Oxidative Stress in AD

Subjects: Pathology

Contributor: Laura Gómez-Virgilio

Alzheimer's disease (AD) is the most common cause of dementia and the sixth cause of death in the world, constituting a major health problem for aging societies. This disease is a neurodegenerative continuum with well-established pathology hallmarks, namely the deposition of amyloid-β (Aβ) peptides in extracellular plaques and intracellular hyperphosphorylated forms of the microtubule associated protein tau forming neurofibrillary tangles (NFTs), accompanied by neuronal and synaptic loss. Interestingly, patients who will eventually develop AD manifest brain pathology decades before clinical symptoms appear. Among all the proposed pathogenic mechanisms to understand the etiology of Alzheimer's disease (AD), increased oxidative stress seems to be a robust and early disease feature where many of those hypotheses converge.

Keywords: oxidative stress ; Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and the sixth cause of death in the world, constituting a major health problem for aging societies [1]. This disease is a neurodegenerative continuum with well-established pathology hallmarks, namely the deposition of amyloid-β (Aβ) peptides in extracellular plaques and intracellular hyperphosphorylated forms of the microtubule associated protein tau forming neurofibrillary tangles (NFTs), accompanied by neuronal and synaptic loss [2]. Interestingly, patients who will eventually develop AD manifest brain pathology decades before clinical symptoms appear [3][4]. Nevertheless, AD is still frequently diagnosed when symptoms are highly disabling and yet there is no satisfactory treatment.

Although the manifestations of AD are preponderantly cerebral, cumulative evidence shows that AD is a systemic disorder [5]. Accordingly, molecular changes associated with AD are not exclusively manifested in the brain but include cells from different parts of the body, ranging from the blood and skin to peripheral olfactory cells. More recently, neurons derived from induced pluripotent stem cells (iPSCs) from AD patients have contributed to glean a more realistic insight of brain pathogenic mechanisms [6]. Alternatively, the culture of olfactory neuronal precursors (ONPs) has emerged as a relatively simpler tool to study different brain disorders, taking advantage of their neuronal lineage and their readily non-invasive isolation [7][8]. For instance, patient-derived ONPs manifest abnormal amyloid components together with tau hyperphosphorylation, which have recently led to the proposal of these cells as a novel diagnostic tool for AD [9][10][11].

Different hypotheses have attempted to explain AD pathogenesis. Some of them include Aβ cascade, tau hyperphosphorylation, mitochondrial damage, endoplasmic reticulum (ER) stress, and oxidative stress. Interestingly, although it has been difficult to establish a prevailing causative mechanism, increased levels of oxidative stress seem to be a common feature for many of these models. Furthermore, oxidative stress due to increased levels of reactive oxygen species (ROS) has been broadly recognized as a very early signature during the course of AD [12][13][14]. Interestingly, AD-related oxidative stress is by no means restricted to neuronal cells but is also related to astrocytes' oxidative damage and antioxidant capacity [15]. Indeed, since the acknowledgment of the tripartite synapse, it has become increasingly clear that different antioxidant mechanisms of astrocytes can be harnessed by synaptically active neurons and surrounding cells [16][17][18]. In the tripartite synapse, the astrocyte's endfeet are close to synapses and can be activated by the spillover of synaptic glutamate to provide a timely antioxidant response [19][20]. Moreover, it is not entirely understood how other glial cells such as pericytes may contribute to the damage induced by AD-related oxidative stress. For instance, oxidative damage may compromise the integrity of pericytes, which in turn could alter the blood-brain barrier's integrity, favoring the infiltration of cytotoxic cells and the emergence of brain edema [21][22]. In coherence with a broader systemic manifestation of this disease, the peripheral olfactory system shows AD-associated oxidative stress, which has been measured both in the olfactory neuroepithelium and in cultured ONPs [23][24][25]. However, while the intriguing relationship between oxidative stress and AD has been long known, their translational impact has remained limited.

2. Olfactory Neuroepithelium and the Non-Invasive Isolation of ONPs

The olfactory neuroepithelium is a key structure for odor sensing. It consists of a pseudostratified columnar epithelium located on the outer domain of the olfactory mucosa settled on the basement membrane (BM) and the lamina propria (LP) [26]. The cellular composition of these layers has been widely documented based on morphological analysis and the use of characteristic markers for each cell type [27][28][29][30]. Figure 1 schematizes the location, cellular components, and molecular markers of the human olfactory mucosa.

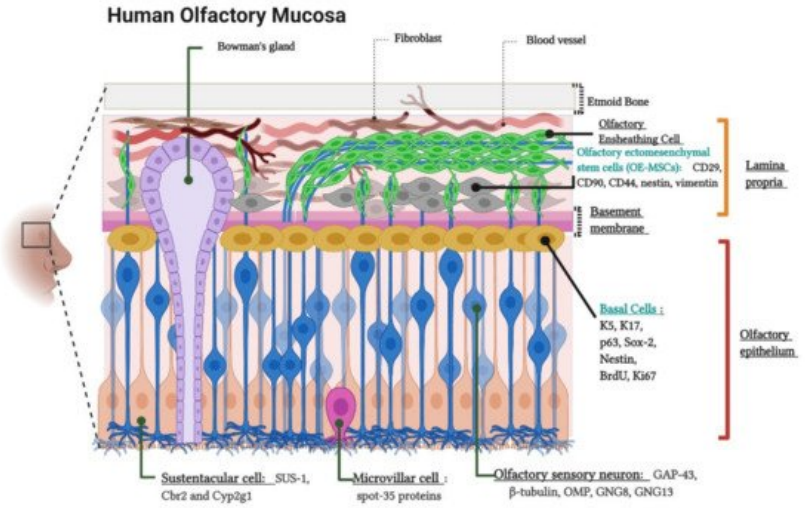

Figure 1. Cytoarchitecture and cellular components of the human olfactory mucosa. Lamina propria components. Olfactory Ensheathing Cells, Bowman's gland and Olfactory Ectomesenchymal Stem Cells (OE-MSCs). The image indicates the OE-MSCs markers: CD29, CD90, CD44, Nestin, and Vimentin. Olfactory epithelium components. Basal Cells, Olfactory sensory neurons (OSNs) or Olfactory receptor neurons (ORNs), Sustentacular cells, and Microvillar cells. The figure shows basal cell markers: K5 (Keratin 5), K17 (Keratin 17), p63, Sox-2 (SRY-Box Transcription Factor 2), Nestin, BrdU (Bromodeoxyuridine), and Ki-67; ORNs markers: GAP-43 (Growth Associated Protein 43), β-tubulin, OMP (Olfactory Marker Protein), GNG8 (Guanine Nucleotide-binding protein subunit Gamma), and GNG13 (Guanine Nucleotide-binding protein G(I)/G(S)/G(O) subunit Gamma-13)); sustentacular cell markers (SUS-1, Cbr2 (Carbonyl Reductase 2) and Cyp2g1 (Cytochrome P450, family 2, subfamily G, polypeptide 1)) and, microvillar cell marker: (spot-35 proteins). Created with BioRender.com.

