitochondria and their resulting failure to populate the distal axon.[67] Finally, the plasticity of spines and synapses was demonstrated to be perturbed in cells after an alteration of DLP-1 or OPA-1 that yielded a lack of dendritic mitochondria.[68]

Clearly, alterations in mitochondria dynamics and distribution are profound in AD neurons. While there is no certainty as to their origins, evidence implicates the gradual accumulation of oxidative damage over the course of decades in the generation of malfunctioned mitochondria, and increasing data identifies such abnormalities as the primary mediator in neurodegeneration.

3. Oxidative Stress in AD

The abundant evidence for mitochondrial malfunctions in AD, coupled with the immense impact of mitochondria on cell vitality and function, implicate the metabolic organelle as a primary mediator of the neurodegeneration in AD. While much has yet to be elucidated, the 'age-induced mitochondrial cascade' of neurodegenerative events seems a likely key operator in AD pathogenesis.

There is no doubt that oxidative stress is an instigating factor in AD onset and progression. Current research, in fact, suggests it to be the primary producer of pathology traditionally descriptive of AD, and much evidence corroborates this theory. Our two-hit hypothesis, for example, describes a system whereby a long-term, pathological condition, such as oxidative stress in late-onset AD, instills a degree of damage upon the affected cell such that it must enter a compensatory 'steady state' to maintain basic functions.[8] Indeed, oxidative markers generally precede all of those associated with typical hallmarks of AD, such as NFT formation and A β aggregation. Specifically, 8-hydroxyguanosine (8-OHG), a marker of oxidative damage, appears decades prior to A β senile plaques, and A β PP-mutant Tg2576 transgenic mice demonstrate oxidative damage preceding that due to A β aggregation.[69-76] This repeated oxidative stress eventually overwhelms the cell's antioxidant machinery, producing cumulative alterations in vital macromolecules: indeed, lipid peroxidation, nitration and nucleic acid oxidation are all prevalent in AD and AD models.[8]

As such, because the new 'oxidative steady state' represents the cell under repeated and consistent stress, vulnerabilities to damage produced by other aberrant mechanisms, such as

mitotic re-entry and aggregation of non-soluble A β , become the progenitors of the cell's death (because it cannot fight these alterations in its weakened state).[8] In fact, oxidative stress itself seems to be the direct precursor of several AD pathologies. Evidence demonstrates that A β secretion, for example, initially occurs as an antioxidant response to elevated ROS. A β has been shown to have antioxidant activity and to protect lipoproteins from oxidation in cerebrospinal fluid and plasma (via metal sequestration),[77-80] and AD cases with the most extensive A β deposition show the lowest levels of 8-OHG while neurons lacking such AD pathology have significantly higher levels of 8-OHG.[81] Tau hyperphosphorylation and the formation of NFTs have similarly been demonstrated as a possible compensation for overwhelming concentrations of ROS.[82,83] Neurons with NFTs have significantly lower 8-OHG levels despite obvious oxidative damage (i.e., the presence of advanced glycation endproducts or lipid peroxidation),[81] and phosphorylation of tau has been demonstrated to antagonize apoptosis by stabilizing β -catenin.[84] Therefore, a chronic oxidative stress situation, as initiated by altered mitochondrial dynamics, may in fact elicit the hallmark pathologies of AD.[85]

Interestingly, while the hallmark pathologies of AD seem to originate in response to excessive cellular oxidative damage, their presence eventually inflicts burden on the associated cells and only intensifies the cascade of events that leads to neurodegeneration. Specifically, once secreted, A β becomes subject to oxidation itself, and its resulting dityrosine cross-linkages make the peptide insoluble and thus more likely to aggregate. [80,86] A β , in its aggregated form, then has a detrimental effect on the cell because it elicits further oxidative stress[80,81] and inflicts damage on mitochondrial functioning. The latter process has been demonstrated in M17 cells overexpressing mutant A β PP (these cells exhibited more than a 4-fold decrease in the rate of mitochondrial fusion[87]), and studies further indicate that A β overproduction induces mitochondria fragmentation, dysfunction, heightened ROS production and reduced ATP generation.[60] These detriments to the cell directly stem from oxidative damage, and as we discuss next, it is the mitochondria that are responsible for the accumulation of oxidative stress.

4. Mitochondrial Mediation of Oxidative Stress and Neurodegeneration: an Attractive Culprit

Mitochondria are the centres of energy production in the cell, and, over the course of aging, the metabolic machinery they possess inevitably produce ROS. As stated in section 2, key enzyme complexes in both the TCA cycle and the electron transport chain function as oxidizing/reducing agents, and dysfunction in one of these complexes results in aberrant electron transfer and the generation of oxidative free radicals. Ketoglutarate dehydrogenase, cytochrome oxidase and pyruvate dehydrogenase have all been shown to elicit ROS *in vitro*; in particular, in the electron transport chain, superoxide radical (O $_2^-$) and hydrogen peroxide (H $_2$ O $_2$) are predominantly produced.[81] Furthermore, the sheer number of oxidation/reduction reactions that take place within a given neuron statistically guarantees the production of a large number of ROS on a daily basis: the average non-neuronal cell uses 10¹³ O $_2$ molecules per day in metabolic processes, and approximately 1% of these molecules (i.e., 10¹¹) become O $_2^-$. [81] As the brain utilizes 20% of the body's oxygen supply despite constituting only 2–3% of its mass,[81] the ROS generation in the brain is likely much higher than 10¹¹ molecules per day. Although the cell contains antioxidant mechanisms, this astounding number of radicals eventually overwhelms these mechanisms, leading to a cascade of mtDNA mutation and oxidative damages characteristic of the 'oxidative steady state'.

Notably, mtDNA damage and general mitochondrial malfunction takes years to accumulate; the integrity of these organelles is strictly maintained via the delicate balance of fission and

fusion. As stated in section 1, fusion provides defective mitochondria with replenished supplies of mtDNA and mitochondrial proteins, and fission allows the sequestration and elimination of irreversibly damaged mitochondria and mitochondrial proteins.[28] However, despite these efforts, mutations in vital mitochondrial proteins eventually cross a threshold beyond which mitochondrial dysfunction propagates uncontrollably.[28,65] Once mutations in mitochondrial dynamics become manifest, the cell's mitochondrial safety net quickly dissipates and the cascade of neurodegeneration begins.

Research has shown that mutations in over 80% of mtDNA genes elicit abnormal mitochondria morphology, including fragmentation and elongation.[88-90] In addition, short exposure of mitochondria to ROS causes mitochondrial imbalances in fission and fusion as a result of mtDNA mutation.[91] Mfn1/2-null cells and OPA-1 deficient cells also have excessively fragmented mitochondria and demonstrate greatly reduced endogenous and uncoupled respiratory rates. The latter phenomena are due to attenuation of electron transport rates in complexes I, III and IV.[19,23] Similarly, Purkinje cells of Mfn2 knockout mice demonstrate aberrant electron transport activity,[16] and genetic inhibition of DLP-1 causes a reduced rate of ATP synthesis due to decreased complex IV activity and inefficient oxidative phosphorylation.[24,28] Fission/fusion imbalance as a result of mtDNA mutation can also disrupt calcium homeostasis,[92,93] and both excessive fragmentation and elongation of mitochondria lead to increases in ROS produced in the cell, with excessive deposition of iron.[22,25,94-96]

Once excessive fragmentation or elongation takes place within the cell (as a result of accumulating oxidative damages and corresponding mtDNA mutations), the sequestration mechanisms for defective mitochondria become incapable of controlling the accumulation of these damages. As the defective mitochondria directly produce neuronal insults, such as oxidative free radicals and reduced metabolism, a vicious cycle ensues in which ROS generation, oxidative steady state compensation and mitochondrial deterioration upregulate each other. It is this feedback cascade that ultimately proves fatal to the cell. Mitochondrial malfunctions thus seem to be the primary medium through which age produces neurodegeneration.

5. Potential Treatment Strategies

The profound influences of brain mitochondria in the pathogenesis of AD afford a new perspective on potential therapeutics for the disease. Indeed, recent research has focused on mitochondrial repair strategies and mitochondrial antioxidants to prevent and control the neurodegenerative cascade for which the metabolic organelles are responsible. Mitochondrial antioxidant therapy has been found to be most effective in producing pathological changes without any adverse effects.[97-99] In particular, the restoration and rescue of mitochondrial complexes can be achieved via selective mitochondrial antioxidant treatment.[100]

Studies of the brains of aged rats have specifically demonstrated the protective effects of such mitochondrial antioxidants. The antioxidants acetyl-L-carnitine (ALCAR) and R- α -lipoic acid (LA) reduced oxidative stress and mitochondrial abnormalities and restored cognitive function in rat parenchyma cells,[98,100-102] and such targeting of mitochondrial oxidative stress also improved the overall cognitive ability of aged rats and dogs.[102-106]

Furthermore, administration of ALCAR 0.5% and LA 0.2% greatly reduced mitochondrial damage in hippocampal neurons of aged rats.[98] Neuronal cell bodies showed fewer giant mitochondria (i.e. less fusion abnormalities) compared with age-matched controls, and treated mitochondria lacked ultrastructural abnormalities and appeared intact or with minimal damage. ALCAR/LA administration was followed by statistically significant

decreases in the prevalence of damaged mitochondria ($p < 0.001$), increases in normal, intact mitochondria ($p < 0.02$) and significant improvements in the differences in damaged mitochondria between old and young rats. In addition, dietary supplementation of these antioxidants in young and old rats indicated that more significant treatment effects can be achieved with early supplementation.[98] Thus, there appear to be significant benefits associated with mitochondrial dysfunction treatment, and it is to be hoped that increased investigation will see efficient and reliable therapies become a clinical reality.