The olfactory neuroepithelium is also a source of stem cells, which are capable of self-renewal and can generate neuronal precursors throughout the entire human lifetime. These precursors include neural stem cells known as basal cells. As expected for neural stem cells, basal cells are multipotent and allow the continuous replacement of neuronal and non-neuronal cells such as olfactory receptor neurons (ORNs) and sustentacular cells (of astrocytic lineage), respectively [31][32][33]. In addition, the LP contains another less accessible population of stem cells, whose features meet most of the minimum criteria of the mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy [34]. As such, they are named as olfactory ectomesenchymal stem cells (OE-MSCs) [35][36][37].

Isolation of cells of the olfactory neuroepithelium from patients provides a source of cultured neural stem cells, which has been used to model different brain disorders such as schizophrenia, Parkinson's disease, autism, ataxia-telangiectasia, hereditary spastic paraplegia (HSP), and AD [7][38][39][40][41][42]. These neural stem cells can be frozen and stored for subsequent use and tolerate several passages without significantly losing their main properties. Furthermore, purified cultures obtained by cloning selection through limiting dilution significantly increases cell viability at least until passage 60 [43]. In this work, we will refer to neural stem cells isolated from the olfactory neuroepithelium as olfactory neuronal precursors (ONPs), similar to [8][9][43][44].

Different strategies have been used to isolate and culture patient-derived ONPs, ranging from biopsies to non-invasive exfoliation of the nasal turbinate. Human ONPs were first isolated by Wolozin et al. from the olfactory neuroepithelium of cadavers or from adult biopsied samples [10][45]. Another similar isolation approach demonstrated that a significant subpopulation of these cells express markers of mature olfactory neurons such as OMP, Golf, NCAM, and NST and look small and bright to the microscope, in contrast to the remaining "dark phase" cells that do not express OMP, but glial markers [46]. However, a systematic characterization of these cultures has shown that after a few days in vitro, both dark and bright phase cells show an intracellular calcium increase in response to odorants, highlighting the neuronal features of these cells [47]. In addition, cells with features of ONPs have also been obtained from dissociated neurospheres, which have been denominated "olfactory neurosphere-derived" (ONS) cells [36]. Alternatively, ONPs can be non-invasively

isolated by an exfoliation of the nasal cavity [44]. These exfoliated cells can be cultured in a modified media to propitiate neural lineage maintenance and proliferation. Notably, these neuronal precursors conserve their capability to differentiate into ORNs in the presence of dibutyryl adenosine 3',5'-cyclic monophosphate (Db-cAMP) and, strikingly, maintain their electrical response to odorants [44]. Thus, non-invasively isolated ONPs retain neuronal features similar to those obtained by biopsy. A simplified extraction protocol and the molecular characterization of non-invasively isolated ONPs is shown in Figure 2.

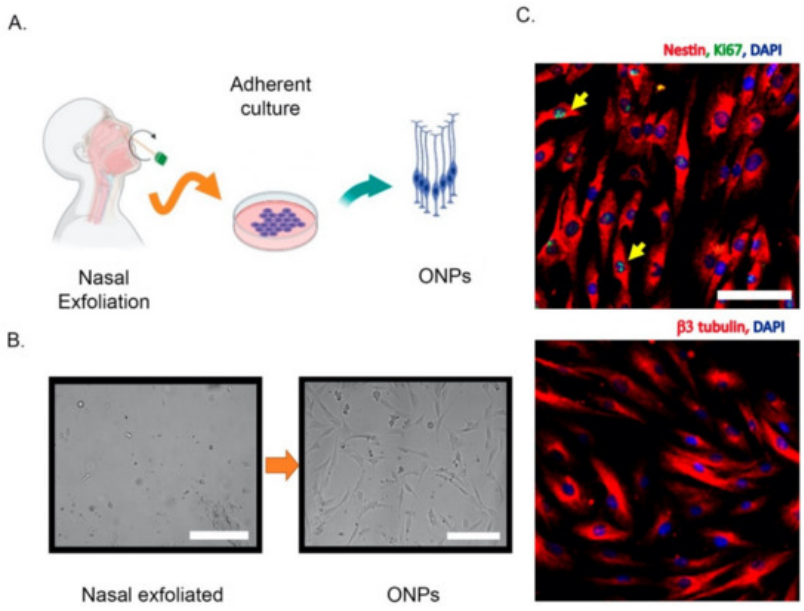

Figure 2. Non-invasive isolation of olfactory neuronal precursors (ONPs). (**A**) Schematic cartoon of the isolation protocol based on the extraction of nasal exfoliate with the subsequent adherent culture and enrichment of ONPs. (**B**) Left, the nasal exfoliate is directly seeded on adherent plates, showing a mixture of cell morphologies. Right, after 1–2 weeks ONPs dividing colonies are easily observed with their characteristic morphologies. (**C**) Upper panel, immunofluorescence of cultured ONPs, depicting the stem cell marker Nestin and Ki67 (yellow arrows) to show active cell proliferation. Lower panel, cultured ONPs express neuronal markers such as β3 tubulin. Cell nuclei are shown by DAPI staining. All scale bars = 100 µm. All images were generated in our lab. Created with BioRender.com.

3. Alzheimer's Disease-Related Oxidative Stress in the Olfactory Epithelium and ONPs

Oxidative stress is the result of an imbalance between oxidant and antioxidant cellular pathways. One of the most studied oxidant compounds are ROS, which are highly reactive molecules, including peroxide (H_2O_2), superoxide anion radical (O_2 • −), and hydroxyl radical (• OH), among others. These molecules may covalently interact with lipids, proteins, and carbohydrates, generating molecular adducts and cumulative damage that, when sensed by cells, may actively trigger different death programs [48].

It was well established almost three decades ago that oxidative stress damage is linked to AD [14]. Furthermore, it has been proposed that oxidative stress at different brain neuronal and non-neuronal cells might be the earliest event of a pathogenic cascade [13]. Whether oxidative stress is a causative agent or just a consequence in neurodegenerative disorders has been thoroughly debated for several years, but still remains an open question [49][50][51]. The most parsimonious interpretation of this evidence is that oxidative stress as well as other potential AD causative agents (such as Aβ accumulation) are part of a highly interconnected vicious cycle rather than a linear chain of events with a unique origin. The molecular mechanisms and implications of oxidative stress on the nervous system and, potentially, during AD pathogenesis have been thoroughly reviewed elsewhere [12][52]. Here, we focus on evidence showing AD-associated oxidative stress in the peripheral olfactory system rather than reviewing mechanistic explanations.

Oxidative stress associated with AD is manifested in the olfactory neuroepithelium. Accordingly, increased immunoreactivity of the antioxidant enzyme manganese and Copper-Zinc superoxide dismutases have been detected in ORNs and basal and sustentacular cells of the olfactory neuroepithelium of AD patients compared with age-matched controls [53]. Analogously, AD patients harbor a higher immunoreactivity against the antioxidant protein Metallothionein both in the olfactory neuroepithelium and the Bowman's Glands and the LP [54]. Both results suggest that cells from olfactory neuroepithelium elicit an increased antioxidant defense, due to increased oxidative stress during AD. With respect to the direct measurement of oxidation products, post-mortem staining showed an increase in 3-nitrotyrosine (3-

NT) in the brain and olfactory neuroepithelium of AD patients [23]. Figure 3 schematizes the antioxidant response and oxidative damage reported in ONPs and OE from AD patients. It would be of interest to uncover whether some AD genetic factors such as the *ApoE* ε4 allele (*ApoE4*) (the single most important genetic risk factor for AD) also manifests oxidative stress signatures in the olfactory epithelium. It is plausible that this is the case because deficits in odor fluency, identification, recognition memory, and odor threshold sensitivity have been associated with the inheritance of the *ApoE4* genotype in several studies [55][56][57]. For a more thorough compiling of evidence showing AD-associated oxidative damage across other domains of the nervous system, readers may refer to the following excellent articles [12][52][58].

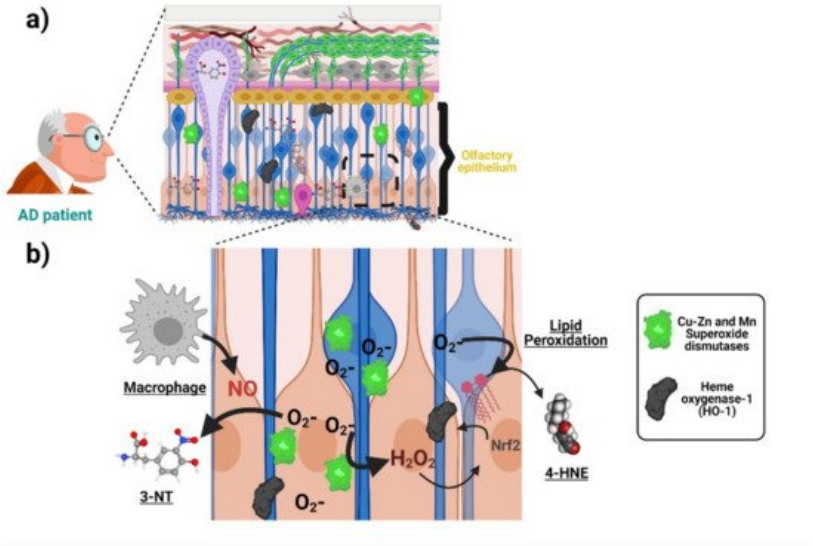

Figure 3. Oxidative stress associated with AD in the olfactory neuroepithelium. (**a**) ONPs and sustentacular cells in the olfactory epithelium (OE) show an increased antioxidant defense with elevated levels of manganese and copper-zinc superoxide dismutases as well as heme oxygenase-1 due to increased oxidative stress in AD patients compared with age-matched controls. Moreover, there is an increase in 3-nitrotyrosine (3-NT) and 4-hydroxynonenal (lipid peroxidation indicator) levels, suggesting AD-associated oxidative damage. (**b**) The increased generation of superoxide anion activates superoxide dismutases (SOD) as an antioxidant response. The generation of other reactive oxygen species (ROS), such as H_2O_2, induces the expression of other antioxidant enzymes (heme oxygenase-1). On the other hand, the accumulation of superoxide anion increases the levels of compounds such as 4-hydroxynonenal (4-HNE). Moreover, the increased levels of 3-NT are produced from the interaction of superoxide anion and nitric oxide (NO), whose probable source is located at activated macrophages in the OE of AD patients. Created with BioRender.com.

The relationship between oxidative stress and AD has been extensively studied mainly through cellular and animal models [40][47]. However, these models may not fully capture key features of the disease. This limitation potentially leads to wrong conclusions about the pathogenic mechanisms and ultimately may dampen the development of effective therapies. Alternatively, patient-derived cells of neuronal lineage such as those from the olfactory epithelium may provide a convenient solution to this problem [5][9][35].

Interestingly, cultured patient-derived ONPs and other peripheral cells also manifest AD-associated oxidative stress. For example, an increase in the level of hydroxynonenal and Nε-(carboxymethyl)lysine) (indicating lipid peroxidation), as well as a higher content of heme oxygenase-1, has been found in ONPs isolated from AD patients compared with age-matched controls (Figure 3) [24]. Furthermore, ONPs from AD patients are also more susceptible to oxidative stress-induced cell death [25]. This is strikingly similar to what has been found by our group in blood-derived lymphocytes from AD patients [59][60]. Indeed, manifestations of oxidative stress associated with AD have been reported in different patient-derived peripheral cells ranging from blood cells to fibroblasts and iPSCs-derived neurons. These changes may include compensatory antioxidant responses and a rise in the concentration of oxidation by-products, as well as increased susceptibility to ROS-induced cell death, which has been demonstrated in different cellular types from AD patients. Many of those findings are summarized in the Table 1. In addition, Table 1 also summarizes similar evidence of other relevant pathogenic mechanisms proposed for AD pathogenesis, including Amyloid/Tau, mitochondria, and ER-stress. Thus, different cells throughout the body show signs of different proposed AD pathogenic mechanisms, including oxidative stress at early stages of the disease continuum. The robustness of this tendency highlights the potential of patient-derived cells, and in particular ONPs, for monitoring oxidative stress associated with AD.

Table 1. Signatures of oxidative stress and other AD mechanistic hypotheses are manifested in patient-derived peripheral cells, iPSCs and ONPs.

Pathogenic Mechanism	Main Finding	Cellular Type	Lineage	References
Amyloid/Tau	Platelets from AD patients reproduce the increased amyloidogenic processing of AβPP	Platelets	Non-neuronal	[61]
Amyloid/Tau	AD platelets harbor increased levels of a higher molecular weight tau isoform	Platelets	Non-neuronal	[62]
Amyloid/Tau	Alteration of AβPP, BACE, and ADAM 10 levels in early stages of the disease	Platelets	Non-neuronal	[63][64][65]
Amyloid/Tau	It is suggested a decreased non-amyloidogenic processing of AβPP by a lack of nicastrin mRNA expression in samples obtained from AD patients	Lymphocytes	Non-neuronal	[66]
Amyloid/Tau	Altered balance between Aβ-oligomers and PKCε levels in AD. Loss of PKCε-mediated inhibition of Aβ	Fibroblasts	Non-neuronal	[67]
Amyloid/Tau	Higher $A\beta_{42}/A\beta_{40}$ ratio compared to control cells	*PSEN1* iPSC-derived neural progenitors	Neuronal	[68]
Amyloid/Tau	Mutation alters the initial cleavage site of γ-secretase, resulting in an increased generation of $A\beta_{42}$, in addition to an increase in the levels of total and phosphorylated tau	Neuron-derived iPSCs from patients harboring the London FAD *AβPP* mutation V717I	Neuronal	[69]
Amyloid/Tau	Oligomeric forms of canonical Aβ impairs synaptic plasticity	Cortical neurons from three genetic forms of AD —*PSEN1* L113_I114insT, *AβPP* duplication (*AβPP*Dp), and Ts21— generated from iPSCs	Neuronal	[70]
Amyloid/Tau	Increase in the content and changes in the subcellular distribution of t-tau and p-tau in cells from AD patients compared to controls	Non-invasively isolated ONPs	Neuronal	[9]
Mitochondria	Compromise of mitochondrial COX from AD patients	Platelets	Non-neuronal	[71]
Mitochondria	Platelets isolated from AD patients show decreased ATP levels	Platelets	Non-neuronal	[72]
Mitochondria	AD lymphocytes exhibit impairment of total OXPHOS capacity	Lymphocytes	Non-neuronal	[73]
Mitochondria	AD skin fibroblasts show increased production of CO_2 and reduced oxygen uptake suggesting that mitochondrial electron transport chain might be compromised	Fibroblasts	Non-neuronal	[74]
Mitochondria	AD fibroblasts present reduction in mitochondrial length and a dysfunctional mitochondrial bioenergetics profile	Fibroblasts	Non-neuronal	[75]
Mitochondria	SAD fibroblasts exhibit aged mitochondria, and their recycling process is impaired	Fibroblasts	Non-neuronal	[76]
Mitochondria	Patient-derived cells show increased levels of oxidative phosphorylation chain complexes	Human induced pluripotent stem cell-derived neuronal cells (iN cells) from SAD patients	Neuronal	[77]