6. Conclusions

The effects of mitochondria and mitochondrial balances within the cell are immense. As accumulating evidence confirms, mitochondrial behaviour in the cell is dynamic and complicated, and maintaining the exact balance in their processing is absolutely necessary for full cell functioning. In our proposed 'age-induced mitochondrial cascade' (figure 1), this balance is eventually tipped by aggregation of oxidizing agents that are the natural result of cellular respiration. Although this rate-limiting step takes years, perhaps decades, to become harmful, it nonetheless seems to be an inevitable part of the aging process, and presents substantial concern for the aged community. Fortunately, though, antioxidant therapies are demonstrating significant benefits for damaged and potentially damaged mitochondria, and the results of studies of these agents indicate an overall improvement in cognitive ability and function. Although much investigation is necessary in the future, there is certainly a light at the end of the neurodegenerative tunnel that will hopefully relieve society of the burden of AD.

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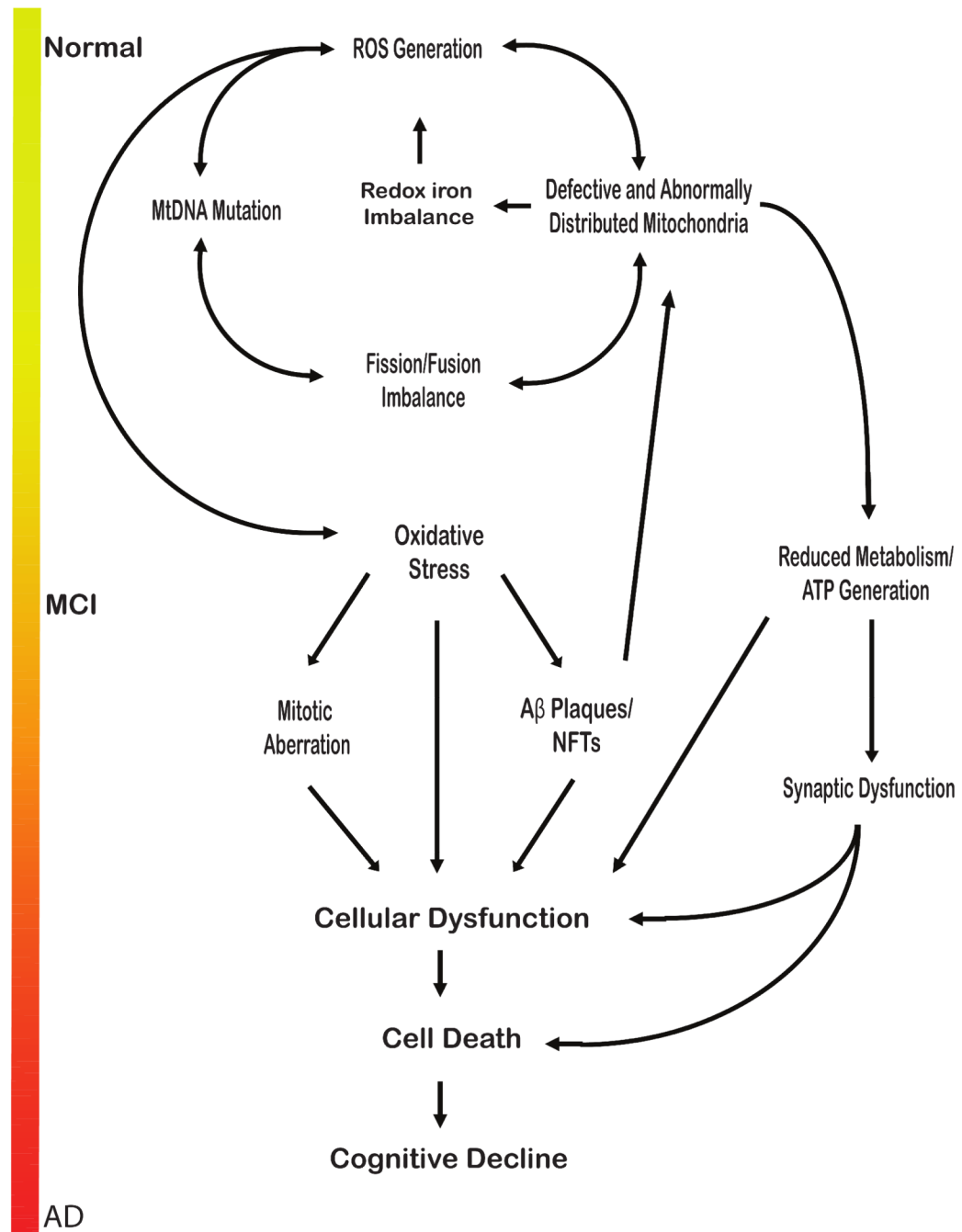


Fig. 1.

The age-induced mitochondrial cascade of neurodegeneration. The reactive oxidative species (ROS) inevitably generated in the respiration process accumulate within the cell over years, gradually damaging mitochondrial DNA (mtDNA) and related mitochondrial proteins. Eventually, an imbalance in mitochondrial dynamics (i.e., fission/fusion) occurs and initiates a detrimental cycle of further ROS generation, increased mitochondrial damage and dysfunction, and cell death. It is through this sequence of events that the neurodegeneration typical of Alzheimer's disease (AD) occurs. **A β** = amyloid β ; **ATP** = adenosine triphosphate; **MCI** = mild cognitive impairment; **NFT** = neurofibrillary tangle.