Pathogenic Mechanism	Main Finding	Cellular Type	Lineage	References
Mitochondria	Mitophagy failure as a consequence of lysosomal dysfunction	iPSC-derived neurons from FAD1 patients harboring *PSEN1* A246E mutation	Neuronal	[78]
Mitochondria	Neurons exhibit defective mitochondrial axonal transport	iPSC-derived neurons from an AD patient carrying *AβPP* -V715M mutation	Neuronal	[79]
Oxidative Stress	Increased activity of the antioxidant enzyme catalase in probable AD patients	Erythrocytes	Non-neuronal	[80]
Oxidative Stress	Increased production and content of thiobarbituric acid-reactive substances (TBARS), superoxide dismutase (SOD), and nitric oxide synthase (NOS)	Erythrocytes and Platelets	Non-neuronal	[81]
Oxidative Stress	Increase in the content of the unfolded version of p53 as well as reduced SOD activity	Peripheral blood mononuclear cells (PBMCs)	Non-neuronal	[82]
Oxidative Stress	Exacerbated response to NFKB pathway	PBMCs	Non-neuronal	[83]
Oxidative Stress	Increased ROS production in response to H_2O_2	PBMCs	Non-neuronal	[59]
Oxidative Stress	AD lymphocytes were more prone to cell death after a H_2O_2 challenge	Lymphocytes	Non-neuronal	[84]
Oxidative Stress	Reduced antioxidant capacity of FAD lymphocytes and fibroblasts together with increased lipid peroxidation on their plasma membrane	Lymphocytes and Fibroblasts	Non-neuronal	[85]
Oxidative Stress	Aβ peptides were better internalized and generated greater oxidative damage in FAD fibroblasts	Fibroblasts	Non-neuronal	[86]
Oxidative Stress	Aβ peptide caused a higher increase in the oxidation of HSP60	Fibroblasts	Non-neuronal	[87]
Oxidative Stress	Reduction in the levels of Vimentin in samples from AD patients	iPSCs-derived neurons from AD patient	Neuronal	[58]
Oxidative Stress	Increased levels of hydroxynonenal, Nε-(carboxymethyl)lysine), and heme oxygenase-1 in samples from AD patients	Biopsy-derived ONPs	Neuronal	[24]
Oxidative Stress	Increased susceptibility to oxidative-stress-induced cell death	Biopsy-derived ONPs	Neuronal	[25]
ER-Stress	Impaired ER Ca^{2+} and ER stress in PBMCs from MCIs and mild AD patients	PBMCs	Non-neuronal	[88]
ER-Stress	Accumulation of Aβ oligomers induced ER and oxidative stress	iPSC-derived neural cells from a patient carrying *APP*-E693Δ mutation and a sporadic AD patient	Neuronal	[89]
ER-Stress	Aβ-S8C dimer triggers an ER stress response more prominent in AD neuronal cultures where several genes from the UPR were upregulated	iPSC-derived neuronal cultures carrying the AD-associated *TREM2* R47H variant	Neuronal	[90]

Pathogenic Mechanism	Main Finding	Cellular Type	Lineage	References
ER-Stress	**Accumulation of Aβ oligomers in iPSC-derived neurons from AD patients leads to increased ER stress**	**iPSC-derived neurons from patients with an *AβPP*-E693Δ mutation**	**Neuronal**	[91]

References

1. Haque, R.U.; Levey, A.I.; Alzheimer's disease: A clinical perspective and future nonhuman primate research opportunities. *Proceedings of the National Academy of Sciences of the United States of America* **2019**, *116 (52)*, 26224-26229, 10.1073/pnas.1912954116.
2. Serrano-Pozo, A.; Frosch, M.P.; Masliah, E.; Hyman, B.T.; Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor perspectives in medicine* **2011**, *1*, a006189, 10.1101/cshperspect.a006189.
3. Perrin, R.J.; Fagan, A.M.; Holtzman, D.M.; Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature* **2009**, *461*, 916–922, 10.1038/nature08538.
4. Jack, C.R., Jr.; Knopman, D.S.; Jagust, W.J.; Shaw, L.M.; Aisen, P.S.; Weiner, M.W.; Petersen, R.C.; Trojanowski, J.Q.; Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *The Lancet. Neurology* **2010**, *9*, 119–128, 10.1016/S1474-4422(09)70299-6.
5. Trushina, E.; Alzheimer's disease mechanisms in peripheral cells: Promises and challenges. *Alzheimer's & dementia* **2019**, *5*, 652–660, 10.1016/j.trci.2019.06.008..
6. Penney, J.; Ralvenius, W.T.; Tsai, L.H.; Modeling Alzheimer's disease with iPSC-derived brain cells. *Molecular psychiatry* **2020**, *25*, 148–167, 10.1038/s41380-019-0468-3.
7. Mackay-Sim, A; Concise review: Patient-derived olfactory stem cells: New models for brain diseases. *Stem cells* **2012**, *30*, 2361–2365, 10.1002/stem.1220.
8. Jimenez-Vaca, A.L.; Benitez-King, G.; Ruiz, V.; Ramirez-Rodriguez, G.B.; Hernandez-de la Cruz, B.; Salamanca-Gomez, F.A.; Gonzalez-Marquez, H.; Ramirez-Sanchez, I.; Ortiz-Lopez, L.; Velez-Del Valle, C.; et al. Exfoliated Human Olfactory Neuroepithelium: A Source of Neural Progenitor Cells. *Molecular neurobiology* **2018**, *55*, 2516–2523, 10.1007/s12035-017-0500-z.
9. Riquelme, A.; Valdes-Tovar, M.; Ugalde, O.; Maya-Ampudia, V.; Fernandez, M.; Mendoza-Duran, L.; Rodriguez-Cardenas, L.; Benitez-King, G.; Potential Use of Exfoliated and Cultured Olfactory Neuronal Precursors for In Vivo Alzheimer's Disease Diagnosis: A Pilot Study. *Cellular and molecular neurobiology* **2020**, *40*, 87–98, 10.1007/s10571-019-00718-z.
10. Wolozin, B.; Zheng, B.; Loren, D.; Lesch, K.P.; Lebovics, R.S.; Lieberburg, I.; Sunderland, T.; Beta/A4 domain of APP: Antigenic differences between cell lines. *Journal of neuroscience research* **1992**, *33*, 189–195, 10.1002/jnr.490330202.
11. Wolozin, B.; Bacic, M.; Merrill, M.J.; Lesch, K.P.; Chen, C.; Lebovics, R.S.; Sunderland, T.; Differential expression of carboxyl terminal derivatives of amyloid precursor protein among cell lines. *Journal of neuroscience research* **1992**, *33*, 163–169, 10.1002/jnr.490330121.
12. Butterfield, D.A.; Halliwell, B.; Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nature reviews. Neuroscience* **2019**, *20*, 148–160, 10.1038/s41583-019-0132-6.
13. Nunomura, A.; Perry, G.; Aliev, G.; Hirai, K.; Takeda, A.; Balraj, E.K.; Jones, P.K.; Ghanbari, H.; Wataya, T.; Shimohama, S.; et al. Oxidative damage is the earliest event in Alzheimer disease. *Journal of neuropathology and experimental neurology* **2001**, *60*, 759–767, 10.1093/jnen/60.8.759.
14. Smith, M.A.; Nunomura, A.; Lee, H.G.; Zhu, X.; Moreira, P.I.; Avila, J.; Perry, G.; Chronological primacy of oxidative stress in Alzheimer disease. *Neurobiology of aging* **2005**, *26*, 579–580, 10.1016/j.neurobiolaging.2004.09.021.
15. Gonzalez-Reyes, R.E.; Nava-Mesa, M.O.; Vargas-Sanchez, K.; Ariza-Salamanca, D.; Mora-Munoz, L.; Involvement of Astrocytes in Alzheimer's Disease from a Neuroinflammatory and Oxidative Stress Perspective. *Frontiers in molecular neuroscience* **2017**, *10*, 427, 10.3389/fnmol.2017.00427.
16. Habas, A.; Hahn, J.; Wang, X.; Margeta, M.; Neuronal activity regulates astrocytic Nrf2 signaling. *Proceedings of the National Academy of Sciences of the United States of America* **2013**, *110*, 18291–18296, 10.1073/pnas.1208764110.
17. Qiu, J.; Dando, O.; Febery, J.A.; Fowler, J.H.; Chandran, S.; Hardingham, G.E.; Neuronal Activity and Its Role in Controlling Antioxidant Genes. *International journal of molecular sciences* **2020**, *21*, 1933, 10.3390/ijms21061933.

18. Baxter, P.S.; Hardingham, G.E.; Adaptive regulation of the brain's antioxidant defences by neurons and astrocytes. *Free radical biology & medicine* **2016**, *100*, 147–152, 10.1016/j.freeradbiomed.2016.06.027.

19. Araque, A.; Parpura, V.; Sanzgiri, R.P.; Haydon, P.G.; Tripartite synapses: Glia, the unacknowledged partner. *Trends in neurosciences* **1999**, *22*, 208–215, 10.1016/s0166-2236(98)01349-6.

20. Perea, G.; Navarrete, M.; Araque, A.; Tripartite synapses: Astrocytes process and control synaptic information. *Trends in neurosciences* **2009**, *32*, 421–431, 10.1016/j.tins.2009.05.001.

21. Wang, Q.; Wang, Y.; Shimony, J.S.; Owen, C.J.; Liu, J.; Fagan, A.M.; Cairns, N.J.; Ances, B.; Morris, J.C.; Benzinger, T.L.S.; et al. IC-P-172: Simultaneous Quantification of White Matter Abnormalities and Vasogenic Edema in Early Alzheimer Disease.. *Alzheimer's & dementia* **2016**, *12*, P125-P126, 10.1016/j.jalz.2016.06.203.

22. Kitchen, P.; Salman, M.M.; Halsey, A.M.; Clarke-Bland, C.; MacDonald, J.A.; Ishida, H.; Vogel, H.J.; Almutiri, S.; Logan, A.; Kreida, S.; et al. Targeting Aquaporin-4 Subcellular Localization to Treat Central Nervous System Edema. *Cell* **2020**, *181*, 784–799 e719, 10.1016/j.cell.2020.03.037.

23. Getchell, M.L.; Shah, D.S.; Buch, S.K.; Davis, D.G.; Getchell, T.V; 3-Nitrotyrosine immunoreactivity in olfactory receptor neurons of patients with Alzheimer's disease: Implications for impaired odor sensitivity. . *Neurobiology of aging* **2003**, *24*, 663–673, 10.1016/s0197-4580(02)00195-1.

24. Ghanbari, H.A.; Ghanbari, K.; Harris, P.L.; Jones, P.K.; Kubat, Z.; Castellani, R.J.; Wolozin, B.L.; Smith, M.A.; Perry, G.; Oxidative damage in cultured human olfactory neurons from Alzheimer's disease patients. *Aging cell* **2004**, *3*, 41–44, 10.1111/j.1474-9728.2004.00083.x.

25. Nelson, V.M.; Dancik, C.M.; Pan, W.; Jiang, Z.G.; Lebowitz, M.S.; Ghanbari, H.A.; PAN-811 inhibits oxidative stress-induced cell death of human Alzheimer's disease-derived and age-matched olfactory neuroep-ithelial cells via suppression of intracellular reactive oxygen species. *Journal of Alzheimer's disease : JAD* **2009**, *17*, 611–619, 10.3233/JAD-2009-1078.

26. Jafek, B.W.; Ultrastructure of human nasal mucosa. *The Laryngoscope* **1983**, *93*, 1576–1599, 10.1288/00005537-198312000-00011.

27. Moran, D.T.; Rowley, J.C., 3rd; Jafek, B.W.; Lovell, M.A.; The fine structure of the olfactory mucosa in man. *Journal of neurocytology* **1982**, *11*, 721–746, 10.1007/bf01153516.

28. Morrison, E.E.; Costanzo, R.M.; Morphology of the human olfactory epithelium. *The Journal of comparative neurology* **1990**, *297*, 1–13, 10.1002/cne.902970102.

29. Verhaagen, J.; Oestreicher, A.B.; Gispen, W.H.; Margolis, F.L.; The expression of the growth associated protein B50/GAP43 in the olfactory system of neonatal and adult rats. *The Journal of Neuroscience : The official journal of the Society for Neuroscience* **1989**, *9*, 683–691, 10.1523/JNEUROSCI.09-02-00683.1989.

30. Holbrook, E.H.; Wu, E.; Curry, W.T.; Lin, D.T.; Schwob, J.E.; Immunohistochemical characterization of human olfactory tissue.. *Laryngoscope* **2011**, *121*, 1687–1701, 10.1002/lary.21856..

31. Fletcher, R.B.; Das, D.; Gadye, L.; Street, K.N.; Baudhuin, A.; Wagner, A.; Cole, M.B.; Flores, Q.; Choi, Y.G.; Yosef, N.; et al. Deconstructing Olfactory Stem Cell Trajectories at Single-Cell Resolution. *Cell stem cell* **2017**, *20*, 817–830 e818, 10.1016/j.stem.2017.04.003.

32. Hahn, C.G.; Han, L.Y.; Rawson, N.E.; Mirza, N.; Borgmann-Winter, K.; Lenox, R.H.; Arnold, S.E.; In vivo and in vitro neurogenesis in human olfactory epithelium. *The Journal of comparative neurology* **2005**, *483*, 154–163, 10.1002/cne.20424.

33. Chen, X.; Fang, H.; Schwob, J.E.; Multipotency of purified, transplanted globose basal cells in olfactory epithelium. *The Journal of comparative neurology* **2004**, *469*, 457–474, 10.1002/cne.11031.

34. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E.; et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* **2006**, *8*, 315–317, 10.1080/14653240600855905.

35. Delorme, B.; Nivet, E.; Gaillard, J.; Haupl, T.; Ringe, J.; Deveze, A.; Magnan, J.; Sohier, J.; Khrestchatisky, M.; Roman, F.S.; et al. The human nose harbors a niche of olfactory ectomesenchymal stem cells displaying neurogenic and osteogenic properties. *Stem cells and development* **2010**, *19*, 853–866, 10.1089/scd.2009.0267.

36. Murrell, W.; Feron, F.; Wetzig, A.; Cameron, N.; Splatt, K.; Bellette, B.; Bianco, J.; Perry, C.; Lee, G.; Mackay-Sim, A.; et al. Multipotent stem cells from adult olfactory mucosa. *Developmental dynamics: An official publication of the American Association of Anatomists* **2005**, *233*, 496–515, 10.1002/dvdy.20360.

37. Tanos, T.; Saibene, A.M.; Pipolo, C.; Battaglia, P.; Felisati, G.; Rubio, A.; Isolation of putative stem cells present in human adult olfactory mucosa. *PLoS ONE* **2017**, *12*, e0181151, 10.1371/journal.pone.0181151.

38. Matigian, N.; Abrahamsen, G.; Sutharsan, R.; Cook, A.L.; Vitale, A.M.; Nouwens, A.; Bellette, B.; An, J.; Anderson, M.; Beckhouse, A.G.; et al. Disease-specific, neurosphere-derived cells as models for brain disorders. *Disease models & mechanisms* **2010**, *3*, 785–798, 10.1242/dmm.005447.

39. Feron, F.; Gepner, B.; Lacassagne, E.; Stephan, D.; Mesnage, B.; Blanchard, M.P.; Boulanger, N.; Tardif, C.; Deveze, A.; Rousseau, S.; et al. Olfactory stem cells reveal MOCOS as a new player in autism spectrum disorders. *Molecular psychiatry* **2016**, *21*, 1215–1224, 10.1038/mp.2015.106.

40. Stewart, R.; Wali, G.; Perry, C.; Lavin, M.F.; Feron, F.; Mackay-Sim, A.; Sutharsan, R.; A Patient-Specific Stem Cell Model to Investigate the Neurological Phenotype Observed in Ataxia-Telangiectasia. *Methods in molecular biology* **2017**, *1599*, 391–400, 10.1007/978-1-4939-6955-5_28.

41. Fan, Y.; Wali, G.; Sutharsan, R.; Bellette, B.; Crane, D.I.; Sue, C.M.; Mackay-Sim, A.; Low dose tubulin-binding drugs rescue peroxisome trafficking deficit in patient-derived stem cells in Hereditary Spastic Paraplegia. *Biology open* **2014**, *3*, 494–502, 10.1242/bio.20147641.

42. Ayala-Grosso, C.A.; Pieruzzini, R.; Diaz-Solano, D.; Wittig, O.; Abrante, L.; Vargas, L.; Cardier, J.; Amyloid-abeta Peptide in olfactory mucosa and mesenchymal stromal cells of mild cognitive impairment and Alzheimer's disease patients. *Brain pathology* **2015**, *25*, 136–145, 10.1111/bpa.12169.

43. Solis-Chagoyan, H.; Flores-Soto, E.; Valdes-Tovar, M.; Cercos, M.G.; Calixto, E.; Montano, L.M.; Barajas-Lopez, C.; Sommer, B.; Aquino-Galvez, A.; Trueta, C.; et al. Purinergic Signaling Pathway in Human Olfactory Neuronal Precursor Cells. *Stem cells international* **2019**, *2019*, 2728786, 10.1155/2019/2728786.

44. Benitez-King, G.; Riquelme, A.; Ortiz-Lopez, L.; Berlanga, C.; Rodriguez-Verdugo, M.S.; Romo, F.; Calixto, E.; Solis-Chagoyan, H.; Jimenez, M.; Montano, L.M.; et al. A non-invasive method to isolate the neuronal linage from the nasal epithelium from schizophrenic and bipolar diseases.. *Journal of neuroscience methods* **2011**, *201*, 35–45, 10.1016/j.jneumeth.2011.07.009.

45. Wolozin, B.; Sunderland, T.; Zheng, B.B.; Resau, J.; Dufy, B.; Barker, J.; Swerdlow, R.; Coon, H.; Continuous culture of neuronal cells from adult human olfactory epithelium. *Journal of molecular neuroscience: MN* **1992**, *3*, 137–146, 10.1007/bf02919405.

46. Gomez, G.; Rawson, N.E.; Hahn, C.G.; Michaels, R.; Restrepo, D.; Characteristics of odorant elicited calcium changes in cultured human olfactory neurons. *Journal of neuroscience research* **2000**, *62*, 737–749, 10.1002/1097-4547(20001201)62:5<737::AID-JNR14>3.0.CO;2-A.

47. Yazinski, S.; Gomez, G.; Time course of structural and functional maturation of human olfactory epithelial cells in vitro. *Journal of neuroscience research* **2014**, *92*, 64–73, 10.1002/jnr.23296.

48. Kagan, V.E.; Tyurina, Y.Y.; Sun, W.Y.; Vlasova, II.; Dar, H.; Tyurin, V.A.; Amoscato, A.A.; Mallampalli, R.; van der Wel, P.C.A.; He, R.R.; et al. Redox phospholipidomics of enzymatically generated oxygenated phospholipids as specific signals of programmed cell death. *Free radical biology & medicine* **2020**, *147*, 231–241, 10.1016/j.freeradbiomed.2019.12.028.

49. Andersen, J.K.; Oxidative stress in neurodegeneration: Cause or consequence? . *Nature medicine* **2004**, *10 Suppl*, S18-25, 10.1038/nrn1434.

50. Sutherland, G.T.; Chami, B.; Youssef, P.; Witting, P.K.; Oxidative stress in Alzheimer's disease: Primary villain or physiological by-product?. *Redox report: Communications in free radical research* **2013**, *18*, 134–141, 10.1179/1351000213Y.0000000052.

51. Butterfield, D.A.; Boyd-Kimball, D; Oxidative Stress, Amyloid-beta Peptide, and Altered Key Molecular Pathways in the Pathogenesis and Progression of Alzheimer's Disease. *Journal of Alzheimer's disease: JAD* **2018**, *62*, 1345–1367, 10.3233/JAD-170543.

52. Tonnies, E.; Trushina, E.; Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *Journal of Alzheimer's disease: JAD* **2017**, *57*, 1105–1121, 10.3233/JAD-161088.

53. Kulkarni-Narla, A.; Getchell, T.V.; Schmitt, F.A.; Getchell, M.L.; Manganese and copper-zinc superoxide dismutases in the human olfactory mucosa: Increased immunoreactivity in Alzheimer's disease. *Experimental neurology* **1996**, *140*, 115–125, 10.1006/exnr.1996.0122.

54. Chuah, M.I.; Getchell, M.L.; Metallothionein in olfactory mucosa of Alzheimer's disease patients and apoE-deficient mice. *Neuroreport* **1999**, *10*, 1919–1924, 10.1097/00001756-199906230-00023.

55. Calhoun-Haney, R.; Murphy, C.; Apolipoprotein epsilon4 is associated with more rapid decline in odor identification than in odor threshold or Dementia Rating Scale scores. *Brain and cognition* **2005**, *58*, 178–182, 10.1016/j.bandc.2004.10.004.

56. Gilbert, P.E.; Murphy, C.; The effect of the ApoE epsilon4 allele on recognition memory for olfactory and visual stimuli in patients with pathologically confirmed Alzheimer's disease, probable Alzheimer's disease, and healthy elderly controls. *Journal of clinical and experimental neuropsychology* **2004**, *26*, 779–794, 10.1080/13803390490509439.

57. Wang, Q.S.; Tian, L.; Huang, Y.L.; Qin, S.; He, L.Q.; Zhou, J.N.; Olfactory identification and apolipoprotein E epsilon 4 allele in mild cognitive impairment. *Brain research* **2002**, *951*, 77–81, 10.1016/s0006-8993(02)03137-2.

58. Chen, M.; Lee, H.K.; Moo, L.; Hanlon, E.; Stein, T.; Xia, W.; Common proteomic profiles of induced pluripotent stem cell-derived three-dimensional neurons and brain tissue from Alzheimer patients. *Journal of proteomics* **2018**, *182*, 21–33, 10.1016/j.jprot.2018.04.032.

59. Ponce, D.P.; Salech, F.; SanMartin, C.D.; Silva, M.; Xiong, C.; Roe, C.M.; Henriquez, M.; Quest, A.F.; Behrens, M.I.; Increased susceptibility to oxidative death of lymphocytes from Alzheimer patients correlates with dementia severity. *Current Alzheimer research* **2014**, *11*, 892–898, 10.2174/1567205011666141001113135.

60. Salech, F.; Ponce, D.P.; SanMartin, C.D.; Rogers, N.K.; Chacon, C.; Henriquez, M.; Behrens, M.I.; PARP-1 and p53 Regulate the Increased Susceptibility to Oxidative Death of Lymphocytes from MCI and AD Patients. *Frontiers in aging neuroscience* **2017**, *9*, 310, 10.3389/fnagi.2017.00310.

61. Tang, K.; Hynan, L.S.; Baskin, F.; Rosenberg, R.N.; Platelet amyloid precursor protein processing: A bio-marker for Alzheimer's disease. *Journal of the neurological sciences* **2006**, *240*, 53–58, 10.1016/j.jns.2005.09.002.

62. Neumann, K.; Farias, G.; Slachevsky, A.; Perez, P.; Maccioni, R.B.; Human platelets tau: A potential peripheral marker for Alzheimer's disease. *Journal of Alzheimer's disease: JAD* **2011**, *25*, 103–109, 10.3233/JAD-2011-101641.

63. Colciaghi, F.; Marcello, E.; Borroni, B.; Zimmermann, M.; Caltagirone, C.; Cattabeni, F.; Padovani, A.; Di Luca, M.; Platelet APP, ADAM 10 and BACE alterations in the early stages of Alzheimer disease. *Neurology* **2004**, *62*, 498–501, 10.1212/01.wnl.0000106953.49802.9c.

64. Colciaghi, F.; Borroni, B.; Pastorino, L.; Marcello, E.; Zimmermann, M.; Cattabeni, F.; Padovani, A.; Di Luca, M.; [alpha]-Secretase ADAM10 as well as [alpha]APPs is reduced in platelets and CSF of Alzheimer disease patients. *Molecular medicine* **2002**, *8*, 67–74, 10.1007/BF03402076.

65. Vignini, A.; Sartini, D.; Morganti, S.; Nanetti, L.; Luzzi, S.; Provinciali, L.; Mazzanti, L.; Emanuelli, M.; Platelet amyloid precursor protein isoform expression in Alzheimer's disease: Evidence for peripheral marker. *International journal of immunopathology and pharmacology* **2011**, *24*, 529–534, 10.1177/039463201102400229.

66. Herrera-Rivero, M.; Soto-Cid, A.; Hernandez, M.E.; Aranda-Abreu, G.E; Tau, APP, NCT and BACE1 in lymphocytes through cognitively normal ageing and neuropathology. *Anais da Academia Brasileira de Ciencias* **2013**, *85*, 1489–1496, 10.1590/0001-376520130013.

67. Khan, T.K.; Sen, A.; Hongpaisan, J.; Lim, C.S.; Nelson, T.J.; Alkon, D.L.; PKCepsilon deficits in Alzheimer's disease brains and skin fibroblasts. *Journal of Alzheimer's disease: JAD* **2015**, *43*, 491–509, 10.3233/JAD-141221.

68. Sproul, A.A.; Jacob, S.; Pre, D.; Kim, S.H.; Nestor, M.W.; Navarro-Sobrino, M.; Santa-Maria, I.; Zimmer, M.; Aubry, S.; Steele, J.W.; et al. Characterization and molecular profiling of PSEN1 familial Alzheimer's disease iPSC-derived neural progenitors. *PLoS ONE* **2014**, *9*, e84547, 10.1371/journal.pone.0084547.

69. Muratore, C.R.; Rice, H.C.; Srikanth, P.; Callahan, D.G.; Shin, T.; Benjamin, L.N.; Walsh, D.M.; Selkoe, D.J.; Young-Pearse, T.L.; The familial Alzheimer's disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons. *Human molecular genetics* **2014**, *23*, 3523–3536, 10.1093/hmg/ddu064.

70. Hu, N.W.; Corbett, G.T.; Moore, S.; Klyubin, I.; O'Malley, T.T.; Walsh, D.M.; Livesey, F.J.; Rowan, M.J.; Extracellular Forms of Abeta and Tau from iPSC Models of Alzheimer's Disease Disrupt Synaptic Plasticity.. *Cell reports* **2018**, *23*, 1932–1938, 10.1016/j.celrep.2018.04.040.

71. Bosetti, F.; Brizzi, F.; Barogi, S.; Mancuso, M.; Siciliano, G.; Tendi, E.A.; Murri, L.; Rapoport, S.I.; Solaini, G.; Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alz-heimer's disease. *Neurobiology of aging* **2002**, *23*, 371–376, 10.1016/s0197-4580(01)00314-1.

72. Cardoso, S.M.; Proenca, M.T.; Santos, S.; Santana, I.; Oliveira, C.R.; Cytochrome c oxidase is decreased in Alzheimer's disease platelets. *Neurobiology of aging* **2004**, *25*, 105–110, 10.1016/s0197-4580(03)00033-2.

73. Leuner, K.; Schulz, K.; Schutt, T.; Pantel, J.; Prvulovic, D.; Rhein, V.; Savaskan, E.; Czech, C.; Eckert, A.; Muller, W.E.; et al. Peripheral mitochondrial dysfunction in Alzheimer's disease: Focus on lymphocytes. *Molecular neurobiology* **2012**, *46*, 194–204, 10.1007/s12035-012-8300-y.

74. Sims, N.R.; Finegan, J.M.; Blass, J.P.; Altered metabolic properties of cultured skin fibroblasts in Alzheimer's disease. *Annals of neurology* **1987**, *21*, 451–457, 10.1002/ana.410210507.

75. Perez, M.J.; Ponce, D.P.; Osorio-Fuentealba, C.; Behrens, M.I.; Quintanilla, R.A.; Mitochondrial Bioenergetics Is Altered in Fibroblasts from Patients with Sporadic Alzheimer's Disease. *Frontiers in neuroscience* **2017**, *11*, 553, 10.33

89/fnins.2017.00553.

76. Martin-Maestro, P.; Gargini, R.; Garcia, E.; Perry, G.; Avila, J.; Garcia-Escudero, V.; Slower Dynamics and Aged Mitochondria in Sporadic Alzheimer's Disease. *Oxidative medicine and cellular longevity* **2017**, *2017*, 9302761, 10.1155/2017/9302761.
77. Birnbaum, J.H.; Wanner, D.; Gietl, A.F.; Saake, A.; Kundig, T.M.; Hock, C.; Nitsch, R.M.; Tackenberg, C.; Oxidative stress and altered mitochondrial protein expression in the absence of amyloid-beta and tau pathology in iPSC-derived neurons from sporadic Alzheimer's disease patients. *Stem cell research* **2018**, *27*, 121–130, 10.1016/j.scr.2018.01.019.
78. Martin-Maestro, P.; Gargini, R.; A., A.S.; Garcia, E.; Anton, L.C.; Noggle, S.; Arancio, O.; Avila, J.; Garcia-Escudero, V.; Mitophagy Failure in Fibroblasts and iPSC-Derived Neurons of Alzheimer's Disease-Associated Presenilin 1 Mutation. *Frontiers in molecular neuroscience* **2017**, *10*, 291, 10.3389/fnmol.2017.00291.
79. Li, L.; Roh, J.H.; Kim, H.J.; Park, H.J.; Kim, M.; Koh, W.; Heo, H.; Chang, J.W.; Nakanishi, M.; Yoon, T.; et al. The First Generation of iPSC Line from a Korean Alzheimer's Disease Patient Carrying APP-V715M Mutation Exhibits a Distinct Mitochondrial Dysfunction. *Experimental neurobiology* **2019**, *28*, 329–336, 10.5607/en.2019.28.3.329.
80. Repetto, M.G.; Reides, C.G.; Evelson, P.; Kohan, S.; de Lustig, E.S.; Llesuy, S.F.; Peripheral markers of oxidative stress in probable Alzheimer patients. *European journal of clinical investigation* **1999**, *29*, 643–649, 10.1046/j.1365-2362.1999.00506.x.
81. Kawamoto, E.M.; Munhoz, C.D.; Glezer, I.; Bahia, V.S.; Caramelli, P.; Nitrini, R.; Gorjao, R.; Curi, R.; Scavone, C.; Marcourakis, T.; et al. Oxidative state in platelets and erythrocytes in aging and Alzheimer's disease. *Neurobiology of aging* **2005**, *26*, 857–864, 10.1016/j.neurobiolaging.2004.08.011.
82. Ihara, Y.; Hayabara, T.; Sasaki, K.; Kawada, R.; Nakashima, Y.; Kuroda, S.; Relationship between oxidative stress and apoE phenotype in Alzheimer's disease. *Acta neurologica Scandinavica* **2000**, *102*, 346–349, 10.1034/j.1600-0404.2000.102006346.x.
83. Ascolani, A.; Balestrieri, E.; Minutolo, A.; Mosti, S.; Spalletta, G.; Bramanti, P.; Mastino, A.; Caltagirone, C.; Macchi, B.; Dysregulated NF-kappaB pathway in peripheral mononuclear cells of Alzheimer's disease patients. *Current Alzheimer research* **2012**, *9*, 128–137, 10.2174/156720512799015091.
84. Behrens, M.I.; Silva, M.; Salech, F.; Ponce, D.P.; Merino, D.; Sinning, M.; Xiong, C.; Roe, C.M.; Quest, A.F.; Inverse susceptibility to oxidative death of lymphocytes obtained from Alzheimer's patients and skin cancer survivors: Increased apoptosis in Alzheimer's and reduced necrosis in cancer. *The journals of gerontology. Series A, Biological Sciences and Medical Sciences* **2012**, *67*, 1036–1040, 10.1093/gerona/glr258.
85. Cecchi, C.; Fiorillo, C.; Sorbi, S.; Latorraca, S.; Nacmias, B.; Bagnoli, S.; Nassi, P.; Liguri, G.; Oxidative stress and reduced antioxidant defenses in peripheral cells from familial Alzheimer's patients. *Free radical biology & medicine* **2002**, *33*, 1372–1379, 10.1016/s0891-5849(02)01049-3.
86. Cecchi, C.; Fiorillo, C.; Baglioni, S.; Pensalfini, A.; Bagnoli, S.; Nacmias, B.; Sorbi, S.; Nosi, D.; Relini, A.; Liguri, G.; et al. Increased susceptibility to amyloid toxicity in familial Alzheimer's fibroblasts. *Neurobiology of aging* **2007**, *28*, 863–876, 10.1016/j.neurobiolaging.2006.05.014.
87. Choi, J.; Malakowsky, C.A.; Talent, J.M.; Conrad, C.C.; Carroll, C.A.; Weintraub, S.T.; Gracy, R.W.; Anti-apoptotic proteins are oxidized by Abeta25-35 in Alzheimer's fibroblasts. *Biochimica et biophysica acta* **2003**, *1637*, 135–141, 10.1016/s0925-4439(02)00227-2.
88. Mota, S.I.; Costa, R.O.; Ferreira, I.L.; Santana, I.; Caldeira, G.L.; Padovano, C.; Fonseca, A.C.; Baldeiras, I.; Cunha, C.; Letra, L.; et al. Oxidative stress involving changes in Nrf2 and ER stress in early stages of Alzheimer's disease. *Biochimica et biophysica acta* **2015**, *1852*, 1428–1441, 10.1016/j.bbadis.2015.03.015.
89. Piccini, A.; Fassio, A.; Pasqualetto, E.; Vitali, A.; Borghi, R.; Palmieri, D.; Nacmias, B.; Sorbi, S.; Sitia, R.; Tabaton, M.; et al. Fibroblasts from FAD-linked presenilin 1 mutations display a normal unfolded protein response but overproduce Abeta42 in response to tunicamycin. *Neurobiology of disease* **2004**, *15*, 380–386, 10.1016/j.nbd.2003.11.013.
90. Martins, S.; Muller-Schiffmann, A.; Erichsen, L.; Bohndorf, M.; Wruck, W.; Sleegers, K.; Van Broeckhoven, C.; Korth, C.; Adjaye, J.; IPSC-Derived Neuronal Cultures Carrying the Alzheimer's Disease Associated TREM2 R47H Variant Enables the Construction of an Abeta-Induced Gene Regulatory Network. *International journal of molecular sciences* **2020**, *21*, 4516, 10.3390/ijms21124516.
91. Kondo, T.; Asai, M.; Tsukita, K.; Kutoku, Y.; Ohsawa, Y.; Sunada, Y.; Imamura, K.; Egawa, N.; Yahata, N.; Okita, K.; et al. Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Abeta and differential drug responsiveness. *Cell stem cell* **2013**, *12*, 487–496, 10.1016/j.stem.2013.01.009.